THE DEVELOPMENT AND VALIDATION OF A PATIENT BASED HEALTH OUTCOME MEASURE FOR ADULTS WITH BETA THALASSAEMIA MAJOR (BTM)

A thesis submitted for the degree of Doctor of Philosophy

by

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Declaration

I, Xenya Kantaris, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Xenya Kantaris

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Abstract

Beta Thalassaemia Major (BTM) is a chronic, genetic disorder of haemoglobin (Hb) production which has an important effect on patients' quality of life (QoL) yet to date there are no instruments to evaluate the impact of this illness on patients' daily functioning. The aim of the current work was to develop and validate a patient-based, disease-specific, multidimensional measure of the impact of BTM designed for use with adult patients. Standard psychometric methods were used to develop the Thalassaemia Adult Life Index (THALI-35), in three stages. In stage 1 (item generation) a pool of questionnaire items was generated from interviews with adult patients on the impact of BTM on their lives. Five domains were identified: general physical health (GPH), coping (C), body image, appearance and confidence (BIAC), social relationships (SR) and autonomy (A). Stage 1 resulted in a 61-item questionnaire. Preliminary testing resulted in a 63-item questionnaire. In stage 2 (item reduction) the 63-item questionnaire was administered by postal survey to a community sample of adult members of the UK Thalassaemia Society (UKTS). Standard item reduction techniques were used to develop a 35-item questionnaire measuring the physical, psychological and social impact of BTM. In stage 3 (psychometric evaluation) the developed 35-item questionnaire was evaluated in a separate postal survey in a clinical sample of adult patients. The initial assessment of the psychometric properties of the THALI-35 e.g. reliability and internal consistency, convergent and concurrent validity, indicates satisfactory results such that further research appears warranted and required. It is anticipated that the THALI-35 may be utilised in clinical research to assess the effects of new therapies and/or interventions from the patient's perspective and to inform clinical practice and/or to identify areas of concern.

List of Abbreviations

A	Autonomy	HRQoL	Health Related Quality of Life
BIAC	Body Image, Appearance and Confidence	ICT	Iron Chelation Therapy/Treatment
BIQLI	Body Image Quality of Life Inventory	PCA	Principal Component Analysis
BMA	British Medical Association	PROM(s)	Patient Reported Outcome Measure(s)
BTM	Beta (β) Thalassaemia Major	QoL	Quality of Life
C	Coping	RSE	Rosenberg's Self-esteem scale
CF	Cystic Fibrosis	SCD	Sickle Cell Disease
CTT	Classical Test Theory	SCES	The Sickle Cell Self-Efficacy Scale
DFO	Desferrioxamine	SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
EFA	Exploratory Factor Analysis	SR	Social Relationships
GPH	General Physical Health	THALI	Thalassaemia Adult Life Index
Hb	Haemoglobin	UKTS	UK Thalassaemia Society
HCP(s)	Health Care Professional(s)	WHO	World Health Organisation

The most frequently used abbreviations in this research report are listed here. Well-known abbreviations e.g. G.P. and other less used abbreviations are used and defined in the text, as are non-standard abbreviations used only in the figure(s)/table(s)/appendices as they are defined in the figure(s)/table(s)/appendices key or at the end of the table.

Overview of Research Report

This report describes the development and validation of the Thalassaemia Adult Life Index (THALI-35) a new measure of the physical, psychological and social impact of Beta Thalassaemia Major (BTM), from the patient's perspective. The THALI-35 was developed and tested in three stages. In stage 1 (item generation) a 61-item questionnaire was generated from 16 patient interviews. In stage 2 (item reduction) the 63-item questionnaire was administered by postal survey to the 381 adult members of the UK Thalassaemia Society (UKTS) to identify items for elimination on the basis of psychometric performance. This process generated the THALI-35. In stage 3 (psychometric evaluation) an initial evaluation of the psychometric properties of the THALI-35 (reliability, convergent and concurrent validity) was undertaken in a postal survey of a clinical sample of 35 patients receiving treatment and being cared for and managed by, a UK hospital.

Chapter 1 gives an overview of the clinical features and clinical management of BTM.

Chapter 2 reviews the seminal research surrounding the underlying psychosocial impact upon adults with thalassaemia.

Chapter 3 considers the conceptualisation and measurement of 'quality of life' (QoL), as an outcome variable for healthcare intervention and research. Additionally, it examines the role of QoL in the BTM.

Chapter 4 gives a synopsis of the history and background of psychometric theory. This is followed by the general aims and objectives of the research.

Chapter 5 presents the methods and results of the qualitative aspect of the research and stage 1 (item generation) followed by an evaluation of this stage of the research.

Chapter 6 presents the methods and results of stage 2 (item reduction) followed by an evaluation of this stage of the research. This chapter also includes an alternative item reduction addendum.

Chapter 7 presents the methods and results of stage 3 (psychometric evaluation) followed by an evaluation of this stage of the research.

Chapter 8 presents a general discussion of the study results, study strengths and limitations and the implications of the THALI-35 for healthcare. It also provides recommendations for future research. This is followed by a study conclusion.

The appendices include a copy of the THALI-35 and the instructions for its administration.

Chapter 1

An Introduction to Beta (β) Thalassaemia Major (BTM)

"Illness can dominate all aspects of life in adults who have thalassaemia however for a few, life is much more important than illness"

Eugenia T. Georganda (1990), p471
Psychologist and beta (β) thalassaemia major patient

Chapter Overview

This chapter gives an overview of the clinical features and clinical management of beta (β) thalassaemia major (BTM). Information conveyed here, focuses primarily on the clinical work and research done by leading medical doctors and allied health professionals in the fields of haematology and genetics. The phrases thalassaemia and BTM are used interchangeably throughout this chapter.

1.1 A Historical Perspective

The initial description of thalassaemia was made by Cooley and Lee (1925) in several Italian children who presented with severe anaemia, splenic and liver enlargement, discoloration of the skin and bone changes. The term thalassaemia was not used until seven years later when Whipple and Bradford (1932; 1936) published a paper describing the pathophysiology of the disease. The term thalassaemia, literally meaning 'anaemia of the sea', came into use to note the association of this disease with the Mediterranean region (Weatherall and Clegg, 1972). At that time, most diagnosed cases of the disease were in families originating from countries bordering the Mediterranean Sea, particularly Greece and Italy (Eleftheriou, 2000). Even as early as the 1930's, there were case reports indicating that thalassaemia occurred in Asians as well, yet it was not until the publication by Minnich (1954), (as stated in Weatherall and Clegg, 1972), that thalassaemia was no longer considered exclusively a Mediterranean affliction but was accepted as occurring in high frequency in Asia and Southeast Asia as well (UK Thalassaemia Society, (UKTS), 2005). Further publications both in Europe and in the USA defined the complications of anaemia in BTM (Olivieri, Koren, Hermann, Bentur, Chung, Klein et. al. 1990; Perrimond,

Chagnon, Moulanier, Michel, Guidicelli, Bernard, 1991). These children usually presented within the first year of life and rarely survived beyond their first few years (Olivieri et. al. 1990; Perrimond et. al. 1991). Profound anaemia, failure to thrive, recurrent infections, and progressive enlargement of the abdomen due to hepatosplenomegaly, (simultaneous enlargement of both the liver (hepatomegaly) and the spleen (splenomegaly)), were uniformly the pre-clinical profile (Nick, Wong, Acklin, Faller, Jin, Lattmann et. al. 2002). Those with the severest anaemia would die within the first few months of life from cardiac failure and/or infection and those with less severe anaemia would start to develop other manifestations of the anaemia such as poor growth and varicose veins (Nick et. al. 2002). Thrombocytopenia (low platlets), and the inability to fight bacterial infections is secondary to an enlarged spleen; associated bleeding and bleeding complications was also seen (Modell and Berdoukas, 1984). X-ray images of the bones show cortical thinning, and a 'moth eaten' or lace like' appearance, in the area where small bones are supposed to join; the skull x-rays were the most dramatic with the classical 'hair on end' appearance due to expansion of the diploic space, (in the bones of the vault of the skull) (Modell and Berdoukas, 1984). Pathological fractures were frequent occurrences (Nick et. al. 2002). Extramedullary haematopoiesis, (separation of the blood outside the norm, the bone marrow into organs like the spleen and liver), could be seen on chest X-rays and some children would go onto develop spinal cord paraparesis, (or weakness/slight paralysis of the lower extremities e.g. legs, due to cord compression) (Nick et. al. 2002). If untreated, bone marrow cavities expand leading to a characteristic enlargement of the skull and facial bones (British Medical Association, (BMA), 2002). As children developed beyond the age of 7 years, there was evidence of delayed growth and sexual development that was thought to be secondary to severe anaemia and possibly the siderosis or the deposition of iron in tissue from increased gastrointestinal iron absorption (Weatherall and Clegg, 1972). The prognosis of children with BTM was poor (Lehmann and Huntsman, 1966) yet advances have been made in the care of children with thalassaemia, primarily aimed at improving quality of life, (QoL), and include the removal of the spleen by operative means, (splenectomy), and blood transfusions, both of which can have significant impact on health outcome (Telfer, Constantinidou, Andreou, Christou, Modell and Angastiniotis, 2005). Today, in the absence of diagnosis and treatment, most patients with BTM would die before the age of five years (Telfer et. al. 2005). With recommended treatment, complications are avoidable and/or treatable and, as a result, the overall prognosis is currently open-ended (BMA, 2002).

1.2 Pathophysiology and Geographical Distribution

Beta thalassaemia major (BTM) is a genetic disorder of haemoglobin (Hb) production (BMA, 2002). It is inherited in an autosomal recessive pattern, (a gene which can be passed onto offspring by a mother or a father), and which if inherited with a 'normal' equivalent gene from the other parent, gives rise to no health problems i.e. a healthy carrier (BMA, 2002). The inheritance of BTM is a 25% chance in each pregnancy (Anionwu, 2004). It is common in people originating from the Mediterranean, the Middle East, South Asia, South East Asia and the 'Far East' (UKTS, 2005) however, due to the continual migration of populations from one area to another, there is currently, virtually no country of the world in which thalassaemia does not affect some percentage of its inhabitants (Thalassaemia International Federation (TIF), 2000). Weatherall and Clegg (2001) noted the overall distribution of haemoglobin disorders by percentage (%) with specific reference to BTM by World Health Organisation (WHO) region; Sub-Saharan Africa (AFR) up to 12%, the Americas (AMR) upto 3%, Eastern Mediterranean (EMR) 2-18%, Europe (EUR) upto 19%, South East Asia (SEAR) upto 11%, West Pacific (WPR) upto 13%. It has been estimated that there are probably as many as 100,000 living patients with BTM in the world (TIF, 2000). In the UK, BTM is more or less restricted to ethnic minority populations, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi (Modell, Khan and Darlinson, 2000). Hickman, Modell, Greengross, Chapman, Layton, Falconer et. al. (1999) mapped the prevalence of BTM in England and found that the majority of BTM births are in London, the Midlands and the north of England; these are the traditional areas where migrant families have settled. When the UK Thalassaemia Register closed at the end of 2003, the total number of living thalassaemia patients was 857 (Modell et. al. 2000). Although there was no differentiation between BTM and other types of thalassaemia diagnoses in the register, 532 adult BTM patients were thought to be alive and on treatment and 71 BTM adult patients were alive with a bone marrow transplant (BMT) (Modell et. al. 2000).

Micro-mapping by individual groups has shown how the frequency of thalassaemia can vary significantly throughout regions often that are just a few miles apart (Ahmed, Saleem, Modell and Petrou, 2002; Araujo, Silva, Leao, Bandeira, Petrou, Modell et. al. 2003; Old, Khan, Verma, Fucharoen, Kleanthous, Ioannou et. al. 2001). Khattak and Saleem (1992) have commented that this may be due to social factors, as in many South East Asian communities, marriages occur within tribal/family group confines and this has resulted in a

higher gene frequency in specific groups. For example, in Pakistan the frequency of thalassaemia trait is 5.4% for the general population (Khattak and Saleem, 1992) but on family testing based on index cases, the incidence was 31% and there was a 25% risk that the carrier would be in a marriage at risk of producing an affected child (Ahmed et. al. 2002). In Oman the carrier rate for the indigenous Arab population is 1-2% (Rajab and Patton, 1997) but in the Belushi tribe which migrated from the province of Baluchistan (Pakistan), the incidence is 10% (Angastiniotis and Modell, 1998). According to the UKTS (2005), a 1 in 8 Asian person is a carrier of BTM.

Due to migration the prevalence of the BTM has altered in a number of countries (TIF, 2000). The greatest increase in births of children with BTM is in the Asian communities and predominantly Pakistani families (Modell, Harris, Lane, Khan, Darlinson, Petrou et. al. 2000). The UK distribution of these disorders reflects this, as where large pockets of ethnic minorities settled, the BTM frequency is greatest (Hickman et. al. 1999).

About 200,000 people in Britain are carriers of β Thalassaemia and at least 100,000 children are born around the world with the disorder each year (Genetic Interest Group, (GIG), 2007). The disorder is due to a range of mutations associated with the beta globin gene, resulting in reduced or absent production of β globin, one of the constituents of the adult haemoglobin molecule (HbA) (Cao, Rosatelli and Galanello, 1991; Modell, 1999). Reduced β globin production leads to excess free alpha (α) globin chains that damages red cell precursors in the bone marrow (Cao et. al. 1991; Modell, 1999). This results in ineffective erythropoiesis (the process of red cell formation), severe anaemia and compensatory erythroid marrow hyperplasia, (overgrowth of the bone marrow), caused by increased red cell production (BMA, 2002).

The frequency of the alpha and beta globin defects have not been analysed in all countries worldwide, primarily due to the lack of resources and greater clinical priorities however a number of studies have been undertaken in individual countries (Weatherall and Clegg, 2001). Worldwide figures from the WHO suggest that there are 270 million carriers for globin gene defects and that 300,000 to 400,000 children are born annually with a severe haemoglobin disorder (Weatherall and Clegg, 2001). As the socioeconomic circumstances improve worldwide a greater number of children will survive into adulthood and the

economic burden of treatment of the haemoglobinopathies will increase (Telfer, Prescott, Holden, Walker, Hoffbrand and Wonke, 2000).

1.3 What is Haemoglobin (Hb)?

The thalassaemia syndromes comprise a heterogeneous (varied), family of disorders that arise from defects in the rate of synthesis of alpha or beta chains that form the globin component of haemoglobin (BMA, 2002).

Haemoglobin is the coloured pigment inside red blood cells (RBCs) that carries oxygen round the body (BMA, 2002). Haemoglobin levels in the blood are measured in grammes per 100 millilitres, which is abbreviated to g/dl (BMA) (2002). The normal range of haemoglobin for a man is 13.5 to 17.5 g/dl and for a woman is 11.5 to 15.5 g/dl; anything less than these numbers is called anaemia (BMA, 2002). As the haemoglobin level starts to fall, the body is very good at compensating for the drop in red cells (Porter and Davis, 2002). The heart will beat faster and more forcefully and the lungs increase the amount of air they move each minute to increase the amount of oxygen they deliver to the blood; the body also gets better at taking up oxygen into the red cells and releasing it where it is needed (Porter and Davis, 2002). This is why we can often cope with slightly lower than normal haemoglobin levels especially if they develop gradually (Borgna-Pignatti, Rugolotto, De Stefano, Zhao, Cappellini, Del Vecchio et. al. 2004). However, when the level drops too low, people start to feel tired, breathless and may start to run into problems with too little oxygen getting to important organs like the heart and brain (Borgna-Pignatti et. al. 2004). This can cause palpitations, angina (chest pains), headache or dizzy spells (Borgna-Pignatti et. al. 2004) but not everyone will get symptoms at the same level (Olivieri, Nathan, MacMillan, Wayne, Liu, McGee et. al. 1994; Angelucci, Brittenham, McLaren, Ripalti, Baronciani, Giardiani et. al. 2000). Recent studies by physicians like Porter and Davis (2002) and Modell, Khan, Darlinson, King, Layton, Old, Petrou and Varnavides (2001), have shown that most people feel less tired if their haemoglobin is above 12g/dl. At present, medical doctors tend to treat a moderately low haemoglobin (below 11 or 12), particularly if someone is feeling weary (UKTS, 2005). To some extent it is a matter of finding the haemoglobin where patients feel most comfortable but severe anaemia is not safe and always needs to be treated**;** often this will involve a simple blood transfusion which can rapidly correct the problem (UKTS, 2005). It is also possible to correct your haemoglobin by giving a chemical called Erythropoietin but this takes a long

time to work, is not effective in everyone and requires regular injections (BMA, 2002). It is also very expensive (Rund and Rachmilewitz, 2005).

1.4 Treatment and Management of Beta (β) Thalassaemia Major (BTM)

Prior to the 1970s, the prognosis of patients with BTM was very poor; death was expected to occur before puberty due to the pathophysiology of the disease (Modell, Letsky, Flynn, Peto, Weatherall, 1982; Modell and Berdoukas, 1984). Now the picture is very different. Until the final goal of a complete cure for BTM is achieved, patients are offered the most complete and up-to-date system of treatment available (Vardaki, Phialithis and Vlachonikolis, 2004). Despite the many difficulties and expenses such a system may incur, as long as it is possible to offer a good quality of life to thalassaemics, it is the duty of health professionals to provide the means (Rund and Rachmilewitz, 2005). Guidelines outlined by the UKTS (2005) and contributing national authors specialising in thalassaemia, provide information about what is currently regarded as the most effective treatment and serves as a goal for the management and care of all patients with BTM worldwide. The outlook for people with BTM is improving as treatment improves (Porter and Davis, 2002). A BMT is possible for some children with BTM but is not without risk, and is best done when the child is still young; the donor must be a close family member who is an exact tissue match (UKTS, 2005).

1.4.1 Standard Treatment of Beta (β) Thalassaemia Major (BTM)

Standard treatment consists of regular blood transfusions given every three to four weeks, at about Hb 9.5 (UKTS, 2005). Blood transfusion as a therapeutic measure has only been a practical option since the late 1920's due to the widespread use of blood group typing (Modell and Berdoukas, 1984). Transfusions correct the anaemia, which enables the body's growth and normal activity levels and prevents enlargement of the spleen therefore inhibiting the overgrowth of the bone marrow caused by increased red cell production (BMA, 2002). The most important long-term problem associated with regular transfusions in thalassaemia is iron overload (Ward, Caro, Green, Huybrechts, Arana, Wait et. al. 2002). Blood contains iron, which cannot be excreted from the body and a typical thalassaemia patient on a regular transfusion programme will accumulate 0.3-0.5mg/kg of iron per day (Ward et. al. 2002). Excessive iron is toxic, the most vulnerable organs being the heart, liver and endocrine glands (Porter and Davis, 2002). Once the body has

accumulated 12-24g of iron, significant clinical manifestations of iron toxicity can be expected (Gabutti and Borgna-Pignatti, 1994). Without treatment to remove the iron, the majority of patients develop cardiac problems and die of heart failure by the age of 20 (UKTS, 2005). Iron overload, whether through increased iron absorption or as a result of transfusional iron loading, constitutes the most important complication in BTM and the major focus of clinical management (Hoffbrand and Wonke, 1997; Piga, Longo, Consolati, De Leo, Carmellino, 1997; Porter and Davis, 2002; Eleftheriou, 2000). In the past 20 years, the treatment of thalassaemia major has improved tremendously in countries with access to adequate and safe blood and iron chelation therapy (ICT) with Desferrioxamine (DFO) (Olivieri, 1999; Eleftheriou, 2000). Therapy to remove or 'chelate' excess iron is therefore essential and this must be started within a year or so of starting regular transfusions (Porter and Davis, 2002). The established regime requires subcutaneous or below the skin infusions via a small pump-like device of the chelating agent DFO given 5-7 nights per week over 8-12 hours (Ratip, Skuse, Porter, Wonke, Yardumian and Modell, 1995; Caro, Huybrechts and Green, 2002). This treatment regime can stabilise the body iron load at an acceptable level in a majority of patients and has been shown to reduce the risk of cardiac disease and to improve survival (Modell and Berdoukas, 1984; Olivieri and Brittenham, 1997). Complications of iron overload such as short stature and failure of the normal activities of the testes in men and ovaries in women may be prevented (Olivieri, 1999). This reference treatment is free under the National Health Service (NHS) (Rund and Rachmilewitz, 2005) and the first patients to receive it are now in their early 50's (UKTS, 2005).

Desferrioxamine (DFO) was first introduced in the early 1960's as a chelating agent to treat acute iron poisoning (Moeschlin and Schnider, 1964; Pittman, 1964). Despite the very clear benefits of chelation therapy, it is a difficult treatment to use and adherence to therapy has been a major issue for both clinicians and patients over the last 30 years (Porter and Davis, 2002). The efficacy of DFO in preventing complications of iron overload in patients with BTM is clear (Gabutti and Piga, 1996; Brittenham, Griffith, Nienhuis, McLaren, Young, Tucker, et. al. 1994). Controlling excess iron has been shown to reduce injury to vital organs, improve QoL and extend the lives of patients (Gabutti and Piga, 1996; Brittenham et. al. 1994). Borgna-Pignatti et. al. (2004) can confirm a reduced frequency of complications due to iron overload in patients who had received chelation from an early age. In addition, survival data from the UK Thalassaemia Register (Modell

et. al. 2000) showed that despite good access to chelation therapy the outcome was still poor with over 50% of patients dead by the time they reached 35 years of age.

The term adherence implies active collaboration of patients, working together with the clinician in planning and implementing treatment regimens (Myers and Midence, 1998). Although it is not the focus here, the adherence to treatment for BTM is discussed in more detail in section 1.4.2.

The search for an alternative chelator, which is easier to administer, has been the goal for many physicians looking after patients with thalassaemia (Wonke, Wright and Hoffbrand, 1998; Vardaki et. al. 2004; Abetz, Baladi, Jones and Rofail, 2006; Rofail, Viala, Trudeau and Baladi, 2006).

1.4.2 Adherence to Treatment by Beta (β) Thalassaemia Major (BTM) patients

For BTM patients, adoption of lifelong adherence to regular administration of DFO is very important for their long-term health (Modell and Berdoukas, 1984; Olivieri, 1999; Modell et. al. 2000; Porter and Davis, 2002). Careful monitoring together with adherence to established regimens results in a 78% survival rate at 40 years of age with steadily improving survival as progressive cohorts receive chelation earlier in life (Porter and Davis, 2002). However, adherence to treatment is very difficult, and many adolescents and young adults allow their iron load to rise, as the treatment is lengthy, complex and time consuming i.e. repeated blood tests and transfusions, repeated hospital admissions and appointments (Hoffbrand and Wonke, 1997).

Approximately 50% of people with BTM in the UK die before the age of 35 years from failure to adhere to their burdensome treatment (Modell et. al. 2001). According to the Hellenic Red Cross Thalassaemia Unit, 30% of patients complied only moderately to iron chelation therapy (Politis, Vrettou, Fragatou, Hatzilaou, Flessa and Richardson, 1996). This was associated with a 60% incidence of generalised and local reactions to DFO, (Politis, Vrettou, Fragatou, Hatzilaou, Richardson and Salem, 1993), an extra factor deterring patients from adhering to their treatment schedules (Politis, 1998). These numbers are consistent with adherence rates of other chronic regimens for life threatening diseases such as severe asthma (Lemanek, 1990), cystic fibrosis (CF), (Geiss, Hobbs,

Hammersley-Maereklein, Kramer and Henley, 1992), rheumatoid arthritis (Anderson, Bradley, Young, McDaniel and Wise, 1985) and diabetes that arise during childhood. A meta-analysis by DiMatteo (2004) offers insights into the literature on patient adherence, and reported the average non-adherence rate as 24.8% in disease in general. Adherence was reported as highest in Human Immuno-deficiency Virus (HIV), arthritis, gastrointestinal disorders and cancer, and lowest in pulmonary disease, (persistent disruption of air flow into or out of the lungs), and diabetes. Achieving a balance between adherence and psychological adjustment has been found to be of paramount importance in chronically ill adult patients like those with CF (Geiss et. al. 1992), and sickle cell disease (SCD), an inherited blood disease in which the red blood cells contain Hb S, an abnormal type of Hb (Thompson, Gil, Abrams and Phillips, 1992). The necessity for strict adherence to treatment has been found to have a detrimental effect on patients' QoL in various chronic illnesses and is well recognised to have major medical, psychological and economic consequences (Myers and Midence, 1998). Adherence to drug treatment and QoL are both related to the patient and are important to consider when assessing the impact of any type of intervention in healthcare at the patient level (Myers and Midence, 1998), yet Cote, Farris and Feeny (2003) found weak positive correlations (a statistical relationship between two or more random variables or observed data values), between these two variables in hypertensive adults. A positive impact on QoL as perceived by the patients is an important criterion for evaluating treatment success in adult gastroparesis patients, (paralysis of the stomach and intestines) (Revicki, Rentz, Dubois, Kahrilas, Stanghellini, Talley et. al. 2000). Adherence and QoL are two outcomes representing very different points in time following processes of care; adherence is thought to be an intermediate outcome whilst QoL is thought to be an ultimate outcome (Cote et. al. 2003). This implies that the impact of any type of intervention will be revealed by a change in adherence first and consequently by a change in QoL (Cote et. al. 2003).

The main problem with ICT is adherence to the regular subcutaneous infusions of DFO (Abetz et. al. 2006; Rofail et. al. 2006). Desferrioxamine infusions are time consuming to set up and require introduction of a subcutaneous needle on each occasion followed by continued attachment to an infuser device over hours at a time (Telfer et. al. 2005). They are unpopular and often resisted especially by older children and teenagers as they report local discomfort and feeling set apart from their peers (Atkin and Ahmad, 2001).

In a large, well-organised specialist thalassaemia centre, physical and psychological problems with adherence are addressed methodically and excellent survival can be expected in younger patients (Porter and Davis, 2002). Effective management of iron overload in BTM requires monitoring both for iron toxicity and the effects of excessive chelation (Modell et. al. 2000; Porter and Davis, 2002). In the UK, according to the Thalassaemia Register, survival has not improved to the extent hoped 30 years ago when DFO became available (Modell et. al. 2000), possibly due to the problems patients experience in tolerating regular self-administered infusions (Porter and Davis, 2002). However, a national register for the surveillance of inherited disorders primarily for BTM in the UK, showing the status of patients born with the disorder (alive, dead, successful BMT or lost to follow-up), by region of residence, reported that by the end of 1999, 77% of its patients were alive (Modell et. al. 2001). Constant monitoring for complications and their timely treatment goes hand in hand with organising regular blood transfusions and managing chelation therapy throughout their lifetime (Porter and Davis, 2002). Patients require an individually tailored treatment plan, incorporating new, more reliable approaches (Modell et. al. 2001).

Deferiprone or L1 was the first oral iron chelator identified in the late 1980's (Kontoghiorghes and Evans, 1985; Kontoghiorghes, Sheppard, Hoffbrand, Charalambous, Tikerpae and Pippard, 1987b) however it is also a demanding treatment to undertake as multiple tablets have to be taken three times daily that have significant gastrointestinal side effects (Ceci, Baiardi, Felisi, Cappellini, Carnelli, De Sanctis et. al. 2003; Cohen, Galanello, Piga, Di Palma, Vullo and Tricta, 2000; Maggio, D'Amico, Morabito, Capra, Ciaccio, Cianciulli et. al. 2002). Nevertheless, deferiprone has helped to improve adherence to treatment and has improved iron burdens in a significant number of patients who were unable to administer DFO treatment (al-Refaie, Hershko, Hoffbrand, Kosaryan, Oliveri, Tondury et. al. 1995, Kontoghiorghes, Bartlett, Hoffbrand, Goddard, Sheppard, Barr et. al. 1990; Olivieri, al. 1990). In a randomised clinical trial (RCT) of 144 patients with BTM, iron levels were shown to reduce using Deferiprone (Maggio et. al. 2002). However, Pennell, Berdoukas, Karagiorga, Ladis, Piga, Aessopos et. al. (2006) found no significant differences between 61 BTM patients in an RCT on DFO or Deferiprone. Pennell et. al. (2006) identified that adherence to DFO and Deferiprone, can be very good, (94% and 93% respectively), yet clinicians report that patients are still faced with difficulties in adhering to treatment (Cappellini, Cohen, Piga, Bejaoui, Perrotta, Agaoglu

et. al. 2006). Deferasirox or Exjade the new, once-daily oral chelator is now available for prescription. The drug that is taken as a tablet dissolved in a drink was launched in September of 2006. To quote an adult BTM patient, "*Exjade is a lifesaver that shall enable us to socialise, work, study and go on holiday without the worry and constraints associated with DFO infusions"* (UKTS matters issue number 106, p1, 2006). Nevertheless, as with other chronic conditions that demand a high level of medical intervention, it is not just the technical care that affects the patient's life experience but also the way in which their care is delivered (Kaplan and Saccuzzo, 1993). The impact of Deferasirox on survival and adherence is likely to be significant because patients who find chelation with DFO difficult and/or have serious side effects with Deferiprone will now have the option of a once daily oral medication (Cappellini et. al. 2006). The long-term impact on survival and the incidence of iron associated complications will become clearer over the next 10 years or so (Cappellini et. al. 2006).

Thalassaemia affects the individual who is chronically sick not only in a physical way but in psychological and social ways too (psychosocial) (UKTS, 2005). Chapter 2 reviews research surrounding the underlying psychosocial impact upon adults with thalassaemia.

Chapter 2

The Psychology of Beta (β) Thalassaemia Major (BTM)

"Sickness shows us what we are"

A Latin pro-verb

Chapter Overview

This chapter reviews the seminal research surrounding the underlying psychosocial impact upon adults with thalassaemia. The research has essentially been undertaken by healthcare professionals (HCPs) working in transfusion centres and thalassaemia centres in the Western world, and there is overwhelming evidence that suggests that the psychological element is significant in the survival of people with thalassaemia. The phrases thalassaemia and BTM are used interchangeably throughout this chapter.

2.1 The General Situation

2.1.1 Setting the Scene

Studies surrounding the psychological and social wellbeing of chronically ill and disabled people in general found the presence of significant levels of emotional problems and poor social adaption (Cadman, Boyle, Szatmari and Offord, 1987). As a chronic illness, the nature of thalassaemia and its intensive and demanding treatment can also place a severe psychosocial burden on the people whom it affects (Ratip et. al. 1995). Ratip et. al. (1995) stated that the most common cause of death in thalassaemia is psychosocial in nature in Western countries. Consequently, psychosocial aspects of the illness have been widely studied. This research shall be discussed in some detail in the following sections with the discussion focusing upon the situation in the developed world.

Thalassaemia is no longer considered a fatal illness and advances in medical treatment and management have greatly increased the life expectancy of these patients (Bush, Mandel and Giardina, 1998). As the mean age and life expectancy of BTM patients has expanded, psychosocial issues related to QoL have become an increasingly important focus of attention (Bush et. al. 1998). Until now, data regarding the psychosocial aspects of thalassaemia has been inadequate (DiPalma, Vullo, Zani and Facchini, 1998). DiPalma et. al. (1998) consider that this may be because the medical problems of the disease are so severe that all other aspects have been more or less neglected. Research by HCPs such as

Politis, DiPalma, Fisfis, Giasanti, Richardson, Vullo et. al. (1990), DiPalma et. al. (1998), Georganda (1988), Ratip et. al. (1995) and Politis (1998) has shaped the psychology of thalassaemia. It shall become evident from the literature that a number of challenges faced by patients' compromise their psychosocial functioning. Examples of challenges include demands of regular blood transfusions and chelation therapy, physical deformities e.g. growth retardation and delayed puberty that may result in body image issues, the adjustment to the illness as an adolescent and adult, the hereditary nature of the illness, mortality issues and the ever present knowledge that thalassaemia is a life long illness and the loss of peers with thalassaemia due to complications associated with the disease (Bush et. al. 1998; Politis et. al. 1990; Georganda, 1990).

2.1.2 The Psychosocial Impact of Thalassaemia

A précis paper by Politis (1998) depicts the psychosocial burden of thalassaemia in the past. This included stigmatisation, impulsivity, secrecy about the illness, capriciousness, isolation of patients and their family, controlled temper, physical handicap, withdrawal, absence of sexual development, dependency, fear of death and dying before adulthood. In this same paper, Politis (1998) summarised the current developments concerning psychosocial burden of thalassaemia in the present including physical appearance, pubertal growth and sexual development and social integration i.e. schooling, working, establishing relationships, getting married, raising a family. Politis (1998) found it important to mention therapeutic novelties such as oral chelators, BMT and gene therapy, of which patients are highly aware. There does seem to be a major psychological burden in coping with the many problems of the illness and its therapy therefore the provision and continuity of psychosocial support for patients is therefore of paramount importance (Politis, 1998). In accordance with the burdensome treatment of thalassaemia one would expect that people with thalassaemia would be at an increased risk of psychosocial disturbances (DiPalma et. al. 1998). Tsiantis (1990) found that 42% of a group of patients with thalassaemia had psychiatric problems even if they had a normal self-concept. Parallel research studies did not confirm this and showed that adolescents and young adults with thalassaemia have psychosocial development comparable to people of the same age without thalassaemia (DiPalma et. al. 1998). The aim of a noteworthy paper by DiPalma et. al. (1998) was to explore the effect of thalassaemia on the psychosocial adjustment of adolescents and young adults. Ninety unmarried patients completed an ad hoc questionnaire. Rather unusually a matched control group was formed for comparison

instead of another group of chronically ill patients. Nineteen married patients were interviewed about marriage and family life. The behaviour of the married patients did not differ from the couples in the control group. Patients with thalassaemia reported having a 'normal' marital life e.g. understanding a partner's needs, being happy in the relationship, having comparable expectations, having a loving partner, happiness and contentment. Unmarried patients had 'normal' psychosocial development and scored better than the control group with regard to social adjustment, self-esteem and self-description. These data show that thalassaemia patients cope with life's difficulties in the same way as those without thalassaemia. Even though replies were anonymous, it is not possible to be sure that all patients with thalassaemia gave honest answers (DiPalma et. al. 1998). However, DiPalma et. al. (1998) are confident that the results of their investigation reflect the psychosocial adjustment of patients with thalassaemia as the numbers of the patients who did not participate is too small to affect the general conclusion.

Canatan, Ratip, Kaptan and Cosan (2003) considered the psychosocial burden of over 30 BTM patients. The adult patients were interviewed on their own using a structured questionnaire. As pre-existing questionnaire measures of psychosocial adjustment are either inappropriate for this specific chronic inherited illness or too cumbersome for use in a clinical setting (Rutter, Tizard and Whitmore, 1970; Goldberg and Hillier, 1979; Deasy-Spinetta, Spinetta and Osman, 1988; Achenbach, 1992), a questionnaire designed to measure the psychosocial burden of thalassaemia (Ratip et. al. 1995), was used. The four most pronounced aspects of life affected by thalassaemia for adult patients were anxiety (27), sport (22), self-image (21) and feelings of difference (16). Joint fifth was education (15), time off school and social integration. Aspects of life not reported as frequently as impacting on the life of the patients were family interactions (2), social isolation (6), stigmatisation (6) and denial (8). These results illustrate that there is a need for psychosocial as well as medical aid for patients with BTM therefore the multidisciplinary care team should include mental health professionals (Canatan et. al. 2003). A questionnaire study surrounding the psychosocial aspects of 90 transfusion dependent thalassaemia adolescent and adult patients was done by Zani, DiPalma and Vullo (1995). Akin to the study of DiPalma et. al. (1998), a 'healthy' control group, rather than a 'case' group was used for comparison. The questionnaire topics included level of social integration, relationships and self-concept. The results showed that adolescents with thalassaemia have normal psychological and social development and score even better than

their healthy peers in tests concerning self-esteem and self-description. Patients with thalassaemia are more cautious than the control group as far as relationships are concerned but half affirm they have a partner. Patients show a very positive self-image with regard to self-esteem and indicate a high degree of confidence in their abilities although they consider finding a job, getting married and having children as more distant targets than the control group. It should be noted that not all patients asked agreed to participate in the study; it is possible that it was these patients who had psychosocial problems. This study supports the hypothesis by Cappelli, Megrath, Heick, Macdonald, Feldman and Rowe (1989) that chronic illness does not necessarily imply psychopathologies but can strengthen patients' resources, contrary to the traditional stereotype view of chronic patients having poor psychological and social profiles e.g. reports that their illness disrupts freedom and popularity, more concerned with peer relations than healthy controls and twice as likely to report as being unhappy (Cappelli et. al. 1989).

Innovatively, Georganda (1990) explored the impact of thalassaemia on body image, (a multidimensional construct including the perception of one's body shape as well as attitudes toward different aspects of one's body), and self-esteem and ultimately self-image, by presenting two case studies of adult patients. These two cases showed that such patients suffer from low self-esteem and a devalued sense of self, looking for approval and acceptance from others. Both the cases presented were of women who reported wanting approval and affirmation of femininity from their male partners. They felt very easily hurt and rejected and believed that the only way they could keep a man was via sex, even so believing that their partner did not like their body or general appearance. When discussing feelings of weakness (physical) and vulnerability (psychological), they were related to the overprotection of the family which made them feel fragile and weak. They reported that fear of being hurt, physically or emotionally, prevented them from enjoying their life. They reported experiencing great difficulty in expressing themselves and their fears and used to somatise their problems in general. Health professionals were also accused of reinforcing the view that they were fragile. It was difficult for them to express their anger and resentment for their condition because they were afraid others would reject them. Georganda (1990) ultimately identified three important issues surrounding body image, self-esteem and self- image: (1) how the illness is perceived by and dealt with by others e.g. parents, doctors and other significant adults, (2) how and whether feelings, worries and concerns about the illness are expressed, and (3) fear of death, anxiety, anger and

depression. *"Clearly, the presence of a chronic, hereditary illness like thalassaemia is a very demanding condition that will unavoidably cause a number of intense emotional reactions"* (Georganda, 1990, p471). The author concludes that to successfully adapt to the presence of thalassaemia, patients should focus on the attitude towards to illness itself. *"Illness can dominate all aspects of life in adults who have thalassaemia however for a few, life is much more important than illness. This might be taken as the key message for our patients' psychosocial support strategies"* (Georganda, 1990, p471).

A quantitative analysis of the frequency of psychosocial problems in adults with thalassaemia, from a London based representative sample, was evaluated in a study by Ratip et. al. (1995), whereby 28 patients were interviewed using specifically designed questionnaires; these questionnaires shall be considered in some depth in Chapter 3, section 3.5.2. A wide variation in results was found ranging from patients being virtually unaffected to severely affected by thalassaemia. Patients mentioned that normal sexual function and setting up a family is particularly important; intriguingly 58% of the patients had problems with sexual maturation and functioning. Forty three percent of patients reported that their education was affected; sports activity was affected in 62% of patients. Sixty seven percent of patients felt a degree of stigmatisation, ranging from relationships being broken or being unemployed, due to their illness. Nineteen percent had problems with social integration in that they were unable to set up a family or were unemployed. A similar proportion expressed some degree of feeling different from their peers and siblings. More than half of the patients described themselves as being anxious and worried about their illness. The suggestion that a high clinical burden is associated with a high psychosocial burden both defined by medical doctors and Ratip et. al. (1995) is supported in this investigation. Ratip et. al. (1995) noted that attitudes and psychosocial burden could possibly differ between ethnic groups hence such a study should be extended to groups under-represented in this sample i.e. Indians, Italians and Iranians. In addition, personal attitudes towards the illness as identified by Georganda (1990) should be considered. Whilst Ratip et. al. (1995) considered their instrument as convenient for identifying the need for psychological support for patients 'psychological burden' and the items in the instrument itself were defined and 'weighted' by clinicians not by patients. More information on the limitations of this instrument is detailed in Chapter 3, section 3.5.2.

Future orientation and other aspects of social functioning were evaluated with 33 patients with thalassaemia, aged 16-28 years, unusually in comparison to 30 of their healthy peers (Bush et. al. 1998). All participants were compared on measures of future orientations, perceived social support, life orientation, health locus of control and hopelessness. The results of their investigation showed no significant differences between the patients and their peers on all measures except for higher levels of internal locus of control among the patient group. The patient group expressed significantly higher beliefs that one stays or becomes healthy as a result of their behaviour. The source of cognitive reinforcements for health related behaviours as internal, a matter of chance or under the control of powerful others has been documented as a variable in health behaviours (Wallston, Wallston and DeVellis, 1978). Neither group attributed their health to chance. The patient group also believed that they are in control of their health and that their behaviours determined their health outcomes. Traditionally chronic illness has been viewed as negatively affecting the psychological functioning of patients (Cadman et. al. 1987). On the contrary, the results of this study showed that patients can have positive and numerous expectations about their future e.g. having a loving relationship in the future, reaching goals set for the future. The study also confirms previous findings that patients do not necessarily experience psychological dysfunction as a result of their thalassaemia (Politis et. al. 1990). The positive future orientation of patients in this study offers import QoL implications for patient care and research (Bush et. al. 1998). Factors influencing relationships with the opposite sex and/or 'dating' is another area to be studied as it relates to issues of psychosocial development and self-concept. Bush et. al. (1998) found that half the adolescents with thalassaemia have a significant partner. Although coping mechanisms are not the focus of this discussion, it is noteworthy that Bush et. al. (1998) propose that the positive orientation of thalassaemia patients could relate to denial and argue that these patients utilise denial as a coping mechanism i.e. hope not realism.

2.1.3 Methodological Limitations of Psychosocial Studies of Thalassaemia Patients

Studies surrounding the psychosocial aspects of thalassaemia patients are not without flaws. Studies involving thalassaemia patients include survivors of the illness. Bush et. al. (1998), Pearson, Cohen, Giardina and Kazazian (1996), Ehlers, Giardina, Lesser, Engle and Hilgartner (1991), Calleja, Shen, Lesser, Grady, New and Giardina (1998) all suggest that perhaps these patients have benefited from certain coping resources, advanced medical treatment and consistent care throughout their lives. Additionally, these types of samples

may be weighted in favour of possessing resources necessary for adherence (Bush et. al. 1998; Pearson et. al. 1996; Ehlers et. al. 1991; Calleja et. al. 1998). For these reasons bias in results may occur; whether this bias affects results remains to be seen. Sample sizes are generally small and are essentially volunteer or self-selected therefore restricting the generalisation of study findings in general.

2.2. The Psychosocial Impact of Other Chronic Illnesses

Sufferers of thalassaemia are beset by similar psychological problems as other physically ill persons attending out-patient clinics e.g. patients with SCD (Ohaeri, Shokunbi, Akinlade and Dare, 1995). Sickle cell disease (SCD) is the most common genetic disorder of the blood affecting people mainly but not exclusively from African, Caribbean and Asian origin (Anie, Dasgupta, Ezenduka, Anarado and Emodi, 2007). The disease produces significantly abnormal Hb molecules in RBCs (BMA, 2002). The 'sickling' of RBCs occurs when partially or totally deoxygenated Hb molecules distort their normal disk shape, producing stiff, sticky, sickle-shaped cells that obstruct small blood vessels as well as the disruption of oxygen to body tissues (BMA, 2002). Predominant symptoms are recurrent and unpredictable episodes of pain i.e. crises (Edwards, Scales, Loughlin, Bennett, Harrris-Peterson, DeCastro et. al. 2005). Due to tissue damage, patients are at risk from various medical complications including but not limited to delayed growth and sexual maturation, stroke, severe chronic pain (Edwards et. al. 2005). Treatment of SCD can and does include blood transfusions and consequently chelation treatment (BMA, 2002). Unlike previous qualitative reviews of SCD, in an article by Edwards et. al. (2005) relevant clinical and research data are described on the relationship between psychosocial functioning and SCD and suggest that to thoroughly understand SCD is to understand the psychosocial influences. The chronicity of the illness combined with frequent hospitalisations for treatment and medical management contributes significantly to impaired psychosocial functioning, altered intrapersonal and interpersonal relationships and reduced QoL (Edwards et. al. 2005).

With the view to highlighting the psychosocial issues than worry them, Ohaeri et. al. (1995) interviewed 170 adult patients with SCD. Ohaeri et. al. (1995) presented the following findings aiming to highlight the issues of social living experience and how much concern over how SCD affects the emotional lives of patients. Thirteen complaints were found in total. All of the patients reported feeling SCD affected their social life in some

way, 50% felt worried about the shape and size of their body, 25% felt inferior for having the illness and some patients reported feeling discriminated against because of this illness. Over 10% of patients denied being worried by any complaints but over 60% of patients reported at least some worry. The above complaints bothered at least a quarter of the sample. The most common complaints were the limitations illness placed upon social life, depressive feelings on thinking about the illness, abnormal habits, irritability, suicidal ideation during crises and loss of useful opportunities. Worry over the psychosocial consequences of SCD seems to add consistently to the burden of illness; occasionally, a substantial number felt that illness had ruined their lives (24%), 18% had difficulty making friends and had feelings of loneliness (Ohaeri et. al. 1995). Sickle cell disease (SCD) sufferers also perceive themselves inadequate in social relationships (Ohaeri et. al. 1995). Anie et. al. (2007) suggest that generally the psychosocial issues for people with SCD mainly result from the impact of pain and symptoms on their daily lives in relation to their physical coping mechanisms. Barrett, Wisotzek, Abel, Rouleau, Platt, Pollard et. al. (1988) assessed the psychosocial functioning of adults patients with SCD. The results indicated that these patients had significant psychosocial distress in the areas of employment and finances, sleeping and eating and performance of normal daily activities. Fear and anxiety regarding body deterioration and lack of assertiveness in social relationships was also found. Barrett et. al. (1988) suggest that depression may be a common problem among SCD patients.

In common with other genetic illnesses like thalassaemia and SCD, CF is traditionally conceptualised as an often fatal childhood illness (Lowton and Gabe, 2003). Cystic fibrosis (CF) is an inherited disorder of the lungs and digestive system and is the UK's most common, life threatening illness among Caucasian people; it occurs approximately in 1 in every 2500 live births (Kettler, Sawyer, Winefield and Greville, 2002). Cystic fibrosis (CF) is the most common autosomal recessive genetic illness in the UK today with an estimated annual incidence of 1:2415 (Dodge, Morison, Lewis, Coles, Geddes, Russell, G., et. al. 1997). The major symptoms of CF arise from abnormal sticky secretions in the respiratory and digestive tracts produced by the CF gene identified by scientists in 1989 (Rommens, Iannuzzi, Kerem et. al. 1989). The most common symptom of CF is recurring chest infections resulting in lung damage; the majority of deaths occurring through respiratory failure (Madden, 2000). Other associated problems include diabetes (Dodge and Morrison, 1992). Akin to thalassaemia, increasing numbers of CF patients are

surviving into adulthood, consequently authors Pfeffer, Pfeffer and Hodson (2003) found it important to review the psychosocial and psychiatric literature surrounding adolescents and adults with CF from 1990 onwards. From this review, Pfeffer et. al. (2003) concluded that whilst there is evidence to suggest that the psychological and psychosocial functioning of people with CF is similar to that of well people, until the illness becomes severe, there are aspects in which they have significant distress and disability, patients do suffer an increased likelihood of psychiatric problems such as depression and score poorly on physical functioning measures of QoL, patients have problems with sexuality, platonic relationships and independence and adherence to treatment. Pfeffer et. al. (2003) suggest that now that treatment and prognosis of CF, and indeed other chronic illnesses is changing, aged studies are becoming increasingly inapplicable and as a result more research is needed in this field in general.

Now that well over half of patients with CF will live into adult life, due to the improvement and management of the illness e.g. improved antibiotic therapies, pancreatic enzyme (protein) preparations (White, Stiller and Haensel, 2007), far more information is needed on the psychosocial status and needs of this patient group (Strauss and Wellisch, 1981). One of the first preliminary studies of adults with CF was that of Boyle, diSant'Agnese and Sack (1976), who noted that in young adults there were four main issues of concern: physical appearance, interpersonal relationships, social isolation and the future. Boyle et. al (1976) and Coffman, Levine, Althof and Stern (1984) also noted higher levels of sexual dissatisfaction. At odds with these findings are those from a study by Shepherd, Hovell, Harwood, Granger, Hofstetter, Molgaard and Kaplan (1990), who in a comparative study of the psychological assets of adults with CF (n=36) and their healthy peers (n=47) revealed that adults with CF function are on par with their healthy peers with regard to sexual satisfaction and satisfaction with work and social life. Shepherd et. al. (1990) suggested that previous conclusions about the psychosocial health of adults with CF have been unwarranted. Perhaps future psychosocial studies involving patients with CF could include control groups without inferences about the effect of patients' physical illness and their psychosocial health, unless they are related to admissions in medical records (Shepherd et. al. 1990). Strauss and Wellisch (1981) explored the psychosocial adaptation in older CF patients. Patients reported a high commitment to work, low self-esteem and a poor social life; 71% of the male patients and 66% of the female patients dated less than once a month. Strauss and Wellisch (1981) also found that 43% were

depressed occasionally or frequently, 29% felt frustrated by their illness, 86% indicated that they were able to express angry feelings only rarely or sometimes. By contrast, authors Moise, Drotar, Doershuk and Stern (1987) found that adults with CF have essentially normal self concepts and adequate psychosocial adjustment and that autonomy is an important issue (Hodson and Geddes, 1995). With regard to autonomy, Shepherd et. al. (1990) found that whilst a subset of adults (43%) in their study enjoyed as much autonomy as their healthy peers, 30% remained highly dependent living at home and depending upon others for financial support. One can conclude from these studies that although many adults with CF lead contented and satisfying lives, a substantial proportion are dependent, socially isolated, concerned about their appearance and have low self-esteem (Hodson and Geddes, 1995). Analogous to the findings of Bush et. al. (1998), CF patients aspire to good health and satisfying interpersonal relationships.

The concept of body image has received increasing research attention resulting, in part, from a growing awareness of its clinical relevance upon the psychosocial impact of chronic illness (Georganda, 1990). Body image has not only been recognized to be related to psychopathology but also plays an important role in chronic physical illness (Wenninger, Weiss, Wahn and Staab, 2003). As is true for many severe, chronic, somatic illnesses, CF is characterized by a number of symptoms and conditions which predispose patients to a 'conflict' experience of their own body (Wenninger, et. al. 2003). Developing a positive self-image and body image in the presence of physical problems due to CF or another illness is one of the challenges patients face as they grow into adulthood (Georganda, 1990) however only very little research has been conducted studying body image issues in CF patients (Wenninger et. al. 2003). One study focused on the aspect of perception and satisfaction with body shape/body parts in relation to patients' eating behaviour. Problematic dieting behaviour, namely restricting calorie intake, in young female adults with CF was found to be associated with a greater perceived body silhouette, less body satisfaction and less self-esteem (Abbott, Conway, Etherington, Fitzjohn, Gee, Morton et. al. 2000). In general, little difference was found between the body image of CF patients and healthy control participants (Abbott et al. 2000). It has already been discussed that due to delayed growth and sexual maturation, chronic illnesses like thalassaemia, can and may have an impact upon self-image, physical appearance thus sexual relationships and sexual satisfaction (Politis et. al. 1990; Georganda, 1990). Chavis and Norman (1993) suggested that chronic illness can impact negatively on sexuality and sexual satisfaction. Self-reports

described significant differences in sexual functioning and sexual satisfaction between those in the SCD group (n=44) who were well adjusted to their illness and those who were poorly adjusted; in addition, no significant difference was found between sexual functioning scores in the well adjusted group and the control group (n=42).

A study of health locus of control, anxiety and self-esteem of adolescent patients with diabetes and CF found no significant differences in comparison to their healthy peers (Kellerman, Zeltzer, Ellenberg, Dash and Rigler, 1980). The findings from this study are relevant to the thalassaemia population, in that patients with diabetes and CF have the opportunity, in contrast to other chronic illness groups, to exert some control over their illness through specific health behaviours (Bush et. al. 1998).

Although a substantial proportion of some patient groups are dependent, socially isolated, concerned about their appearance and have low self-esteem (Hodson and Geddes, 1995), the results of investigations on adolescents and adults with chronic illnesses like SCD suggest that these patients are not at greater risk than their healthy peers of developing psychopathologies and that they cope reasonably well with life tasks and have adequate personality adjustment (Cappelli et. al. 1989). Thus, some authors propose that illness and disability may have positive effects on some aspects of adjustment and personality development (Bush et. al. 1998).

2.3 Stigmatisation, Genetic Screening and Social Integration

To the author's knowledge, little research has been published examining the stigmatisation, genetic screening and social integration of thalassaemia patients. Nevertheless this next section shall relay the modest efforts of researchers surrounding research with thalassaemia patients as well as those patients with other hereditary illnesses.

Stigma can be characterised as disrespectful and as a barrier where negative labels are used to identify persons living with illness (Georganda, 1990). Stigmatising is a process in which social meaning is attached to either behaviour and/or to individuals (Joachim and Acorn, 2000). According to Corrigan (2004) three social cognitive structures comprise pubic stigma: stereotyping (negative belief about a group), prejudice (agreement with belief and/or negative emotional reaction), and discrimination (behaviour response to prejudice). Goffman (1963) early on described three types of stigma that may affect adults

with SCD: physical deformities, character blemishes such as addiction or mental illness, and tribal stigma, which is related to race or religion. Goffman (1963) also listed the consequences of stigma: self-deprivation, self-hate, suspiciousness, depression, hostility, anxiety, bewilderment and defensiveness. The stigma of having a chronic illness may affect an individual's self-concept, capacity to adapt to the chronic illness and the quality and quantity of social networks (Millen and Walker, 2001). It is important that healthcare providers understand how patients cope with stigmatising conditions such as SCD in order to deliver comprehensive individualised care (Cummins and Anie, 2003). Jenerette, Funk and Murdaugh (2006) disclose that stigma, associated with chronic illness, and the resulting discrimination discourages individuals from getting the help the psychosocial support they need from services. Individuals with a chronic illness such as SCD are at risk for depression. Moreover, they are at risk for untreated depression and the depression may go untreated because of the stigma and high rates of disability associated with SCD (Jenerette et. al. 2006). The purpose of a cross-sectional study by Jenerette et. al. (2006) was to describe depressive symptoms on a sample of 232 adults with SCD; 62% of the sample was female. Over 25% of patients reported being depressed as a complication of SCD. Additionally, 32% reported depressive symptoms. Snowden (2001) commented that sufferers of SCD tend to deny the threat of mental illness and thrive to overcome mental health problems through self-reliance and determination. Whilst the study by Jenerette et. al. (2006) is informative, it should be noted that the sample is biased towards female patients and it was not known whether any of the patients had a history of depression. Nevertheless, Jenerette et. al. (2006) recommended that all adults with chronic illnesses should be screened for depression in primary care sites where the diagnosis and treatment ought to be co-ordinated.

Concern over stigma as a consequence of genetic testing has grown in response to the recent increase in genetic research and testing resulting from the Human Genome Project however whether a genetic or hereditary basis necessarily confers a stigma to a condition remains unexamined (Sankar, Cho, Wolpe and Schairer, 2006). Sankar et. al. (2006) explored the relationship between genetic cause and felt stigma. They performed a qualitative interview study with 86 people with one of four conditions; two of those conditions included SCD and CF. The patients were divided approximately between those who ascribed their conditions to a genetic or hereditary cause and those who did not. Respondents interpreted genetic or hereditary cause and non-genetic causes in a variety of

ways. Respondents with SCD and CF offered similar and positive interpretations of the genetic cause of their condition insofar as it meant their conditions were not contagious by touch. Although some patients reported feeling stigmatised as a result of their condition, this stigmatisation was not associated with the condition's cause, genetic or otherwise (Sankar et. al. 2006). Instead, stigma emerged from a variety of sources in the context of the lived experience of the condition itself e.g. social relationships, opportunities at work (Sankar et. al. 2006). Psychological responses to screening have been shown to be minimal or with limited long-term sequelae (Honnor, Zubrick, Walpole, Bower and Goldblatt, 2000). Carrier anxiety levels have been shown to increase after receiving a positive result (Clausen, Brandt, Schwarz and Skovby, 1996) but diminished to normal levels with time or when their partner tested negative (Honnor et. al. 2000). Marteau, Dundas and Axworthy (1997) reported that although high levels of anxiety were not present 3 years after screening, emotional and cognitive consequences could occur and need to be considered. Gordon, Walpole, Zubrick and Bower (2003) assessed the knowledge and emotional consequences of CF population testing 18 months after screening was offered. Over 350 people (59.5%) responded to questionnaires sent by post in a study by Gordon et. al. (2003). In this study, all respondents were shown to have sound knowledge of CF disease although carriers were more likely to correctly state the pattern of CF inheritance and CF carrier rate. In addition, 11 of 47 carriers falsely believed they were only very likely to be carriers, whilst nearly a third of test-negative individuals falsely believed they were definitely not carriers. Gordon et. al. (2003) hypothesised that imprecise recall of the meaning of results may be due to memory loss over time, simplification of the result and meaning and minimisation of risk. The emotional consequences of CF carrier testing were assessed after 18 months. Both carrier and test-negative individuals thought most carriers would experience more negative feelings than most non-carriers. Carriers experienced less positive feelings about their test results compared to non-carriers. Interestingly, the carriers' own feelings about their result were more positive compared to how they thought most carriers would feel. The results in the Gordon et. al. (2003) study suggested that carriers experienced minimal adverse psychological effects although a negative social stigma may be attached to carrying the CF gene mutation. In common with other conditions like SCD, Gordon et. al. (2003) showed that although retention of genetic information in CF was reasonable for a high proportion of participants there was some ambiguity in recall. Counselling did not greatly influence

carriers' knowledge at 18 month follow up nor their feelings associated with carrying the CF gene (Gordon et. al. 2003).

Realistic hardships present themselves to individuals that have a chronic physical illness as well as how individuals treat and view them (Georganda, 1990). Georganda (1990), a thalassaemia patient, states that for many years the presence of thalassaemia was identified with and often still is considered as a 'stigma', a source of inferiority. As a blood disease prevalent worldwide, thalassaemia is of utmost importance as more and more communities have been recognized to have abnormal globin synthesis genes in their populations (GIG, 2007). In countries like Greece, the policy in the field of public health is to educate the public for prevention by prenatal diagnosis and screening and promotion of blood donation to save the lives of people with thalassaemia therefore public awareness is good (Politis, 1998). A nationwide survey conducted by the Hellenic Red Cross Thalassaemia Unit in 1989 found that 93% of citizens aged 15-65 years had heard of thalassaemia, 90% knew that is called for blood transfusions, 89% knew that is was not infectious, 80% knew that is was hereditary and 69% knew that it was incurable (Politis, Richardson and Yfantopoulos, 1991). Politis et. al. (1991) does not mention how many patients were involved in their survey. In Greece, people with thalassaemia are recognised as a group with 'special needs' and benefits are provided for them; these include early retirement and free medical care, as well as measures aimed at improving social integration; these include entry to higher education establishments without examinations and work incentives, (large industries are obliged to employ disabled people upto 4% of their labour force) (Politis et. al. 1991). The strong patients' association ensures that its members are well informed about these benefits and it has been shown that 98% of adult patients exploit benefits in some way (Politis, 1998).

Patient care for genetic diseases are provided in the context of medical research, support organisations and affect the community at large therefore it is essential that the needs of the affected community be reflected in the services and research provided (Heer, Choy and Vichinsky, 1998). Targeting at-risk ethnic groups is very common in genetic diseases for example Tay Sachs, a serious inherited metabolic disorders that causes premature death (BMA, 2002), and CF (Heer et. al. 1998). Organisations such as The Cooley's Anaemia Foundation (CAF) is a voluntary organisation which funds medical research, patient services, public information and professional education for Cooley's Anaemia. The

organisation is named after Cooley and Lee (1925) who were the first to describe thalassaemia in Italian children. This support organisation was created by families of individuals with Cooley's Anaemia and focused on mobilising the Mediterranean community around this issue. Families join to support each other and mobilise the ethnic community most at risk. The Thalassaemia Action Group was founded in 1985 by young adult and adult patients to support each other in issues such as adherence with chelation. TIF is a worldwide organisation stated in 1985 to create a worldwide network for hospitals, doctors, drug companies and offers publications. All three support organisations have had to recognise other populations at risk of thalassaemia. In the UK a national charity is named the UKTS.

Although Politis (1998) described the current developments in thalassaemia concerning social integration e.g. gene therapy and genetic screening, little research has materialised since. Chadwick, Ten Have, Husted, Levitt, McGleenan, Shickle et. al. (1998) analysed and compared the genetic screening programs across Europe and showed that they vary widely. They found that the only population screening programs for adults are those for thalassaemia carrier status in Cyprus, Greece and Italy. In addition, they found that social responses to genetic screening range from acceptance to hostility and that there is a fundamental tension between individual and community in the debates in various European countries about implementation of screening programs. Legislation to address discrimination may provide more safeguards than legislation protecting genetic information (Chadwick et. al. 1998).

It is widely recognised that social relationships and affiliation can have powerful effects on physical and mental health (Berkman, Glass, Brissette and Seeman, 2000). It was Durkheim (1928) who contributed to the study of the relationship between society and health as well as the understanding of how social integration and cohesion influence mortality (Berkman et. al. 2000). Social networks, ties that cut across traditional kinship, residential and class groups like access to jobs and or marital jobs (Barnes, 1954; Bott, 1957), or social relationships that surround an individual and the characteristics of those ties (Fischer, Jackson, Steuve, Gerson, Jones and Baldassare, 1977), shape the health of individuals (Berkman et. al. 2000). Social networks influence health promoting or health damaging behaviour and cognitive and emotional states such as self-esteem, depression and affect (Berkman et. al. 2000). A comprehensive study performed in Athens, Greece

investigated the level of social integration these chronically ill people with thalassaemia had achieved (Politis, 1998). The study reported a good level of social integration; the distribution of employment status was found to be the same as in the general population of the same adult age range, 34% had graduated from university or were currently studying than in the general population (22%). It is not mentioned how many people with thalassaemia participated in this research. However, in another study by Trikkas, Politis, Voulgari and Christodoulou (1988), psychometric tests revealed higher hostility in people with thalassaemia than in a control sample. Trikkas et. al. (1988) suggest that this indicates that although social integration of people with thalassaemia is very good in Greece, hostility is an important component of their psychological profile.

In developed countries, the combination of appropriate medical care and the psychosocial support provided to the patient leads to greatly enhanced survival and a good level of social integration, social acceptance and favourable self-esteem (Politis et. al. 1990). Even so Politis (1998) has stated that the psychosocial problems created in patients by the demands of the burdensome treatment may lead to poor adherence and/or death. Various researchers have identified and have studied the issues and characteristics of the psychosocial burden of thalassaemia, focusing upon social acceptance and social isolation, self-esteem, family adjustment, education, problems in the working environment and relationships between adults (Ratip et. al. 1995). Despite all this work, psychosocial support should continue to be an important aspect of investigation in thalassaemia as patients reach adulthood, work, marry and start families (Politis, 1998). Politis et. al. (1990) reported upon the social integration of thalassaemia patients and suggest that thalassaemia is liable to lead to psychosocial problems due to the hereditary nature of the illness, the likelihood of physical deformity e.g. facial appearance, the demands of regular blood transfusions, and painful and time consuming ICT. The difficulties can only increase if the older thalassaemia patients are unable to adopt the normal roles of adults in society like the ability to find adequate employment by the need for frequent time off for transfusions and other treatment, a factor that may already have had an impact on the level of education achieved (Politis et. al. 1990). The probability of marriage and parenthood may in the past have been reduced by the illness's association with retarded sexual development (Politis et. al. 1990). Historically, Massaglia and Carpigano (1985) and Woo, Giardina and Hilgarther (1984) have stated that there are *"formidable"* obstacles to the integration of the patient with thalassaemia into normal life and under these circumstances

it is important to gain an understanding of the patients' position in society to identify relevant psychosocial factors and to establish what can be achieved by the provision of appropriate support facilities. Politis et. al. (1990) offered a comparative description of two preliminary studies of the social integration of adolescent and adult patients with thalassaemia in two 'developed' countries in Southern Europe. Over 280 patients took part in the investigations and were aged 14 years – 34 years. Each patient was interviewed using a questionnaire; topics related to social integration, education, occupation, self-image, attitudes towards physical appearance. One in 5 patients received no more than elementary education, 2 of the adult patients in one sample were married, few patients advanced to higher education and patients with jobs was substantially lower than that that in the general population. Over 30% of one sample was studying or had completed university education. The self-image of patients seemed to be good however unemployed patients indicated a poorer self-image. The results show that it is possible to achieve social integration and indeed normal psychosocial development for transfusion dependent thalassaemia patients if there is psychosocial provision in health centres. Politis et. al. (1990) consider that this kind of management is generally appropriate for chronically ill people in general.

This chapter has focused on the psychosocial aspects of BTM. Chapter 3 considers the concept of QoL, its measurement, its role as a variable for healthcare intervention and research and in BTM.

Chapter 3

Quality of Life (QoL): Conceptualisation, Measurement and Relationship to Beta (β) Thalassaemia Major (BTM)

"Medicine cannot by itself determine the quality of life (QoL). It can only help people to achieve the state of health that enables them to cultivate the art of life but in their own way. It implies also the ability for each person to do what he wants to do and become what he wants to become, according to human values that transcend medical judgement".

R. Dubos (1976) p9

Chapter Overview

This chapter considers the conceptualisation and measurement of QoL, as an outcome variable for healthcare intervention and research. In addition, it examines the role of QoL in the chronic illness BTM.

3.1 Setting the Scene

3.1.1 The Importance, Benefit and Necessity of Studying Quality of Life (QoL) as a Health Outcome

In recent years there has been increasing interest in the QoL of patients (Rettig and Sadler, 1997). Not only is QoL becoming an increasingly important outcome measure in medicine and healthcare (Hickey, Bury, O'Boyle, Bradley, O'Kelly and Shannon, 1996), it has also been shown to be a predictor of survival and hospital utilisation (Parkerson, Broadhead and Tse, 1991). Research on patient-report QoL scales has indicated the following predictors in survival; higher general well-being (Devins, Mann, Mandin, Paul, Hons, Burgess et. al. 1990), lower depression ratings (Kimmel, Weihns and Peterson, 1993), and higher physical function (DeOreo, 1997). Therefore, QoL reflects the perspectives of patients and providers, not only general information about their health and functioning but also specific data on their physical, emotional and social well-being (Rettig and Sadler, 1997) hence it has attracted policy interest (Brown, Bowling and Flynn, 2004). Indeed, the importance of research around QoL is amenable to manipulation by health, social, economic and environmental policy (Bowling and Windsor, 2001). As an outcome variable for healthcare intervention and research, QoL is critical for a number of purposes including

evaluating the UK's progress in achieving population health goals, assessing health disparities across different segments of the population and measuring the effectiveness of healthcare interventions in general (Jenkins, 1992). It can be important to treatment decision-making to maximise the likelihood of longterm survival with the highest QoL possible (Devins et. al. 1990). Quality of Life (QoL) information can also enable health policymakers to compare the impact of different chronic diseases on healthcare costs and to assess the cost-effectiveness of different interventions, given QoL information (Jenkins, 1992). A discussion of QoL as a concept and outcome measure concluded that the ability to demonstrate successful patient outcomes is critical to healthcare decision making for ethical, practical and financial reasons and documenting positive outcomes of interventions is a primary concern of health care researchers and clinicians (Anderson and Burckhardt, 1999).

There is also a growing awareness amongst HCPs that QoL is an important health outcome in assessing the functioning of the chronically ill (Bowling, 1995). Healthcare professionals (HCPs) often have different perceptions of the relative importance of clinical outcomes and rarely agree on health states (Knowles, Griebsch, Bull, Brown, Wren, and Dezateux, 2007). Healthcare professionals (HCPs) may rate side effects of treatment acceptable when patients report much less tolerance for these side effects (Robinson, Anders, Cardozo and Bidmead, 2007). Assessing QoL in patients may help provide better overall care and increase shared decision making and by understanding the burden of disease, patients are potentially useful in helping to guide the treatment, care and management of patients with chronic illness when experimental therapies are being considered (Panepinto, 2008). Quality of life (QoL) is one of the most important outcomes for people with chronic illness therefore it is imperative to assess the degree of illness intrusion (Jenkins, 1992). Documentation of exactly how illness affects vocational, social and personal activities, as well as the general activities of daily living, provides a basis for interventions designed to improve QoL (Devins et. al. 1990). Fitzpatrick, Davey, Buxton and Jones (2001) identified that clinical trials and similar forms of evaluative study should incorporate the patient's perspective of outcome and stated that it is essential to provide evidence of this type of impact on the patient in terms of their health status. The accelerating rate over the last twenty years of bringing new pharmaceutical and other treatments to wider acceptance in illness like CF and multiple sclerosis (MS) has called for much more QoL research to document in a more scientific way, the relative advantages of

these new interventions (Jenkins, 1992). According to Garratt, Schmidt, MacKintosh and Fitzpatrick (2002), unlike conventional medical indicators, broader evidence of the impact of illness and treatment needs should be assessed and reported by the patient wherever possible. Research around QoL has flourished as a result of advances in medical technology and treatment, the growing prevalence of chronic illness in adult and paediatric populations and the need to reduce healthcare costs (Quittner, Buu, Messer, Modi and Watrous, 2005).

The measurement of QoL can help pinpoint which particular problems are likely to emerge for patients with specific illnesses. Such measurement would be helpful in informing and anticipating the kind of interventions that might be required (Schag and Heinrich, 1986). Quality of life (QoL) information can also be used to compare these therapies (Jenkins, 1992). Hunt, McEwen and Mckenna (1985) have stated that measuring health status is a valid and useful way to evaluate the outcome of medical and/or social interventions, and as an adjunct to clinical interviews. Jenkins (1992) identified that earlier in the development of medical treatment technology, targeted interventions usually replaced general supportive non-specific treatments and new interventions were so dramatically better than previous approaches that they became quickly accepted without measurement and with very little debate. No longer are active treatments compared against what amounts to no treatment as new treatments and therapies are compared against currently accepted ones which Jenkins (1992) remarks are generally good. The differences between new and currently practised therapies are not as dramatic as they were years ago (Eiser, 2000) therefore more systematic and quantitative ways to evaluate the outcomes of health interventions are needed (Bowling, Gabriel, Dykes, Marriott-Dowding, Fleissng, Evans et. al. 2003). Many medical and surgical procedures both new and old intuitively seem to be beneficial and each new intervention develops its alliance of persuasive medical advocates (Eiser, 2000). Physicians' enthusiasm about treatment methods determines directly the degree of placebo response in the patients who received that treatment in illness such as MS (Skrabanek and McCormick, 1990). Jenkins (1992) identified that the continuing escalation in medical care costs in many countries demands that new medical and surgical therapies are evaluated, not just in terms of their benefits, but in terms of the comparisons of their cost-benefit ratio with that of the previously standard therapy for the same condition. Furthermore, Jenkins (1992) suggested that appropriate cost-benefit analyses should take into account all the dimensions of QoL, which are discussed in section 3.3, when

computing the benefits side of the cost-to-benefit ratio. In an editorial, Fitzpatrick et. al. (2001) stated that the next generation of medical and surgical interventions may not be better than current therapies in terms of markers like mortality rates or severity of disabilities thus outcome research will need to be sensitive to smaller degrees of improvement and to such dimensions of improvement such as daily activities, morale, social role functions and economic contributions as well as overall clinical changes.

3.2 Definitions and Models of Quality of Life (QoL)

Conceptual clarity of QoL is extremely important since differences in meaning can lead to significant differences in outcome for clinical research and clinical practice. Sections 3.2.1 through to 3.3.7 review these issues.

3.2.1 Why is it Difficult for Researchers to Agree on a Definition of Quality of Life (QoL)?

The reason most often given is that researchers in various disciplines come from different perspectives (Spilker, 1996) and thus on different concerns (Farquhar, 1995). Philosophers are concerned with the nature of human existence and defining the 'good life' (Faden and LePlege, 1992), ethicists debate the shift in healthcare decision making from the concept of 'santality of life' to QoL and social utility (Edlund and Tancrei, 1985), economists are concerned with the allocation of resources to achieve alternate goals (Grabowski and Hansen, 1990), physicians focus on health and illness related variables (Pearlman and Uhlmann, 1988), nurses take the broadest view in defining QoL (Farquhar, 1995), yet due to their frequent preoccupation with the physiological, tend to contaminate their operationalisation of the concept within disease specific items (Anderson and Burckhardt, 1999). Consequently, the achievement of some consensus on a definition of QoL requires, among and within the healthcare field, an appreciation of the extensive body of research available in addition to distinguishing QoL from other related concepts such as well-being, with which it is often confused (Anderson and Burckhardt, 1999).

3.2.2 Defining Quality of Life (QoL)

An examination of the large body of quantitative research shows that there is no single, universally accepted definition of QoL (Lauer, 1999); phenomenological perspectives hold that QoL is a vague concept that is dependent upon the specific interpretations and perceptions of the individual (Ziller, 1974). It could be argued that QoL is defined by what

the individual determines it to be (O'Boyle, 1997). No consensus exists in the healthcare disciplines about what QoL is or how it should be measured (Anderson and Burckhardt, 1999). As the precise meaning of QoL is difficult to define it is open to interpretation (Pfennings, Van der Ploeg, Cohen, Bramsen, Polman and Lankhorst, 1999). A review of the literature has shown that QoL has been defined in terms of 'life satisfaction'.

"The satisfaction of an individual's values, goals and needs through the actualisation of their abilities or lifestyle"
(Emerson, 1985, p58)

"Quality of life is a feeling of overall life satisfaction, as determined by the mentally alert individual whose life is being evaluated. Other people, preferably those from outside that person's living situation, must also agree that the individual's living conditions are not life-threatening and are adequate in meeting that individual's basic needs"
(Meeberg, 1993, p37)

"Satisfaction with the aspects of life that is important to the individual"
Ferrans (1996, p293)

"A conscious cognitive judgement of satisfaction with one's life"
(Rejeski and Mihalko, 2001, p23)

The review of the literature has also recognised the multidimensionality of QoL and the tendency for definitions to focus on its multi-dimensions/domains, comprising objective descriptors as well as subjective evaluations. Haas (1999) also recognised the multidimensionality of QoL and defined it as different from well-being, life satisfaction and functional ability (see Table 1). Sections 3.2.2.1 through to 3.2.2.2.1 discuss this category of QoL definition as well as HRQoL definitions with examples from research.

3.2.2.1 Multidimensional/Domain Definitions including Objective Descriptors and Subjective Evaluations

3.2.2.1.1 The Content of Multidimensional/Domain Definitions including Objective Descriptors and Subjective Evaluations

Beckie and Hayduk (1997) argued that such definitions confound the dimensionality of the concept with the multiplicity of the causal sources of that concept. They argued that QoL could be considered as a global personal assessment of a single dimension which may be causally responsive to a variety of other distinct dimensions i.e. it is a unidimensional concept with multiple causes. Thus, it is logical for a unidimensional indicator of QoL i.e. a self-rating global QoL unidimensional scale, to be the dependent variable in analyses and the predictor variables to be the range of health, social and psychological variables (Beckie and Hayduk, 1997). A global QoL assessment is the consequence of an individual's comprehensive evaluation which includes a wide range of physical, psychological, social, and economic, community and societal considerations. In addition, these factors may interact, adding to the complexity of the evaluation (Beckie and Hayduk, 1997). Felce and Perry (1995) propose that QoL is multidimensional and comprises objective descriptors as well as subjective evaluations, with regard to the extent of personal development, purposeful activity and personal values; changes in some objective facet of life may change satisfaction or one's personal values, or both. Similarly, changes in values may change satisfaction and precipitate change in some objective circumstance in the same way, a change in a sense of satisfaction may lead to reappraisal of values and lifestyle Felce and Perry (1995). As well as affecting each other, these elements are capable of changing independently as a result of external influences such as employment, peer influences and other social, economic and political variables (Felce and Perry, 1995). Objective data should not be interpreted without reference to personal autonomy, preferences and concerns and that expressions of 'life satisfaction' or indeed 'life dissatisfaction' are shaped by circumstance and experiences (Felce and Perry, 1995). Personal concerns that are derived from what a population considers 'normal' should not be applied without reference to individual differences and objective comparisons should be made between the situations of particular groups in society to what is normative (Brown et. al. 2004).

3.2.2.1.2 Multidimensional/Domain Definitions

Table 1 shows examples of multidimensional/domain definitions of QoL found in the literature from the last two decades. This section gives examples of their implementation within research.

3.2.2.1.2.1 Multidimensional/Domain Definitions Research

To investigate the relationship between judgements about different dimensions of QoL (core scores), and the importance attributed to them (importance scores), WHOQoL survey data were obtained from over 4800 ill and well participants in 15 countries (Skevington, O'Connell and the WHOQoL Group, 2004). As a theoretical framework, the WHOQOL Group (1995) definition of QoL (see Table 1), which indicates that those who report the very poorest QoL will be least likely to have met their own '…goals, expectations, standards and concerns'. Those with the poorest QoL would therefore be expected to show the biggest difference between core and importance scores thus being distinguishable from respondents whose QoL was poor, better or best (Skevington et. al. 2004). Quality of life (QoL) was assessed by the WHOQoL-100, an instrument that assesses generic QoL - this measure is discussed in sections 3.4.2.1.1.4 and 3.4.2.1.1.4.1. Those reporting the largest negative differences tended to report the poorest QOL and also attached a high degree of importance to these dimensions (Skevington et. al. 2004). Evidence for a decreasing differential across the four groups, (poorest to best), was confirmed for the majority, (18 of 24), of facets across the six QoL domains. However, only five facets i.e. energy, sleep, positive feelings, activities and personal relationships**,** distinguished those with the poorest QoL from those whose QoL was poor therefore the theory is not well supported (Skevington et. al. 2004). Furthermore, the contribution of core-importance facet differences reduced the overall prediction of QoL when compared with core scores alone i.e. low core scores may not predict poor QoL therefore the importance information and/or scores about specific facets may have limited potential to be used alongside the main instrument to identify areas of the poorest QoL for clinical or social action. The contribution of the QoL domains physical, social and psychological functioning to the explanation of overall QoL was compared by Arnold, Ranchor, Sanderman, Kempen, Ormel, Suurmeijer (2004).

Various disorders have shown to differentially affect QoL domains due to disease-specific factors, consequently the relationship between QoL domains and overall QoL may vary

Table 1: Examples of Multidimensional/Domain Definitions

Definition	Reference
"A multi-faceted construct that encompasses the individual's behavioural and cognitive capacities, emotional well-being, and abilities requiring the performance of domestic, vocational, and social roles".	Tartar, Erb, Biller, Switala and Van Thiel (1988, p33)
"Quality of life (QoL) is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns; it is a broad-ranging concept incorporating in a complex way, the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment; this definition reflects the view that QoL refers to a subjective evaluation which is embedded in a cultural, social, and environmental context. As such, QoL cannot be simply equated with the terms 'health status', 'life-style', 'life satisfaction', 'mental state', or 'well-being'. Rather, it is a multidimensional concept incorporating the individual's perception of these and other aspects of life".	(WHOQOL Group) (1995, p1404)
"'Quality of life (QoL) and more specifically, 'health-related quality of life' refer to the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions (which we refer to here collectively as 'perceptions of health'. Each of these domains can be measured in two dimensions: objective assessments of functioning or health status, and more subjective perceptions of health."	Testa and Simonson (1996, p385)
"Quality of life (QoL) is both objective and subjective, each axis being the aggregate of seven domains: material well-being, health, productivity, intimacy, safety, community and emotional well-being. Objective domains comprise culturally relevant measures of objective well-being. Subjective domains comprise domain satisfaction weighted by their importance to the individual".	Cummins (1997, p58)
"Quality of life (QoL) is a multidimensional evaluation of an	Haas (1999b, p7)

Definition	Reference
individual's current life circumstances in the context of the culture in which they live and the values they hold. Quality of life (QoL) is primarily a subjective sense of well-being encompassing physical, psychological, social and spiritual dimensions. In some circumstances, objective indicators may supplement or, in the case of individuals unable to subjectively perceive, serve as proxy assessment of QoL".	
"Quality of life (QoL) is a concept that reflects a person's desired conditions of living related to eight core dimensions of one's life: emotional well-being, interpersonal relationships, material well-being, personal development, physical well-being, self-determination, social inclusion and rights".	Schalock (2000, p121)
"Quality of life is a term that implies the quality of a person's whole life, not just some component part. It therefore follows that if QoL is to be segmented into its component domains, those domains in aggregate must represent the total construct".	Hagerty, Cummins, Feriss, Land, Michalos, Peterson et. al. (2001, p7)
"Quality of life (QoL) is multidimensional in construct including physical, emotional, mental, social, and behavioural components".	Janse (2004, p654)

between diseases (Sprangers, de Regt, Andries, Van Agt, Bijl, deBoer et. al. 2000). The objective of the study by Sprangers et. al. (2000) was to compare the QoL of a wide range of chronic disease patients (n=15,000). Quality of life (QoL) data were collected. Patients who were older, female, had a low level of education, were not living with a partner and had at least one co-morbid condition, in general, reported the poorest level of QoL. Urogenital conditions, hearing impairments, psychiatric disorders and dermatologic conditions were found to result in relatively favourable functioning. A group of disease clusters assuming an 'intermediate'/in-between position encompassed cardiovascular conditions, cancer, endocrinology conditions, visual impairments and chronic respiratory disease. Gastrointestinal conditions, cerebrovascular,(any disease affecting an artery in and supplying blood to the brain (BMA, 2002)), neurological conditions, renal disease, (illness related to the kidneys (BMA, 2002)), and musculoskeletal conditions, led to the most adverse sequelae. The results showed that the domain psychological functioning

contributed to overall QoL for all disorders and for the healthy group. For the healthy group, all the domains contributed to overall QoL although this could have been due to sample size (Arnold et. al. 2004). Differences were found between most patient groups and the healthy group with respect to physical functioning; patient groups reported poorer functioning. With regard to social functioning, over 60% of the patient reported impairment. This study showed that separate QoL domains make a limited contribution to the explanation of overall QoL however impairments in one or more of the domains of QoL does not automatically result in an impairment of overall QoL (Arnold et. al. 2004). Measuring domains of QoL and overall QoL seem to be two different ways to study the impact of an illness on the lives of patients (Arnold et. al. 2004). Whilst the study showed some interesting results the data are cross-sectional therefore there are no insights into longterm effects as domains of QoL and/or overall QoL may fluctuate over time (Arnold et. al. 2004). In addition, the participants were aged 57 plus and this bias may affect the generalisability of results to younger groups of patients. However, these results can be considered in addition to information on the prevalence of the disease for potential benefits of care and current disease specific expenditures (Arnold et. al. 2004). This information will help to better plan and allocate resources for research, training and healthcare (Arnold et. al. 2004). The data provide a realistic representation of the chronic conditions surveyed therefore the results have sound face validity and are in concordance with the literature (Arnold et. al. 2004).

Veenhoven (2000) distinguished between opportunities and chances for a good life and the good life outcomes themselves and postulated four categories of QoL: i) liveability of the environment, (environmental chances/social capital and gains), ii) life-ability of the individual, (personal capacities/psychological capital), iii) external utility of life, (a good life must have an aim other than the life itself - higher values) and iv) inner appreciation of life, (the perceived QoL). Each area of QoL influences the other areas thus QoL is multidimensional and its parts affect each other as well as the sum (Veenhoven, 2000). It is also a dynamic concept, which poses further challenges for measurement and it is made up of both positive and negative experiences and affect, as well as values and self-evaluations of life that may change over time in response to life and health events and experiences (Veenhoven, 2000). When measuring change in QoL, several variables need to be taken into account including actual changes in circumstances e.g. health, stable or dispositional characteristics of the individual such as personality and behaviour, cognitive

or affective processes which might accommodate the changes such as making social comparisons and the reordering of goals and values (Sprangers and Schwartz, 1999). Social desirability bias might also be a personality characteristic and this might facilitate people when they are adjusting to deteriorating health or circumstances, and lead to an optimistic perception of a higher QoL (Diener, Suh, Lucas and Smith, 1999). Whilst coping is not the focus here, the literature on coping mechanisms is pertinent, with the evidence that personality characteristics such as optimism and self-mastery are related to coping mechanisms and subsequent adjustment (Brissette, Scheier and Carver, 2002). Albrecht and Devlieger (1999) focused on the issue of why so many people with serious and persistent disabilities report their QoL to be good or excellent when their lives would be viewed as undesirable by external observers. In-depth interviews with people indicate that consideration of QoL was dependent upon finding a balance between body, mind and the self (spirit) and on establishing and maintaining harmonious relationships, supporting the theory of homeostas, (the balance of biological and psychosocial aspects of self) (Brown et. al. 2004).

3.2.2.1.2.1.1 Objective Description and Subjective Evaluation Definitions

Research surrounding the subjective and objective components and/or indicators of QoL is discussed in sections 3.3.1 through to 3.3.1.2 with regard to models of QoL therefore only a summary of such research is stated in this segment.

The concept of QoL is abstract, affective, subjective in nature and has a cognitive aspect and its multidimensional facets make it difficult to define (Anderson and Burckhardt, 1999). The WHOQoL Group (1993) describe QoL as multi-faceted and focus upon the subjective perspective of QoL. Others have stated that the QoL concept is broader and includes objective indicators of housing, other material circumstances and indeed health (Ruggeri, Warner, Bisoffi and Fontecedro, 2001). Warner (1999) suggests that subjective appraisal of life often bears little or no relation to objective life circumstances. The same objective indicator, like housing or job, may result in opposite evaluations by the same person depending on their perspective at the time of evaluation (Skantze, Wanke and Bless, 1994). Indeed, objective improvements in life circumstances may produce negative subjective responses (Lehman, 1996). Table 2 shows definitions that state subjective and/or objective assessment components of QoL.

Table 2: Examples of Subjective and Objective Assessment Definitions

Definition	Reference
"Community QoL is a function of the actual conditions in the environment as well as a function of how these conditions are perceived and experienced by the individual residing within the community".	Proshanky and Fabian (1986, p283)
"Personal values as well as life conditions and life satisfaction interact to determine quality of life. The significance of either the objective or subjective assessment of a particular life domain is interpretable only in relation to the importance the individual places on it".	Cummins (1992, p58)
"Quality of life (QoL) is defined as an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values".	Felce and Perry (1995, p60)
"Quality of life (QoL) is properly defined by the relation between two subjective or person-based elements and a set of objective circumstances. The subjective elements of a high quality of life comprise (1) a sense of well-being and (2) personal development, learning growth […] The objective element is conceived as quality of conditions representing opportunities for exploitation by the person living a life".	Lane (1996, p197)

3.2.2.2 Health Related Quality of Life (HRQoL) Definitions

It is common to consider measures apart from traditional indicators of biological functioning as a single category of QoL measures (Ware, 1995). Consequently, QoL encompasses factors generally not considered to be part of biological health; as a result terms such as 'health related quality of life' (HRQoL) (Guyatt, Osoba, Albert, Wyrwich and Norman, 2002), health status (Ware, 1995), psychological well-being (Cummins, 2005) and functional status are used interchangeably (Bergner, 1989).

Health related quality of life (HRQoL) is thought to be a multidimensional concept and/or model of QoL that represents the patients' overall perception of the impact of illness and its treatment (Cummins, 2005). In public health and in medicine, the concept of HRQoL

refers to a person or group's perceived physical and mental health over time (Centres for Disease Control and Prevention (CDC) 2007). Physicians have often used HRQoL to measure the effects of chronic illness in their patients to better understand how an illness interferes with a person's day-to-day life (CDC, 2007). Similarly, HCPs use HRQoL to measure the effects of numerous disorders, short-term and long-term disabilities and diseases in different populations (CDC, 2007). The CDC (2007) have also recognised that by tracking HRQoL in different populations they can identify subgroups with poor physical and/or mental health and can help guide policies or interventions to improve their health. The increasing recognition of the patient perspective and more specifically functioning and health has lead to an impressive effort in research to develop concepts and instruments to measure them (Cieza and Stucki, 2005). The measurement of QoL is discussed in sections 3.4 through to 3.4.2.1.2.

The general or global meaning of QoL to a person may be anchored to objective and/or subjective factors e.g. socioeconomic, demographics and life style factors, personality characteristics, aspects of social and community environments and well-being in physical and mental health (Abeles, Gift and Ory, 1994) but the more specific HRQoL is usually defined with regard to health and physical function, emotional well-being, general health perceptions and role and social function (Brown et. al. 2004). Table 3 shows two definitions of HRQoL from the last decade. Elements that contribute to global QoL are not included necessarily in judgments about HRQoL and reference to HRQoL may suggest predominance on disease (Lawton, 1996). Regardless of whether one is referring to global QoL or HRQoL, the subjective or individual perspective is important to the definition (Brown et. al. 2004). The distinction between QoL and HRQoL is not made easily (Haas, 1999) therefore for the purpose of this research the terms shall be used interchangeably. The model of HRQoL is discussed further in sections 3.3.6 through to 3.3.6.2.

3.2.2.2.1 Health Related Quality of Life (HRQoL) Definitions Research

The Gill and Feinstein (1994) definition was adopted by Solovieva, Santavirta, Santavirta and Konttinen (2004) who assessed the QoL in over 300 individuals with hereditary blood coagulation disorders, (disorders where the main mechanism by which blood clots are formed involving a complex series of reactions in the blood fluid (BMA, 2002)), to that of over 400 healthy controls to identify the dimensions of life the patients consider most

Table 3: Health Related Quality of Life (HRQoL) Definitions

Definition	Reference
"A uniquely personal perception, expressing the way individuals feel about their health status and non-medical aspects of their lives".	Gill and Feinstein (1994, p620)
"Quality of Life (QoL) may be referred to as an individual's assessment of how a health problem and its treatment affect his/her ability to perform activities and roles that he/she values".	Pfennings, Van der Ploeg, Cohen, Bramsen, Polman, Lankhorst (1999, p148)

important. Leisure activities/hobbies, availability of work/study, followed by relationships with other people, own health and relationships with family/relatives appeared most frequently across the patients' and that of the control group. The areas affected most by the disease were financial security, own health and relationships with family/relatives. As blood coagulation disorders are diseases with a predominantly physical impact patients reported lower QoL in most domains compared to healthy persons however, when a wider concept of QoL was applied, no differences between the patients and healthy 'controls' was noted (Solovieva et. al. 2004).

Jenkins (1992) does not propose a definition of QoL rather suggests attributes such a definition should have. Jenkins and Stanton (1984) stated QoL should include the three F's: feelings, functions and futures. The authors explained that the subjective sense of well-being should be explained at all levels including relief from physical and emotional pain, self-condemnation, hopelessness and painful interpersonal relationships i.e. feelings. Physical, cognitive, self-care, interpersonal skills and social role fulfilment including productive activity appropriate to age and such permanent disability as they exist should also be also be adopted in the explanation i.e. functions. The prognosis for future continuation of adequate feelings and functions i.e. the 'futures' component - emphasises that there is a time dimension integral to all QoL determination and that duration of life must be balanced against its quality as in the concept of Quality Adjusted Life Year (QALY's) (Loomes and McKenzie, 1989). The QALY concept asks patients to attempt to equate their life expectancy under their current conditions of discomfort and disability with a lesser duration of 'normal healthy life' in terms of equal desirability. A great deal of

enquiry on the subject of QoL has commented on its diversity. Liu (1976) stated that there were as many definitions as people emphasising the proverb that *"individuals differ in what they find important"*. In their review, Baker and Intagliata (1982) remarked that there are as many definitions as there are number of people studying the phenomenon; a comment that throws the spotlight on the lack of agreement between those attempting to operationalise the concept. Operational definitions of QoL are diverse with variability, fuelled not only by use of societal or individualistic perspectives, (to be discussed in sections 3.3.4 through to 3.3.5.2 respectively) but also by the range of applicable theoretical models or academic orientations (Felce and Perry, 1995). Reaching an accord on the definition of QoL and measurable operationalisation of the concept itself appears to be a fundamental goal for researchers in this field.

3.3 Models and Dimensions/Domains of Quality of Life (QoL)

The main models of QoL have been identified, categorised, overviewed and systematically reviewed at length by researchers. A synopsis of these models and dimensions/domains can be found in the sections that follow (3.3.1 through to 3.3.7). These are objective and subjective models that incorporate social indicators research, needs satisfaction and perceptual needs satisfaction models, psychological and personality models, social health, social cohesion and social capital models, idiopathic models and health and functioning models. Each of these models shall be described with an example of research.

3.3.1 Objective and Subjective Models Incorporating Social Indicators Research

3.3.1.1 An Explanation of Objective and Subjective Models

Traditionally, outcomes in medicine and health care have been determined by objective medical evaluations e.g. changes in health parameters, disease status, and costs of care however it has become increasingly clear that the perspective of the patient is also a critical variable (Bowling et. al. 2004). As a result, it is now increasingly common to include evaluations of medical/health-related outcomes from the patient's perspective (Guyatt et. al. 2002). Current approaches to QoL incorporate both objective and subjective dimensions (Brown et. al. 2004). In contrast to objective indicators, subjective indicators are those which involve some 'person' evaluation of circumstances in life satisfaction or life dissatisfaction, psychological well-being, morale, individual fulfilment, happiness, balance of affect, self-worth and self-esteem (Clarke, Marshall, Ryff, Rosenthal, 2000). Subjective or social indicators are based on the model of subjective well-being as defined

by people's hedonistic feelings and/or cognitive satisfactions (Diener and Suh, 1997). Quality of life (QoL) is thought to reflect overall, large-scale societal and sociodemographic influences as well as specific, smaller scale concerns such as individual's experiences, values, perceptions and psychology, and this poses inevitable challenges for measurement (Brown et. al. 2004). While the division of QoL into pre-defined individual components may be helpful for measurement purposes, this may not tap the most pertinent domains of people's perceptions of QoL and this approach does not capture the subjectivity of people (Bowling and Windsor, 2001).

3.3.1.2 An Outline of Objective and Subjective Models Research

Analyses of the public's perceptions of QoL suggests that many domains prioritised by the public as important are not incorporated into the most popularly used measures of QoL, particularly in the health field e.g. people's values, priorities and judgements (Bowling, 1995a). Bowling and Windsor (2001) investigated perceived priorities and explored the objective and subjective components of QoL in a random sample of over 2000 adults. The vehicle for the study was a questionnaire model on perceptions of QoL which was commissioned by the authors for inclusion in the Office of National Statistics (ONS), Omnibus Survey in Great Britain. In general, overall QoL was not explained by objective, sociodemographic indicators such as housing, marital status, age, gender and education levels. Reported longstanding illness contributed nothing to overall QoL. The subjective ratings of individual areas of importance reported by the sample explained QoL in terms of relationships, finances, own health, others health, work and social life. Overall QoL was not fully explained by both objective and subjective variables therefore reflecting the complexity of measuring QoL (Bowling and Windsor, 2001).

Brown et. al. (2004) suggest that people are routinely engaged in evaluating themselves in relation to the life domains they consider to be of relevance and importance to them; subjective indicators formalise these natural tendencies. Ruggeri et. al. (2001) advocate that subjective and objective information are distinct types of information; objective measures being more suitable in detecting treatment effects in patients whereas subjective information is necessary to complete the QoL picture and to enhance the interpretation of data. Researchers such as Abel-Smith (1976) and the WHO (1971) called for the development of sociomedical or subjective indicators with the hope that such indicators would be capable of measuring the health status of whole populations at a particular time

i.e. assessing the efficacy of healthcare practice accurately. According to Singer, Garfinkel and Cohen (1976), patient perception as an indicator has been found to be an excellent predictor of mortality of the QoL in patients with CF. The seven dimensions found were physical functioning, mental health/psychosocial functioning, social integration, role functioning/pain, economic/material living conditions, partner/family relations and anxiety. These results confirmed that a patient's perception of their HRQoL is not merely a function of their objective health status, so, in measuring QoL the patient should refer to their subjective view on their health (Goldbeck and Schmitz, 2001). Brown et. al. (2004) have commented that measuring the QoL in people with chronic illness is useful with regard to being able to construct and integrate the patients view into clinical practice and into the evaluation of new therapy strategies.

3.3.2 The Needs Satisfaction and Perceptual Needs Satisfaction Models

3.3.2.1 An Explanation of Needs Satisfaction and Perceptual Needs Satisfaction Models

Quality of life (QoL) is thought to be influenced as much by objective social and economic circumstances as by the characteristics of the individual; objective data can encompass all circumstances of life and living conditions (Brown et. al. 2004). The objective approach is essentially a needs-based approach which assumes that there are basic needs in society and that by satisfying these needs people's well-being is determined (Delhey, Böhnke, Habich and Zapf, 2002). Objective indicators have included standard of living, health and longevity, housing and neighbourhood characteristics which are typically measured with indicators of cost of living, mortality rates, health service provision, education levels, neighbourhood structure and density, socio-economic structure and indicators of inequality and crime in the neighbourhood or other area unit of study (Muntaner and Lynch, 2002). It has been argued that human needs are the foundations for QoL hence the concept can be defined in terms of human needs and the satisfactory fulfilment of those needs which could be physical, psychological, social, behavioural, marital or otherwise (Hörnquist, 1982).

3.3.2.2 An Outline of Needs Satisfaction and Perceptual Needs Satisfaction Research

Individual perceptual needs indicators, a person's subjective evaluations of their objective indicators including access to information and advice, money, tangible goods and services (Rettig and Leichtentritt, 1999), rather than sole reliance on societal welfare indicators are often used by researchers adhering to a needs model of QoL (Brown et. al. 2004).

Satisfaction of human needs include objective circumstances such as housing, security, food and warmth and opportunities for self-actualisation, reminiscent of Maslow's (1954) theory of human needs i.e. physiological, safety, security, social and belonging, ego, status and self-esteem. These needs may be measured by indicators of the individual's subjective satisfaction with the extent to which these have been met (Bigelow, Brodsky and Stewart and Olson, 1982). This model and measurement approach is common in mental health research (Brown et. al. 2004).

3.3.3 Psychological and Personality Models

3.3.3.1 An Explanation of Needs Satisfaction and Perceptual Needs Satisfaction Models

These models include influencing/causal and mediating/intervening variables and emphasise personal growth, cognitive competence, efficiency and adaptability, dignity, perceived independence, social competence, control, autonomy, self-efficacy (worth and usefulness), as well as optimism-pessimism (Bowling, Gabriel, Dykes, Marriott-Dowding, Fleissig, Evans et. al. 2003). They also include social comparisons of past experience, present circumstances and aspirations for the future i.e. the individual's achievement of their expectations, hopes and aspirations (Krupinski 1980), particularly in relation to social comparisons with others (Garratt and Ruta, 1999). Brown et. al. (2004) report that whilst these models are attractive, there is still little empirical data to support, or refute the distinction between psychological constructs such as mediating or influencing variables in determining QoL. Further research is required to investigate the intervening variables that cause adverse effects and/or circumstances e.g. level of adaptation, negative cognitive factors that build up over time, the way in which people make social comparisons of themselves with others which influences their expectations for themselves, (after they evaluate the gap between what is desired and which is achieved) (Brown et. al. 2004).

3.3.3.2 An Outline of Needs Satisfaction and Perceptual Needs Satisfaction Research

This is a very large area outside the scope of this thesis and so the research to be discussed, around *autonomy* and *control*, is to demonstrate the type of research that has been undertaken.

The concepts of control over life, self-sufficiency, independence and autonomy, (the freedom to determine one's own actions), are regarded as particularly important for and in

the maintenance of QoL (Brown et. al. 2004). Opportunities for self-actualisation (acknowledgement of reality for self), and self-development may be facilitated or inhibited by wider society; level of income and level of personal social and practical support can enable or inhibit autonomy and self-actualisation (Brown et. al. 2004). In addition, important psychological constructs relate to the perceived control one has over one's own life and the perceived control that others have over one's life. The extent to which people perceive that they determine what happens in their lives leads to a greater sense of internal control. The extent to which they perceive others determine their lives reflects their sense of being controlled by others and weaker internal control (Lefcourt, 1982). A strong locus of internal control theoretically leads to greater self-esteem, to greater perceived self-efficacy over life and thus influences intentions, behaviour and ultimately well-being (Bowling, 2002). Abbey and Andrews (1986) investigated the relationships between these variables. They indicated that internal control, own decision making, self-assessed ability to get on with others, (social performance) and social support, all related moderately and positively to perceived QoL.

3.3.4 Social Health, Social Cohesion and Social Capital Models

3.3.4.1 An Explanation of Social Health, Social Cohesion and Social Capital Models

The largest body of empirical research on the various facets of well-being has focused on the structure, functioning and supportiveness of human relationships, the social context in which people live and integration within society i.e. social health (Brown et. al. 2004). Social cohesion and social capital models include societal, environmental and neighbourhood resources including those which facilitate reciprocity and trustworthiness arising from social connections between people fostered by the availability and type of community facilities and resources (Putnam, 2000). It should be noted that this model encompasses both objective indicators and subjective evaluations of QoL (discussed in section 3.2.2.1.1) and relates to the model discussed in sections 3.3.1 through to 3.3.1.2.

3.3.4.2 An Outline of Social Health, Social Cohesion and Social Capital Models Research

The emphasis on social health is supported by research on the public's priorities in life. A national survey of adults in Britain was reported by Bowling and Windsor (2001). Participants identified the 6 most important things in their life. Relationships with family, relatives, friends and other people like neighbours were rated as most important. Social

life was nominated as important by nearly 20% of participants. Measurement of social health focuses on the individual and is defined in terms of interpersonal interactions e.g. visits with and to friends and social participation and membership in clubs, social activities, holidays, day trips, volunteering (Brown et. al. 2004). Social networks are the identified social relationships that surround an individual, their characteristics, perceptions and valuations of them; network characteristics include their size, connectedness between members and physical boundaries, (neighbourhood), frequency of contact, their duration and reciprocity (Berkman and Glass, 2000). Social support is the interactive process in which emotional, instrumental or financial aid is obtained from network members (Brown et. al. 2004). Human ecology theory focuses on the interactions and interdependent relationships between people, and postulates that families are an important resource and a rich environment for individual members (Rettig and Leichtentritt, 1999). Lack of social integration and social support has been hypothesised as decreasing the individual's resources for dealing with social stress and has been implicated in poor mental health outcomes (George, Blazer, Hughes and Fowler, 1989). The importance of social networks and their characteristics lies in the extent to which they fulfil member's needs (Brown et. al. 2004). There is some evidence to support the buffering effects of social support on health and well-being in the face of life events (Holahan and Moos, 1981). Social support can have a direct effect on health and well-being for example by providing comfort or provision, (money, aid), which can in turn reduce symptoms or stressors; support does not necessarily disturb or mitigate the relationship between stress and health and a lack of support may lead to psychological damage (Brown et. al. 2004).

In relation to social health, most studies of QoL focus on individual social network and support systems rather than on community resources and integration and person-environment fit but human ecology theory maintains that the QoL of humans and the quality of their environment are interdependent and that the former cannot be considered apart from the whole ecosystem (Rettig and Leichtentritt, 1999). Measurement of social cohesion, the connectedness and solidarity between groups of people (Kawachi and Berkman, 2000) includes objective indicators like crime rates, pollution, cost of living, housing and education facilities, policies, (un) employment, wage, travel to work time, leisure facilities (Rogerson, 1995). Other indicators include access to convenient and affordable transport and the general characteristics of neighbourhoods; subjective indicators include public values, perceptions and levels of satisfaction with area of

residence, its facilities, transport, travel to work time, and perceptions of neighbourliness and safety from crime (Cooper, Arber, Fee and Ginn, 1999).

Social cohesion and social capital, (a subset of the concept of social cohesion referring to the extent to which communities offer members opportunities through active involvement in social activities, voluntary work, group membership, leisure and recreation facilities, political activism and educational facilities, all to increase their personal resources or social capital (Brissette, Cohen and Seeman, 2000)), are collective, ecological dimensions of society which are distinct from the concepts of social networks and social support which are measured at the level of the individual (Kawachi and Berkman, 2000). The definition and measurement of social capital are still evolving and currently reflect a conceptual mixture of indicators of both the structure such as community membership and function of social relations such as moral resources of trust and reciprocity (Brown et. al. 2004).

3.3.5 Idiopathic Models

3.3.5.1 An Explanation of Idiopathic Models

Idiographic models are based on individual's values, interpretations and perceptions, satisfaction with their position, circumstances and priorities in life (Garratt and Ruta, 1999). The division of QoL into predefined individual components such as physical, psychological and social functioning does not tap the relevant and important domains of people's perceptions of QoL nor does it capture the subjectivity of people (Brown et. al. 2004). Individuals are the only proper judge of their QoL because people differ in what they value (Ferrans, 1996).

3.3.5.2 An Outline of Idiopathic Models Research

On the basis of its individual nature, Joyce, O'Boyle and McGee (1999) argue that a theory of QoL must integrate knowledge from other cognitive theories for example memory and information processing. They base this argument on the understanding that changes in an organism reflect immediate effects and/or storage processes. Stored information is subject to modification by previously stored information and by other new and existing inputs and thereby reconstructed when recalled to conscious attention. Thus, any stimulus may modify an individual's construction of their QoL at any of these levels; the links between these levels may be stable or unstable, healthy or pathological, and may represent different domains of QoL which may vary in their status as traits or states (Joyce et al. 1999). It

may be argued that health status may be a trait and general QoL measures may assess states; the distinction between what aspects of QoL are states or traits is unclear and requires further investigation (Joyce et al. 1999).

Whilst measurement of QoL is not the focus within this section, it is important to mention measurement within this model as most of the research done around this model centres upon QoL measurement. The model states that measurement scales need to be sensitive to the differing values of various social groups and the change in priorities with increasing age (Bowling and Windsor, 2001). This is supported by results from a national study by Bowling et. al. (2003) that people aged 75 and over are more likely than younger respondents to prioritise their own health and the ability to get out and about. Also, they were less likely than younger people to prioritise relationships with family and other relatives, finances and work. Women of all ages are more likely than men to prioritise relationships with family or relatives and men were more likely to prioritise finances (Bowling and Windsor, 2001). It is clear that different areas of life are given different priorities by different groups in the population (Bowling, 1995b). Researchers have turned towards individualised measures like the Schedule for Evaluation of Individual Quality of Life (SEIQoL) (Hickey, O'Boyle, McGee and Joyce, 1999), or the Patient Generated Index (PGI) (Garratt and Ruta 1999), that ask about the most important things in their lives or about the most important effects of their condition on their lives, and to then prioritise and/or weight the areas mentioned. Ferrans (1996) provides a QoL measure that offers an objective assessment of an individual's QoL yet is connected to a person's judgements, values, life experiences and satisfaction with aspects of life. This assessment tool includes the following QoL domains: health and functioning, psycho-spirituality, socio-economy and family. Evaluating an individuals' QoL can show how satisfying the person considers life (Brown et. al. 2004). Assessments can provide an understanding of the similarities and differences between the person's view and the views held by others (Faden and LePlege, 1992), even though the methods of scoring and weighting are complex (Hickey et. al. 1999) and the reliability and validity of such measures has yet to be confirmed (Bowling and Windsor, 2001). Note that the reliability and validity of measures is discussed in chapter 4, sections 4.2.4 and 4.2.5.

3.3.6 Health and Functioning Models

3.3.6.1 An Explanation of Health and Functioning Models

Health and functioning models are typically based on measures of broader health status and often wrongly referred to as depression scales and scales of physical functioning e.g. activities of daily living like washing, dressing and self-care and activities of instrumental daily living e.g. shopping, housework and social role obligations and are generally referred to negatively as scales of disability as patient/client-based outcome indicators of health and social care interventions (McKevitt, Wolfe, La Placa, 2002). The concept of HRQoL has been based on a pathology disease model of ill-health and poor health status and disease, physical and mental decline, disability and impaired role functioning; the emphasis has been on dysfunctional status (Brown et. al. 2004). Functional status is the degree to which a person is able to perform socially allocated roles free of physical or mental health related limitations (Bowling et. al. 2003). This approach focuses on people's ability to perform activities of daily and instrumental living i.e. HRQoL taps the individual's difficulties in the performance of activities which are essential for the continuing functioning of the wider society i.e. the model of functionalism (Brown et. al. 2004).

3.3.6.2 An Outline of Health and Functioning Models Research

Good levels of physical and mental functioning and general health status are associated with concepts like perceived well-being, morale and overall QoL and the associations have been replicated recently in large surveys where the concept of QoL has emerged as a standard, subjective measure of outcomes of health as well as socialcare (Bowling and Windsor, 2001). Used in such contexts, QoL is generally referred to as HRQoL (Carver, Chapman, Thomas, Stadnyk and Rockwood, 1999).

Descriptive and evaluative research is based upon negative, rather than positive models, that underestimate the QoL of people; the WHO has attempted to redress the balance away from disability and towards ability as reflected in the shift of focus from its International Classification of Impairments, Disabilities and Handicaps (WHO, 1980), which distinguished between physical status, (impairment), physical functioning, (disability) and social functioning (handicap) and towards its more positive International Classification of Impairments activities, (formerly called disabilities) and participation, (formerly called handicaps) (WHO, 1998), and its components of health classification, known as the International Classification of Functioning, Disability and Health (WHO, 2001). The

WHO's (1947; 1948) definition of health as a state of complete physical, mental and social well-being appears to act as the lead for the assessment of QoL as an indicator of health and social care outcomes i.e. HRQoL. This model has generated the development of broader assessment of health outcomes i.e. social, physical and psychological well-being, positive health alongside self-rated health status rather than sole reliance on traditional indicators based on the prevalence of risk conditions like obesity and selected chronic conditions including asthma and diabetes mortality rates. This model has accentuated the interest in measuring the broader concept of QoL in health outcomes research i.e. HRQoL (Brown et. al. 2004). This movement contrasts strongly with the previously narrow, negative and disease-based model as it emphasises not just the absence of ill-health, disease and disability but also the full functioning and efficiency of mind and body, the ability to cope with stressful situations, integration in the community and maintenance of social support and psychological well-being e.g. life satisfaction, morale, physical fitness and health (Brown et. al. 2004). However, the objective and subjective indicators of QoL, ranging from life satisfaction and happiness, income to environmental and community resources, are regarded as too broad and less relevant to the goals of health care interventions (Patrick and Erickson 1993).

Quality of Life (QoL) is influenced by health status hence it is possible to improve QoL by improving an individual's health state (Anderson and Burckhardt, 1999). This is the key element of the conceptual model of clinical outcomes developed by Wilson and Cleary (1995). Their model suggests that a series of health related factors (biological and physiological factors, symptoms, functional status and general health perceptions), have a major effect on overall QoL. Each of these related factors is influenced by the individual, (personality, values, symptom amplification) and environmental, (social, psychological and economic supports) characteristics. Besides these health factors, overall QoL is influenced by non-medical factors and the main limitation of this model is its over emphasis on the influence of general health status and health related variables on overall QoL i.e. non-medical factors ought to be central not incidental (Anderson and Burckhardt, 1999). This work suggests that psychosocial variables such as self-esteem, social support and negative affect are at least as important as illness related variables in determining QoL and tests of models of QoL in arthritis and Chronic Obstructive Pulmonary Disease (COPD), (a persistent disruption of air flow into or out of the lungs (BMA, 2002)), found that psychosocial variables exerted direct effects on QoL while health related variables had

only indirect effects on QoL through the psychosocial variables (Burckhardt, 1985; Anderson, 1995).

3.3.7 A Summary of Models of Quality of Life (QoL)

Quality of life (QoL) is a multi-faceted and complex concept, reflecting objective, subjective, macro-societal, micro-individual, positive and negative influences that interact (Lawton, 1991). There is also no overall agreement on definitions which poses inevitable challenges for measurement (Brown et. al. 2004). The outline of the models reveals that QoL can theoretically encompass a wide ranging array of domains including an individual's physical health and functioning, psychosocial well-being, psychological outlook, social support and resources, independence, autonomy and perceived control over life, material and financial circumstances, community social capital and the external environment including the political fabric of society and most importantly encompasses the individual's perspective and is a concept which is likely to be mediated by cognitive factors (Brown et. al. 2004).

Although there has been little attempt to examine these models systematically and/or critically, the models outlined provide the frameworks for QoL across the health and social outcomes research disciplines (Brown et. al. 2004). Interest in this discipline has flourished over the last two decades from policy makers to professionals, in an era of evidence-based practice, yet, this industry, that has generated health-related, disease-specific QoL outcome scales, has made few attempts at defining and conceptualising QoL therefore limits models on which to base them (Bowling, 2002). A wider research community has accepted no definitive theoretical framework of QoL and no single research framework has been utilised in its investigation, thus, despite a plethora of research there is no widely accepted or supported theory or measurement instrument of quality of life (Brown et. al. 2004). A discussion on the measurement of QoL now follows.

3.4 The Measurement of Quality of Life (QoL)

3.4.1 An Introduction

Two studies in the USA confirmed the value of psychometric methods in assessing health outcomes (Hobart, Riazi, Lamping, Fitzpatrick and Thompson, 2004). These are the RAND Health Insurance Study (HIS) (Brook, Ware, Davies-Avery, Stewart, Donald,

Rogers et. al. 1979) and the Medical Outcomes Study (MOS) (Stewart, Greenfield, Hays, Wells, Rogers, Berry et. al. 1989).

The HIS was a social experiment in which representative samples of different communities were assigned using a non- biased selection process to several different health insurance plans including a prepaid group practice (Brook et. al. 1979). The HIS, is the most important randomised, health insurance experiment ever conducted and addressed two key questions in healthcare financing concerning how much more medical care people use if it is provided free of charge and the consequences for their health (Hobart et. al. 2004). The HIS project was started in 1971 for a decade and funded by the Department of Health, Education and Welfare, now known as the Department of Health and Human Services. It was a 15-year, multimillion-dollar effort that to this day, remains the largest health policy study in American history. The experiment was designed to assess the effects of variation in the cost of health services to the patient and of provision of services in either the fee-for-service system or a pre-paid group practice on use of services, quality of care, patient satisfaction and health status (Brook et. al. 1979). The products of the research were useful to decision-makers and the public in setting future health policies particularly those relating to national health insurance (NHI) (Brook et. al. 1979). A major study objective was to assess the impact of varying the cost of health services on the individual participant's health status. To accomplish this objective, development of reliable and valid health status measures that could be used to detect small but important changes in health status of people sampled from general populations was a key step in the research. Selection and development of HIS health status measures for children and adults began in 1972. One health status battery, designed to measure physical health, was administered on the baseline interview four months prior to 'enrolling' the first HIS sample. The first comprehensive health questionnaire, the enrolment medical history questionnaire contained batteries of items specifically designed to measure physical, mental and general health constructs. The study demonstrated that psychometric methods can be used to generate reliable and valid measures for assessing changes in health status for both adults and children in the general population (Brook et. al. 1979). The study's conclusions encouraged the restructuring of private insurance and helped increase the stature of managed care (Brook et. al. 1979).

Following on from this study, the MOS (Stewart et. al. 1989) demonstrated that psychometric methods of scale construction and data collection were good ways of measuring health status in samples of ill and elderly people. The MOS was a large-scale survey of patients with prevalent and treatable chronic health conditions. The study samples were drawn from patients receiving health care from practices in the USA. Over 23,000 cases were reported with over 4,500 variables. The core MOS survey contained 116 QoL items measuring physical, mental and general health. It was designed to determine whether variations in patient outcomes are explained by differences in systems of care, HCP specialty and clinicians' technical and interpersonal styles and to develop more practical tools for the routine monitoring of patient outcomes in medical practice (Stewart et. al. 1989). Outcomes included clinical end points i.e. physical, social and role functioning in everyday living, patients' perceptions of their general health and well-being and satisfaction with treatment. Over 500 HCPs were randomly sampled from different health care settings in the USA. Nearly 22,500 adult patients evaluated their health status and treatment. A sub-sample of these patients (10%) with chronic illness was selected for the longitudinal study. Hospitalisations and other treatments were monitored; periodically outcomes of care were reported. At the beginning and end of the longitudinal study, physical examinations and laboratory tests were performed. The MOS marks several methodological advances: measurement of three dimensions of health status in parallel, initially and longitudinally, a focus on patients' own personal evaluation of their functional status and well-being-to better address the needs of patient-based assessments of medical outcomes and the use of both standardised patient surveys and clinical evaluations as measures of health status (Hobart et. al. 2004). The MOS was the first large-scale study in which patients with different medical and psychiatric conditions completed the same self-administered questionnaires (Hobart et. al. 2004). This study demonstrated that psychometrically equivalent short-form measures i.e. The MOS 36 item Short Health Survey (SF-36) (Ware and Sherbourne, 1992) could be constructed from the original longer forms thereby reducing respondent and administrative burden and improving measurement efficiency (Hobart et. al. 2004).

These two pivotal studies found that psychometric methods can generate scientifically sound and clinically useful health outcome measures.

3.4.2 Standardised Quality of Life (QoL) Surveys and Scales

The division of QoL into pre-defined individual components such as physical, psychological and social functioning is helpful for measurement purposes (Brown et. al. 2004). As a concept, QoL is clearly complex therefore requires multiple types of instruments for adequate measurement (Edgell, Coons, Carter, Kallich, Mapes, Damush et. al. 1996). The scientific discipline of health measurement grew in response to the need to supplement clinical judgement with reliable and valid patient-based measures of health outcomes (McDowell and Jenkinson, 1996) and since there has been increasing recognition of the importance of assessing more patient-relevant consequences of disease, a practice that is now considered essential in a comprehensive evaluation of healthcare (Peto, Jenkinson, Fitzpatrick and Greenhall, 1995). This conceptual and measurement confusion surrounding QoL is evident in the multitude of different measurement scales used to tap it (Garratt et. al. 2002). A systematic review of the literature on patient assessed measures of health status and QoL, based on a classification of measures developed by Sanders, Egger, Donovan and Frankel (1998), was undertaken by Garratt et. al. (2002). The classification by Sanders et. al. (1998) included dimension-specific measures e.g. psychological well-being measures using anxiety and/or depression scales like the General Health Questionnaire (GHQ) (Goldberg and Williams, 1988), multi-domain disease or population specific measures relevant to specific health problems such as the Asthma Quality of Life Questionnaire (AQOLQ) (Juniper, Guyatt, Ferrie and Griffith, 1993), generic, multi-domain measures of broader health status, (used across population types) like the MOS 36 item Short Health Survey (SF-36) (Ware and Sherbourne, 1992), individualised measures which enable respondents to nominate and weight important areas of their own life like the SEIQoL (Hickey et. al. 1999) or the PGI (Garratt and Ruta, 1999) and utility measures which incorporate preferences for health states, in order to produce a single index used for making comparisons across treatments and health problems for economic evaluation like the EuroQol (EuroQol Group, 1990) and the Health Utilities Index (HUI) (Feeny, Furlong, Boyle and Torrance, 1995). During 1990-1999, Garratt et. al. (2002) reported finding 23,042 records although just 3,921 of these met their inclusion criteria of reporting on the development and testing of the measures. Although there was evidence of the use of a small number of QoL generic measures, suggesting a standardised approach, among QoL disease-specific measures there was little standardisation e.g. 67 trials were reviewed, of those 48 used 62 different measures and 13 reported new measures (Garratt et. al. 2002).

The Scientific Advisory Committee (SAC) (2002) is an independent body of senior academics who report annually on the activities of research programmes. They are an advisory body and play an important role in ongoing review of scientific excellence and policy relevance. The SAC assessed the growth of QoL measures and examined the availability specialities. They found 3921 reports that described the development and evaluation of patient assessments. Over 46% were disease-specific, 865 (22%) were generic, 690 (18%) were dimension-specific and 409 (10%) were individualised measures. During 1990, the number of new reports of evaluation rose from 144 to 650 per year; over 30% were reports of disease-specific measures of evaluations in cancer, rheumatology and musculoskeletal patients' health. Generic measures like the SF-36 and the Sickness Impact Profile (SIP) (Gilson and Bergner, 1976) accounted for 612 (16%) of reports. The SAC (2002) suggest that there is considerable enthusiasm expressed for the potential to provide accurate evidence of outcomes from the patient's perspective as structured review recommendations based on patient and professional consensus are required for application of measures. The SAC (2002) also suggest that researchers should undertake extensive review to ascertain whether a suitable measure is available before they decide to develop another. Upon review of well used measures they identified common attributes: 1) cultural and language adaptations, 2) conceptual and measurement modeling, 3) validity, 4) interpretability, 5) respondent and administrative burden, 6) alternative forms, 7) responsiveness and 8) reliability. The SAC (2002) matched criteria to particular uses and concluded that existing measures should be refined and others be developed to cover clear gaps relating to patient populations and disease groups. Instruments should be improved to make them more culturally appropriate and comparable across diverse populations and enhance ways that results can be interpreted in ordinary terms; they should also deal with the differences in diseases/illness and understand the complementarities of instruments developed with different conceptual frameworks (SAC, 2002).

It has been suggested that patients are the best source of information about therapeutic benefit defined in terms of functioning and well-being (Ware, 1995) and patients, carers and HCPs have been found to differ in their interpretation of their illness e.g. Parkinson's patients (Gothan, Brown and Marsden, 1986; Brown, MacCarthy, Jahanshahi and Marsden, 1989), epilepsy patients (Hays, Vickrey, Hermann, Perrine, Cramer, Meador et. al. 1995; Vickrey, Hays, Engel, Spritzer, Rogers, Rausch et. al. 1995), MS patients (Brosseau, 1994) and generally chronically ill patients (Sprangers and Aronson, 1992).

Therefore, it is important to elicit information from patients about which outcomes are important. Evidence suggests that patients can provide reliable and valid judgments of their health status and the benefits of treatment consequently measures should be seen as ways of capturing patients' opinions and feelings regarding their disease and treatment, their perceived need of healthcare and their preferences for treatment methods and disease outcomes (Abetz et. al. 2006). Patient self-report has been described as the ultimate measure of health status (Ware, 1993). This method affords considerable methodological advantages as large numbers of geographically disparate patients can be accessed by postal survey thus reducing selection bias while minimising patient discomfort and research staff involvement (Hobart, Freeman and Lamping, 1996). Schumaker and Berzon (1995) suggest that a QoL measure should capture, at a minimum physical, psychological including emotional and cognitive, and social functioning. Naughton and Schumaker (2003) propose additional dimensions that should be included in QoL measures; these are role activities, individual's life satisfaction and perception of their health status. They also made suggestions regarding additional dimensions such as sleep disturbance and spirituality, that researchers might want to include in their QoL measure depending upon the given research study (Naughton and Schumaker, 2003). Most importantly, their research emphasises that when selecting a measure to use in research, staff, participant burden, time constraints and resources should and need to be considered. In a review of the literature, Hyland (2003) states that there is no set rule to what the 'best scale' is but only to what the best suited scale is for the research purpose. At this point it is noteworthy that although the concept of QoL is generally defined in positive terms, see Tables 1, 2 and 3, it is generally measured and presented in negative terms and in terms of what people have lost, rather than what people have e.g. loss of health, disability, mental ill-health, loneliness (Brown et. al. 2004).

3.4.2.1 Generic Versus Disease Specific Surveys and Scales

There are two distinct approaches and types of questionnaire used to measure QoL: generic versus disease-specific. A generic QoL questionnaire is not specific to a disease type and usually includes domains that measure biopsychosocial functioning (Bowling and Windsor, 2001). A generic QoL questionnaire can be utilised in healthy individuals and in those with chronic illness (Bowling and Windsor, 2001). Although generic measures have the advantage of enabling comparisons across diseases (Riazi, Hobart, Lamping, Fitzpatrick and Thompson, 2002), it is increasingly recognised that they do not cover some

areas of outcome that are highly relevant in specific diseases (Peto et. al. 1995), may have limited responsiveness (Patrick and Deyo, 1989), and/or may fail to detect change (Patrick and Deyo, 1989).

Researchers propose that the best approach is to supplement QoL measures with disease-specific measures (Fischer, Rocca, Miller, Ritvo, Andrews and Paty, 1999). Disease-specific instruments consisting of items and domains of health that are specific to a particular disease are more relevant and important to patients and clinicians and consequently are more likely to be responsive to subtle changes in outcome (Guyatt, Osoba, Albert, Wyrwich and Norman, 2002). Disease-specific QoL instruments are comprised of questions that address specific areas of importance such as disease-related symptoms as opposed to generic measures that target a specific age, disease or treatment group (Hobart et. al. 2004). They take into account aspects of disease and treatment that are relevant to specific medical conditions that may be preferable when studying a disease longitudinally (Hobart et. al. 2004). Disease-specific instruments have the advantage of being more sensitive to the major features of disease as well as the changes of the disease that affect patients' lives on a daily basis (Spilker, 1996). Such instruments are applicable in the range of different cultural, age and social settings and are valuable in evaluating new forms of treatment and in comparing health outcomes between different clinics, they can be used in cross–sectional studies to describe the impact of the disease and to monitor the natural history of the illness and in clinical trials as well as in biopsychosocial interventions to evaluate therapeutic effectiveness in comparing health outcomes between clinics (Spilker, 1996).

3.4.2.1.1 Generic Surveys and Scales

The main generic measures of QoL are the MOS 36 item Short Health Survey (SF-36) (Ware and Sherbourne, 1992), The Sickness Impact Profile (SIP) (Gilson and Bergner, 1976), The EuroQol (EQ – 5D) (EuroQol Group, 1990), The WHOQoL-100 (WHOQoL Group, 1998) and The Nottingham Health Profile (NHP) (Hunt et. al. 1985). Each of these measures shall be described in turn with an example of research in the sections that follow (3.4.2.1.1.1 through to 3.4.2.1.1.5.1).

3.4.2.1.1.1 A Description of the Medical Outcomes Study (MOS) 36 item Short Health Survey (SF-36)

The MOS 36 item Short Health Survey (SF-36) was developed by Ware and Sherbourne (1992) and is the most commonly used generic questionnaire for adults. A literature search (Web of Science) on the SF-36 in May 2008 indicated that since 1992 over 7500 articles have been published in the area. The SF-36 is a multi-purpose, short-form health survey with only 36 questions originally developed in USA English. The SF-36 is a well standardised health status questionnaire that yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (Ware, Kosinski and Keller, 1996). The scales are, physical functioning (physical) (10 items), role limitations due to physical problems (rolep) (4 items) or emotional problems (role) (3 items), social functioning (social) (2 items), bodily pain (pain) (2 items), mental health (mental) (5 items), vitality (vital) (4 items) and general health perceptions (ghp) (5 items). One additional item that is not scored asks the respondent to compare his or her current health with that of 1 year ago. Each domain is scored out of 100 with a higher score indicating less limitation, better functioning or less pain. A change of 5 points is considered to be clinically and socially relevant (Stewart et. al. 1989).

3.4.2.1.1.1.1 The Medical Outcomes Study (MOS) 36 item Short Health Survey (SF-36) and an Example of Research

The questions in the SF-36 are designed to be easy to understand and relevant to most people's lives and has been proven to be useful in surveys of general and specific populations, comparing the relative burden of diseases and in differentiating the health benefits produced by a wide range of different treatments (Eiser, 2000). In particular, health researchers have found it invaluable in measuring the sometimes subtle changes in health that follow medical interventions and in allowing comparison of one technique against another (Lawton, 1999).

In their Pain in Sickle Cell Epidemiology Study (PiSCES), McClish, Penberthy, Bovbjerg, Roberts, Aisiku, Levenson et. al. (2005) administered the SF-36 to over 300 patients. They compared patient scores with national norms and with three other chronic illness cohorts (asthma, CF, haemodialysis) and assessed whether SCD specific variables like pain and crises, were independently predictive of SF sub-scales. Patients with SCD scored

significantly worse than national norms on all subscales except for mental health. Patients with SCD had lower QoL than CF patients except for mental health. Scores were similar for physical function, role function and mental health as compared to asthma patients but worse for bodily pain, vitality, social functioning and general health subscales. Compared to dialysis patients, SCD patients scored similarly on physical and emotional role function, social functioning and mental health, worse on bodily pain, general health and vitality and better on physical functioning. Scores significantly decreased as pain levels increased. McClish et. al. (2005) concluded that SCD patients experience worse QoL than the general population and in general their scores were most similar to patients undergoing haemodialysis.

3.4.2.1.1.2 A Description of the Sickness Impact Profile (SIP)

The SIP was developed by Gilson and Bergner (1976) and revised in 1981. It may be described as a generic QoL measure used in adult populations to evaluate the impact of disease on both physical and emotional functioning or as a descriptive profile of changes in a person's behaviour due to sickness; patients are asked to respond to the items as they are on the day of administration (Gilson and Bergner, 1976). There are 2 overall domains, (physical and psychosocial) and 12 categories (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour and communication). An overall score can be computed. With regard to scaling of items respondents check the items that apply to them by answering yes or no. To score the measure, items are weighted according to a standardised weighting scheme. Like the SF-36, the SIP was developed in USA English.

3.4.2.1.1.2.1 The Sickness Impact Profile (SIP) and an Example of Research

The measure has been used in patients with COPD and asthma, (a lung disease in which there is an intermittent narrowing of the airways causing shortness of breath, wheezing and coughing), that is administered by the individual (Brown et. al. 2004). Measure reliability and validity compared to clinical indices of asthma and disease-specific QoL measures like The St. George's Respiratory Questionnaire (SGRQ) (Jones, Quirk, Baveystock, 1991), are sound although minimally important differences have not been determined (Brown et. al. 2004). The SIP has been used in research including clinical trials for asthma medication (Juniper et. al. 1993). To the author’s knowledge, its clinical use has yet to be reported.

In their study, DeJong, Kaptein, Van der Schans, Mannes, Van Aalderen, Grevink et. al. (1997) evaluated the QoL in CF adults and examined the relationship between QoL and pulmonary function, (how well the lungs take in and release air and how well they move gases such as oxygen from the atmosphere into the body's circulation (BMA, 2002), exercise capacity and dyspnoea (shortness of breath (BMA, 2002)). They assessed 15 patients in a stable clinical condition with regard to their forced expired volume in the first second, respiratory vital capacity, cycle exercise capacity and subjective degrees of dyspnoea during daily living. Quality of life (QoL) was assessed with the SIP. The overall SIP and physical SIP scores in CF patient were significantly higher than in the control group indicating more impairment in overall and physical functioning in the patients than the control group. These results show that CF affects QoL in adults primarily due to a limitation in physical functioning.

3.4.2.1.1.3 A Description of The EuroQol (EQ – 5D)

The EQ – 5D was developed by the EuroQol Group (1990) and is a simple, quick and standardised instrument for use as a measure of health outcome by clinicians and researchers. It is applicable to a wide range of health conditions and treatment as it provides a simple descriptive profile and a single index value for health status (EuroQol Group, 1990). The EQ-5D was originally designed to complement other instruments such as the SF-36 and/or disease-specific questionnaires but is now increasingly used as a 'stand alone' measure (EuroQol Group, 1990). The EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews; it tkes only a few minutes to complete (EuroQol Group, 1990). The EQ-5D was developed simultaneously in Dutch, English, Finnish, Norwegian and Swedish. The EQ-5D descriptive comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. This information can be used as a health profile for individuals or groups, either at a single point in time or over a period of time (EuroQol Group, 1990). The EQ-VAS records the respondents self-rated health status on a vertical graduated (0-100) visual analogue scale and is used together with the descriptive system to build a composite picture of the respondent's health status and as a quantitative measure. Differences in this scale can be used as a measure of outcome as judged by the individual respondents (EuroQol Group, 1990).

3.4.2.1.1.3.1 The EuroQol (EQ – 5D) and an Example of Research

Data were obtained from a study aimed at establishing a US population-based set of preference weights for the health states defined by the EQ-5D (Ko and Coons, 2006). As part of the study, data regarding sociodemographic characteristics and chronic medical conditions were collected. Approximately three-fifths of the study sample reported having at least one of the 18 chronic medical conditions: sinusitis hypertension and arthritis were the most commonly reported conditions. The chronic condition that had the greatest negative association with EQ-5D scores was arthritis (Ko and Coons, 2006). Unique associations were found between several chronic conditions and QoL after accounting for the presence of other conditions and socio-demographic characteristics (Ko and Coons, 2006). The results of this study provide an indication of the relative QoL judgements associated with various chronic conditions in the general US adult population (Ko and Coons, 2006). However, due to the cross-sectional nature of the study data there is uncertainty of the causal relationship between chronic conditions and QoL because it was unknown how well the conditions were managed (Ko and Coons, 2006).

3.4.2.1.1.4 A Description of The WHOQoL-100

The WHOQoL-100 (WHOQoL Group, 1998) was developed simultaneously in 15 international centres (Thailand, Spain, United Kingdom, Israel, India (2 centres), Zimbabwe, Australia, Panama, France, Russian Federation, USA, The Netherlands, Japan and Croatia). One hundred items are grouped into one facet examining overall QoL and general health perceptions; 24 QoL facets are grouped into six larger domains: physical, psychological, level of independence, social relationships, environment, and spirituality. Subsequently, the domains of independence and spirituality were integrated into the physical and psychological domains. Items are scored on a 5-point Likert scale with only the anchor points being specified (never-always). The WHOQoL-100 has become one of the standard QoL measures in existence and its international and multicultural aspects make it a very useful instrument (Eiser, 2000).

3.4.2.1.1.4.1 The WHOQoL-100 and an Example of Research

The universality of the WHOQoL-100 has been examined in several ways and was found to be remarkably adept at identifying facets of QoL which are cross-culturally important (Power et. al. 1999). Unpublished data shows that test-retest reliability is very good (Power et. al. 1999). Confirmatory factor analysis (CFA), (a special form of factor

analysis used to assess the number of factors and the loadings of variables; it allows for the explicit constraint of certain loadings to be zero; see chapter 4, section 4.4.1 for more details about this type of analysis), of the instrument showed that the 6-domain model was not as good a fit as the 4-domain model. This finding led to the decision to integrate two of the domains into the other 4 i.e. independence and spirituality (The WHOQoL Group, 1995). In a separate survey of the general population in Britain, the WHOQoL-100 was shown to have excellent internal reliability (Skevington, Bradshaw and Saxena, 1999). The scores discriminated well between people who were ill and well and concur with reported health status (Skevington et. al. 1999). The WHOQoL-100 demonstrates excellent reliability and validity and as a result has been used extensively in a variety of settings around the world (Brown et. al. 2004). The structure of the WHOQoL-100 reflects the issues/facets of QoL of a group of HCPs as well as those of 'lay' people in each of the field centres (Skevington et. al. 1999). These facets of QoL are known to be important across countries worldwide (The WHOQoL Group, 1995) although individuals may have different priorities about the importance that they give to the different dimensions of QoL and what these ratings mean for them (Skevington et. al. 2004).

The QoL of people with MS and people from the general population was evaluated using the WHOQoL-100 (McCabe and McKern, 2002). Gender differences between the 2 groups and the influence of coping style on adjustment were also evaluated. The participants were 381 people with MS and 291 people from the general population. The results demonstrated that people with MS experienced lower levels of QoL than people from the general population for both the objective and subjective dimensions of all 5 domains (McCabe and McKern, 2002).

3.4.2.1.1.5 A Description of the Nottingham Health Profile (NHP)

Since there are no agreed criteria for what constitutes QoL (Lauer, 1999), it is often difficult to know what is being measured; instruments may therefore lack validity (Bowling and Windsor, 2001). Thus, it seems more appropriate for those involved in healthcare to consider a 'health profile', which records the perceived health of individuals or groups (Hunt et. al. 1985). This approach is related to the idiopathic model of QoL that states that QoL cannot be measured in a standardised way as QoL is different for every individual (Brown et. al. 2004). See sections 3.3.5 through to 3.3.5.2 for further discussion of the model.

The NHP (Hunt et. al. 1985) is a short and simple measure of perceived health problems that has been shown to be understood by a majority of patients (Hunt et. al. 1985). Extensive testing with selected groups including the chronically ill, has established face, content and criterion validity and the reliability of the instrument (Hunt et. al. 1985). The profile does not directly ask about symptoms so it is more likely to identify people who are in distress or at risk but do not see their problems being specific to their health (Hunt et. al. 1985). The profile can be used to measure general perceived health status or specific conditions of ill health (Hunt et. al. 1985). Above all, it provides a measAure of the perceptions of patients thus can be regarded as a direct reflection on need and possible demand and an accurate guide to the efficacy of healthcare in affecting how people feel (Hunt et. al. 1985). The NHP was intended as a standardised tool for the survey of health problems in a population but it is equally valued and useful as a means of evaluating the outcome of medical and/or social interventions and as an adjunct to the clinical interview (Hunt et. al. 1985).

3.4.2.1.1.5.1 The Nottingham Health Profile (NHP) and an Example of Research

It may be more useful to consider the objectivity and subjectivity of QoL (as discussed in sections 3.3.1 through to 3.3.1.2), as two aspects that are essential to knowledge of human beings and their reactions (Hunt et. al. 1985). Most of the so-called objective QoL criteria involves clinical judgments about normal functioning being high QoL but evidence is accumulating that people judge their experiences in relation to their expectations therefore comparisons of value in health related activities must allow the perceptions of the patients as equal if not greater than clinical evaluations (Hunt et. al. 1985). Subjective assessment of patients may allow more successful interpretations of the impact that disease and treatment have on their QoL whereas objective indicators may merely be projections of professionals (Hunt et. al. 1985).

The aims of the study by Congleton, Hodson and Duncan-Skingle (1996) was to assess QoL in a population of adults with CF to compare QoL with published scores from a healthy population and their patients groups and to examine the relationship between QoL and other measured clinical variables. The NIP was used to assess QoL. The authors concluded that men and women with CF have different patterns of perceived QoL and that there is an age related trend of perceived QoL in men in some dimensions. Quality of life

(QoL) scores in this group, as assessed by the NHP, are similar to those reported in people with minor non-acute conditions.

Limitations of the NHP include questions representing rather severe problems e.g. I have unbearable pain whilst this was found to be necessary to avoid picking up large numbers of false positives, it does mean that some milder forms of distress may not show up on the profile (Hunt et. al. 1985). The profile primarily investigates negative aspects of health only since all the items refer to problems therefore it cannot be used to assess positive feelings (Eiser, 2000). Nevertheless, the profile has some important advantages. It is sensitive to change with time and different patterns of scores can be a useful indication of particular problems being experienced by patients (Bowling and Windsor, 2001). From a clinical perspective, as the principal problems of our time tend to be chronic and difficult, the treatment of which may be associated with a variety of side effects, some assessment of the QoL of the patients and their levels of distress and discomfort would seem to be a necessary addition to the usual outcome measures both in clinical trials and in assessing needs for counselling and support (Hunt et. al. 1985).

3.4.2.1.2 Disease Specific Measures

Reliable disease-specific measures have been developed for various diseases. For example, Sutcliffe, Clarke, Levington, Frost, Gordon and Isenberg (1999), advocated that reliable and sensitive measures were needed to evaluate the QoL in patients with Systemic Lupus Erythematous (SLE), an autoimmune disorder that causes skin inflammation of connective tissue (BMA, 2002). The development and validation of such a measure that assesses the burden of disease and treatment related symptoms of over 100 SLE patients, was undertaken by Grootscholten, Ligtenberg, Derksen, Schreurs, de Glas-Vos, Hagen et. al. (2003). The measure, the SLE Symptom Checklist (SSC) was shown to have sound psychometric properties and to be suitable for both clinical and research purposes.

Hobart, Lamping, Fitzpatrick, Riazi and Thompson (2001) identified the need for a MS disease-specific measure and developed such a tool using the standard psychometric approach of reducing a large item pool generated from people with MS (Testa and Simonson, 1996). Hobart et. al. (2001) developed and validated a 29-item, patient-based Multiple Sclerosis Impact Scale (MSIS-29). It was predominantly developed from a community based sample of over 1500 patients and measures the physical and

psychological impact of MS from the patient's perspective. A comprehensive evaluation of psychometric properties indicated the MSIS-29 to be clinically useful and scientifically sound (Hobart et. al. 2001).

3.5 Beta (β) Thalassaemia Major (BTM) and Quality of Life (QoL)

A chronic disease always causes some limitation of QoL especially when it requires frequent and complex treatment (Porter and Davies, 2002). To the author's knowledge, research into the QoL of people with thalassaemia is very limited. Morbidity and mortality related to thalassaemia have been reduced significantly with modern medical treatment and QoL should now be considered an important index of effective healthcare (Telfer et. al. 2005).

3.5.1 Measurement of Quality of Life (QoL) in Adult Patients with Beta (β) Thalassaemia Major (BTM) Using Generic Measures

Studies tend to emphasise the psychosocial side of coping with thalassaemia (see Chapter 2, section 2.1.2). Clearly the condition itself and its treatment have a major impact on the QoL of patients therefore this is one area where the healthcare provider can make a substantial impact in optimising QoL of these patients (Telfer et. al. 2005). A review by Telfer et. al. (2005) identified some of the major clinical and psychological aspects of BTM and its treatment that they expect to affect the QoL of their adult patients. These include the impact treatment on family stability and family dynamics, being different through having a chronic illness, appearing different e.g. bone deformities, short stature therefore leading to poor self-image, treatment including frequent hospital visits for transfusions and nightly chelation, delayed or absence of sexual development and impaired fertility, complications such as heart and bone disease, diabetes and infections, uncertainties about the future and consequent difficulties in long-term planning.

Mikelli and Tsiantis (2004) investigated depression symptoms and QoL in nearly 70 adolescents with thalassaemia as well as the same number of matched controls. The assessments used were the Beck Depression Inventory (BDI) (Beck, Ward, Medelson, Mock, Erbaugh, 1961), and the SF-36 (Ware and Sherbourne, 1992). The main findings of this study were that adolescents with BTM experienced more depressive symptoms and reported lower QoL. The strong inverse correlation between BDI and SF-36 total scores indicates that symptoms of depression are associated with reduced QoL. Although this

correlation was significant, it may be partly affected by the fact that the SF-36 includes two dimensions which also assesses aspects of psychological well-being i.e. emotional role and mental health (Mikelli and Tsiantis, 2004). Consideration should be given to how representative the results are of the general adolescent population as a whole even though the findings provide some evidence that the presence of depressive symptoms may influence the QoL of adolescents with thalassaemia (Mikelli and Tsiantis, 2004).

The impact of BTM and thalassaemia intermedia (TI) and their associated complications on QoL is largely unknown (Pakbaz, Treadwell, Yamashita, Quirolo, Foote, Quill et. al. 2005). Determining the degree of health impairment as perceived by the patient is important as this information is needed to recommend suitable therapy (Pakbaz et. al. 2005). Evidence-based research suggests that emotional functioning is one of the impaired QoL domains in patients affected by thalasssaemia (Pakbaz et. al. 2005). The objective of the study by Pakbaz et. al. (2005) was to evaluate QoL in transfusion–independent patients with thalassaemia in comparison with that in transfused patients with thalassaemia and to identify the factors that affect QoL in thalassaemia in general. A sample of nearly 50 patients with thalassaemia were invited to complete the Dartmouth Primary Care Co-operative Information Chart System (COOP) (Nelson, Wasson, Kirk, Keller, Clark, Dietrich et. al. 1987), a generic QoL measure used to assess and monitors their function. The questionnaire asked patients to rate their QoL on a 5 point Likert scale on six dimensions of health status i.e. physical, emotional, daily activities, social activities, social support, pain and overall health. Over 40% of transfused patients reported severe impairments in all dimensions; nearly 50% of non-transfused patient reported severe impairments in 2 of the domains. The most commonly reported affected domains were feelings such as anxiety, depression and concern of overall health status or indications of recent deterioration in health. In contrast with subsequent suggestions, non-transfused patients also suffer from serious impairment in QoL (Pakbaz et. al. 2005).

Andreou, et. al. (2003) used the WHOQoL-100 (WHOQoL Group, 1998) to assess QoL in UK patients with thalassaemia. The questionnaire was firstly given to several focus groups consisting of patients and HCPs who were asked to comment on the existing questions and themes and then to suggest possible areas and questions that could be added specifically to thalassaemia. It was then distributed to 212 adults with thalassaemia from the Greek and Turkish Cypriot communities in Cyprus. The WHOQoL-100 (WHOQoL Group, 1998)

was given in conjunction with the Beliefs About Medicine Questionnaire (BMQ) (Horne, Weinman and Hankins, 1999). The QoL score as a whole was not significantly different between the Greek and Turkish Cypriot communities. (It should be noted that the Turkish Cypriot population did not have access to oral ICT). There was some association between the psychosocial QoL scores and belief about medicines across both groups suggesting that those who felt that the benefits of the medication outweighed their concerns about the medication tended to score higher in general in questions about positive thoughts; those who had greater concerns about their medication tended to score higher on negative thoughts (Andreou et. al. 2003).

A review of the literature for the impact of iron overload and infusion ICT on patients' QoL and the availability of QoL instruments for patients undergoing infusion ICT was undertaken by Abetz et. al. (2006). Only 4 studies specifically measuring the impact of ICT with DFO on thalassaemia patients QoL were identified. In the review, QoL domains found to be affected included depression, fatigue, dyspnoea, physical functioning, psychological distress and decrease in QoL during hospitalisation (Abetz et. al. 2006). No iron overload or ICT specific QoL instruments were located in the literature (Abetz et. al. 2006). In addition to the literature review, Abetz et. al. (2006) obtained the experiences of 6 thalassaemia patients of having iron overload and receiving infusion ICT, as well as the opinions of 3 HCPs about the impact of treatment on patients' lives. These interviews revealed that the impact of ICT on patients with thalassaemia is high. The QoL of adolescent thalassaemia patients was reported as fair or poor by 21% of patients in a study by Arboretti, Tognoni, Alberti and Thalassarmia (2001) and 40% of patients perceived their QoL as high. With regard to patients assessing their own health status with regard to physical indicators, a recent review by Kallich, McDermott, Xu, Fayers and Cella (2006) found that 23.2% of over 1000 patients suffering from a haemoglobinopathy knew their Hb levels. Although patient knowledge of their Hb level had modest association with some aspects of self-reported QoL, the magnitude of this association, where it exists, would be unlikely to explain large group differences in QoL reports over time, even for a patient who knows their Hb level (Kallich et. al. 2006).

3.5.2 A Clinical and Psychosocial Instrument for Patients with Beta (β) Thalassaemia Major (BTM)

A reliable, reproducible, disease-specific measure to assess the impact on patients with thalassaemia has yet to be developed. Consequently, health outcomes in thalassaemia patients are simply classified by either HCPs and/or by patients (Telfer, Coen, Christou, Hadjigavriel, Kolnaou, Pangalou et. al. 2006). The most frequently studied HCP outcomes in thalassaemia are iron levels e.g. Porter and Davies (2002) but they only address the medical basis of thalassaemia and evaluate health in terms of quantity (Telfer et. al. 2005). Therefore a complete picture of the disease is not provided as a subjective assessment of health is not incorporated (Peto et. al. 1995). The clinical implications of a QoL disease specific tool for patients with thalassaemia include enabling groups of patients from different geographical, cultural and healthcare settings to be compared in general and specifically in treatment intervention (Telfer et. al. 2005).

From a review of the literature, Ratip (1996) concluded that there were no set questionnaires that were appropriate to measure the clinical and psychosocial burden of people with thalassaemia and as a result aimed to design psychosocial questions that were to be simple, direct, non-judgmental in nature, acceptable to all cultures and specific for thalassaemia patients from discussions with experts in the field and a literature review. A 'clinical' instrument was designed by defining the relevant parameters of clinical burden for patients e.g. transfusions, cardiac problems, diabetes mellitus and bone pain, and devising a scoring system with precise operational definitions for degrees of severity of each clinical burden parameter i.e. 0 =unaffected, 1=mild, 2=moderate, 3=severe. 'Clinical burden' was assessed from the patients' notes in collaboration with the HCP in charge. To allow for comparisons between patients as well as syndromes with different patterns of problems, the clinical parameters were weighted; multipliers were applied to the scores of clinical parameters. Psychosocial parameters i.e. education, social isolation and stigmatisation, sport, social life, anxiety, self-image, feelings of difference, family interactions, social integration, denial and well-being, were identified primarily by HCPs and literature review; a set of 26 questions was devised. Separate versions of the questionnaire were developed: (1) adult patients (aged 16 years+), (2) parents to answer about their children, under the age of 16 years and (3) for parents to answer about themselves. The questionnaires were administered as structured interviews. A scoring system was developed to quantify each psychosocial burden. Each psychosocial burden parameter was graded on a

scale of 0-3, (0= unaffected, 1= mildly affected, 2= moderately affected, 3= severely affected). Individual patient scores on the clinical or psychosocial parameter are added to give an individual score. See Appendix I for a copy of this measure for adult patients (16+).

Patient scores on both instruments are added to give an individual score; in this way the range of individual scores of different groups can then be compared. As identified by Telfer et. al. (2005) this could enable patients from different geographical, cultural and healthcare settings to be compared in general and particularly with regard to treatment intervention. However, whilst it is suggested that the weighting system, (a clinical interpretation of scores on health measures) (Hadhorn and Uerbersax, 1995), is to be used when making clinical comparisons between individual patients or different groups of patients (Ratip, 1996), it is not clear what numbers equate to low, or severe clinical burden, nor are the concepts clinical and psychosocial burden defined in the publication (Telfer et. al. 2005). Numerous attempts have been made by the researcher to contact the author to clarify this, to no avail.

The strengths of Ratip's (1996) instrument have been identified as follows. The instrument attempts to observe a complex clinical picture of this illness and is the first quantitative evaluation of the clinical burden of BTM which has a quantitative scoring system, it has huge coverage of BTM patients 'issues' with a chronic dysfunction focus (disease-specific not generic), questions are specific and direct, non-judgmental and relevant to the patient group, the instrument is culturally appropriate and appropriate to this inherited disease and it deems to be suitable for use in regular clinical practice/setting due to its quick and easy administration. The instrument is best suited in identifying patients who may need psychosocial support and for measuring the psychosocial effects of new treatments. The results of Ratip's (1996) study provide evidence for the need to organise psychosocial assessment for the patients and provide support where necessary. Upon analyses clinical burden equates to psychosocial burden so further instruments developed for this patient group arguably should have physical, social and psychological dimensions (Power et. al. 1999). The instrument takes a multidimensional approach to burden i.e. biomedical viewpoint of health, clinical signs and symptoms, severity of illness, pain level and/or side effects of medication, sociological view of health, in which the functional status of populations are of importance e.g. ability to undertake daily tasks.

In his MD thesis, Ratip (1996) states that *"the investigation and management of psychosocial disturbance in thalassaemics is important for improving the QoL of the patients….. and enabling them to live happy and creative lives. It is also likely to improve compliance with medical treatment with subsequent improvement in survival".* Ratip (1996), a Haematologist, developed a quantitative instrument to integrate a description of BTM, combining genetic, clinical and psychosocial aspects not a health outcome measure. His MD thesis states that the aim of his work was to compare, contrast and correlate the clinical, psychosocial and genetic aspects of inherited diseases like BTM and to devise an instrument specifically directed to the quantitative analysis of psychosocial problems of thalassaemics and to quantitatively analyse the psychosocial aspects of TI patients, (a term used to define a group of patients with BTM in whom the clinical severity of the disease is somewhere between the mild symptoms of the β thalassaemia trait and the severe manifestations of BTM; the diagnosis is a clinical one that is based on the patient maintaining a satisfactory haemoglobin (Hb) level of at least 6-7 g/dL at the time of diagnosis without the need for regular blood transfusions) (BMA, 2002)), to clarify the psychosocial burden of adult patients with BTM and to analyse the relationship between clinical and psychosocial burden for patients. A small sample of BTM patients (n=26) was administered the adult structured interview, whilst the clinician completed the questionnaire. An initial concern here would be how generalisable the results would be due to the sample size. The instrument was not developed according to psychometric theory (Nunnally, 1967) (to be discussed in more detail in chapter 4). No statistical item reduction was undertaken; items included in the instrument seemed to be based upon discussions with experts/HCPs and literature review. No pre-testing was undertaken. The measure has yet to be standardised and/or validated; a requirement if intended to describe the health status of a defined population or a specific disease category as this is particularly important if there is an intention to compare results with other studies (Nunnally, 1967). Statistical analyses were in the form of correlations between variables. No reliability data was presented for either instrument and no descriptive/response data. Psychosocial burden was graded but there was no mention as to why grades ranged from 0-3 although the reliability of grading equalled consensual rating of a proportion of interviews by the author and a HCP within psychological medicine. The issues described in the psychosocial instrument were identified from literature alone and not via patient interview. This is a significant limitation as the instrument was not patient-based (Telfer et. al. 2005) as a primary goal of instrument development is that patients self-report on issues deemed important by

patients (Hobart et. al. 2004). Clinical burden was also graded and HCPs imposed their relevance on clinical parameters, scoring and weighting (Telfer et. al. 2005). Iron chelation therapy/treatment (ICT) was not listed as a clinical burden yet the literature infers that this is a major concern in patient adherence to treatment (Porter and Davies, 2002) (see Chapter 1 section 1.4.2.). Whilst Ratip (1996) deemed the instrument to be suitable for use in regular clinical practice/setting due to its quick and easy administration, one could question its practicality in such a setting due to the interview format.

Despite its shortcomings, Ratip's (1996) instrument was adopted in research. Three publications have since appeared using different versions of the instrument. These are summarised as follows. In a UK study, adult patients reported feelings of denial, anxiety (77%), difference, problems with social integration (67%), social activities and education (Ratip and Modell, 1996). A study of patients and their families in a large clinic in Canada (Klein, Sen, Rusby, Ratip, Modell and Olivieri, 1998), illustrated a substantial difference in perception of illness between parents and older children and in general a lack of correlation between psychosocial and clinical burden. However, a high psychosocial burden for the patients correlated with a high psychosocial burden for the parents (Klein et. al. 1998). A study of children with thalassaemia, their parents and adults with thalassaemia, in a large clinic in South Turkey (Canatan, Ratip, Kaptan and Cosan, 2003) showed high levels of parental anxiety. Treatment was found to have a negative impact on employment and family finances and on the education of the affected children, often due to absences for transfusions and investigations (Canatan et. al. 2003). However, a high psychosocial burden for the patients poorly correlated with a high psychosocial burden for the parents (Canatan et. al. 2003). Adult patients reported feelings of anxiety (84%) and denial and problems with education, social integration and a reduction in social activities.

This chapter considered the concept and measurement of QoL as an outcome variable for healthcare intervention and research. Chapter 4 gives a synopsis of the history and background of psychometric theory, (familiar concepts and methods used in the development and evaluation of health outcome measures like Quality of Life (QoL) scales and Patient Reported Outcome Measures (PROM's). Examples of measures and their psychometric properties are considered.

Chapter 4: Health Outcomes Measurement: History, Concepts and Theory

"Psychometry, it is hardly necessary to say, means the art of imposing measurement and number upon operations of the mind…."

F. Galton (1879)

Chapter Overview

This chapter gives a synopsis of the history and background of psychometric theory, its concepts and methods used in the development and evaluation of health outcome measures, an umbrella term for QoL scales, health status measures and Patient Reported Outcome Measures (PROMs). Examples of measures and their psychometric properties are considered. In addition, the general aims and objectives of this research are discussed. Unless otherwise stated the information discussed and relayed in this chapter has been taken primarily from the following texts: Nunnally (1967) and Nunnally and Bernstein (1994), authors whose texts are comprehensive in psychometric theory and related methods of statistical analyses throughout the behavioural sciences, Kaplan and Saccuzzo (2005) who debate the principles, applications and issues of testing in psychology in general, and Streiner and Norman (1995) whose research focus has been the measurement of QoL from both a conceptual and a measurement point of view.

4.1 Psychometric Theory: Origins and Background

Psychometrics is the field of study concerned with the theory of measurement. It involves two major tasks: 1) the construction of instruments and procedures for measurement e.g. questionnaires, and 2) the development and refinement of theoretical approaches to measurement. Psychometrics is applied widely in educational assessments to measure academic abilities. Personality and attitude testing have also been a focus in psychometrics. The common approach to the measurement of attitudes is the use of the Likert scale (Likert, 1932). More recently, psychometric theory has been applied in health related fields. If the widespread and classical definitions of measurement are taken into account, then the main task in measurement is to discover associations between scores and factors hypothesised to underlie the associations. As the measurement of intangible phenomena is difficult, much of the research within psychometrics has attempted to define and quantify phenomena. Tillery (2005) has argued that the definition and quantification of such phenomena is impossible and measures are often misused. However, supporters of

psychometric techniques suggest that data are often misused as psychometric criteria have not been applied and because phenomena cannot always be observed directly inferences are made from their manifestation(s)/demonstration(s). Figures that have been identified as making significant contributions to psychometrics include Thurstone, Pearson, Galton and Spearman. Much of the early theoretical and applied work in psychometrics was undertaken in an attempt to measure the concept of intelligence; the first psychometric instrument has been identified as the Stanford-Binet IQ test developed by psychologist Alfred Binet. Galton coined the term 'mental test' for any measure of a human attribute; having devised and used 'mental tests', Galton is often referred to as the 'father of psychometrics' (Bulmer, 2003). Galton's colleague Pearson developed and applied the correlation coefficient and this prompted the development of the 'mental test' movement with a widespread interest in the development and application of mental testing, and the measurement of individual differences. A major advance in mental testing was made when Thurstone demonstrated that psychophysical scaling methods could be used to accurately measure educational attainment and psychological attributes like attitudes (Thurstone, 1925; Thurstone, 1928). This finding prompted the development of psychological (or psychometric) scaling methods i.e. procedures for constructing scales for the measurement of psychological attributes. Spurred on by the practical need to measure diverse outcomes, the 'mental test' movement flourished between 1930 and 1950 with the spread of standardised testing for assessing educational achievement, measuring attitudes and personality and selecting and screening personnel. In addition, scientific interest in methods of testing led to the development of psychometrics as a prominent discipline within psychology and established the cornerstones of the scientific evaluation of measuring instruments - reliability and validity testing (to be discussed in sections 4.2.4 and 4.2.5).

Although health measurement as a distinct discipline emerged in the 1980's (McDowell and Newell, 1987) it is derived from well-established theories and methods of measurement in the field of social sciences, the origins of which can be traced to the mid-1800's e.g. Galton (1879) and the 'mental test' movement.

4.2 Instrument Development and Evaluation

The development of an outcome measurement instrument in accordance with psychometric principles involves the generation of a large item pool followed by the reduction of the

initial item pool to form the final instrument. Items can be generated from a variety of sources including patients, opinion of experts in the field, literature review and critical review of existing measures. Items are then pre-tested on a small sample to assess how easily they can be completed and understood, whether there are ambiguities of wording, whether there are any irrelevant, misleading or offensive items and whether the content of each item is appropriate. Items are revised based on pre-testing to produce a version to be evaluated in a preliminary field test. Pre-testing is critical for identifying problems with a questionnaire such as problems with question content which can cause confusion with the overall meaning of an item, as well as the misinterpretation of individual terms or concepts.

The purpose of a first field test is to reduce the number of items and to develop scales. The instrument is administered to a large sample of participants and results are analysed using standard and traditional psychometric techniques for item analysis. Usually, items with poor response rates and very high or low endorsement frequencies are eliminated. The remaining items are analysed using exploratory factor analysis (EFA) (discussed further in section 4.3.1) that determines underlying dimensions (factors) of the instruments e.g. factor analysis, principal component analysis (PCA). Items are analysed for redundancy (the extent to which a pair of items measure the same construct), homogeneity (whether items are tapping different aspects of the same attribute and not different parts of different traits) and discrimination ability (the extent to which an item or scale can distinguish between those individuals who differ in the construct being measured). Based on these results, items are retained or eliminated and grouped into subscales to produce a final version of the instrument.

Instrument evaluation is the assessment of scientific properties namely data quality, scaling assumptions, acceptability, reliability including Cronbach's alpha, validity and responsiveness.

4.2.1 Data Quality

Indicators of data quality such as item non-response and missing scale scores can determine the extent to which an instrument is used. Such indicators reflect respondents' understanding and acceptance of a measure and help to identify items that may be irrelevant, confusing and/or upsetting to patients (McHorney, Ware, Lu and Sherbourne,

1994). Data quality can be determined by calculating percent of missing data for items, item test-retest reproducibility, (degree to which an item of the questionnaire yields stable scores over time among respondents who are assumed not to have changed on the domains being assessed) and percent computable scale scores. When there are missing items, a scale score can be calculated provided that 50% or more of the items are completed. A traditionally, psychometrically sound method of imputing data is to replace missing items with a person-specific mean score i.e. the average score across completed items for that respondent. This was the method used and described Ware, Snow, Kosinki and Gandek (1993) during their development of the SF-36 health survey manual and interpretation guide.

4.2.2 Scaling Assumptions

Once the instrument has been developed and the items are grouped into sub-scales, researchers may now make some (scaling) assumptions about the final version of the measure. Firstly, that items are correctly grouped in scales, secondly, that items in the same scale measure the same construct and thirdly that the items of each scale can be summed to produce scale scores. These three assumptions may be evaluated by examining the following criteria. According to Likert (1932), items of the same attitude scale are summed to produce a score as it is assumed that the scale developed should be roughly parallel and should therefore have similar item response distributions and exhibit equivalent means and standard deviations. The assumption that each item in the same scale contains the same proportion of information about the construct being measured is met if item-total correlations, (the correlation between the score of an individual's item and the scale total score) are approximately equal; criterion is satisfied when values exceed 0.30. If all items in a scale are measuring the same underlying construct, each item should be considerably related to the total score computed from other items in that group; this criterion of item convergent validity is supported if an item correlates substantially with its own scale. Factor analysis or item analysis is used to demonstrate the uni-dimensionality of a scale or subscale i.e. items of the scale can be meaningfully added to form a single score. If the items of an instrument are correctly grouped into scales, items within a particular grouping should correlate more highly with the concept they are hypothesised to represent with the other concepts measured by the instrument therefore hypothesised groupings of items are supported when correlations between an item and its own scale are

significantly higher than with other scales of the measure (Lohr, Aaronson, Alonso, Burnam, Patrick, Perrin et. al. 1996).

4.2.3 Acceptability

An instrument may be considered acceptable, (acceptability), when score distributions adequately represent the true situation of health status and/or general health perceptions in the sample being studied. One criterion is minimal floor and ceiling effects, (percentage of responses for the lowest and highest scores). In statistics, the term floor effect refers to when data cannot take on a value lower than some particular number called the floor. The term ceiling effect refers to when data cannot take on a maximum/higher value than some particular number called the ceiling. Scale score distributions are considered acceptable when scores span the full scale range, when mean scores are situated near the scale midpoint, when scale floor and ceiling effect are minimal, (not in excess of 20%, according to Holmes and Shea (1997)), and score distributions are not excessively skewed i.e. -1 to +1 range (McHorney et. al. 1994). According to Hyland (2003), scales used for cross-sectional studies need to provide good discrimination between the severities of the deficit between patients i.e. the ability to make fine-grained discriminations between the deficits of different patients increases as the number of items increases. For a scale designed for cross-sectional sensitivity, the avoidance of floor and ceiling effects is unnecessary (Hyland, 2003). If a scale is limited to items which show a deficit in the majority of patients then these items will not be able to discriminate between patients at the severe end of the scale because all patients will consistently endorse these items i.e. discrimination occurs only if some of the severe patients, the very severe patients, endorse the item and the not-so-very-severe patients do not; the same logic applies at the non-severe end of the continuum i.e. if all patients at the non-severe end report a problem then there will be no discrimination between non-severe patients, so for this reason a good cross-sectional scale should discriminate between patients over the whole of the severity range and will items relevant to all levels of severity (Hyland, 2003). In such a scale, some items will be endorsed by most patients and some items will be endorsed by very few patients to minimise floor and ceiling effects. The need to discriminate across the full severity range is particularly important where the scale is used for correlational analysis. The size of a correlation depends on the degree of variation of items in the measure and if the range is not satisfied in the questionnaire due to failure to discriminate then correlations will be reduced. For example, if respiratory function correlates poorly with QoL in the case of

severe COPD patients it may be that this is caused by lack of variation in that population of severe patients i.e. they all endorsed almost all items as being problematic (Singh, Sodergren, Hyland, Williams and Morgan, 2001). It is sometimes useful to have a health outcome measure that provides an overall picture of the patient's health outcome which can be used for clinical decision-making. Hyland (2003), states that the content of the items in a scale should be selected on the basis that they inform clinical decision-making. The inconvenience or cost of medicine can have an impact on a patient's health outcome and this may be particularly relevant for patient management (Hyland, 1992). Other than selecting items for clinical purposes, the general principle of cross-sectional comparison remains i.e. a number of items are needed that provide discrimination between the non-severe and most severe patients or at least that provides discrimination within the population that is clinically relevant. However, due to the time and cost constraints of clinical practice the scale may need to be shorter than one which can be used in research settings (Hyland, 1992).

4.2.4 Reliability: Internal Consistency and Reproducibility

In accordance with Classical Test Theory (CTT), the considerations of reliability and validity are viewed as essential elements for determining the quality of any test (Kline, 1999). Classical test theory (CTT) is a psychometric theory that predicts outcomes of psychological testing such as the difficulty of items or the ability of test-takers. Generally speaking, the aim of CTT is to understand and improve the reliability of psychological tests (Allen and Yen, 2002) and is by far the most influential theory of test scores in the social sciences. In contrast with CTT, a more recent, modern and sophisticated model referred to as item response theory (IRT) aims to supersede the traditional model and is being incorporated more and more in health outcomes measurement (Hays, Morales and Reise, 2000). Item response theory (IRT) models the relationship between latent traits and responses to test items and provide a basis for obtaining an estimate of the location of a test-taker on a given latent trait as well as the standard error of measurement of that location (Hambleton, Swaminathan and Rogers, 1991). Scores derived by CTT do not have this characteristic as scores are assessed in comparison to those of a 'norm group'; all measures derived from CTT are dependent on the sample tested and those derived from IRT are not (Embretson and Reise, 2000). Item response theory (IRT) has a number of potential advantages over CTT in assessing self-reported health outcomes that include the inclusion of items with different response formats in the same scale, assessment of person

fit and assessing change over time (Hays et. al. 2000). However, one of the main problems with IRT methods is that it is not included in the standard, user-friendly, widely available software statistical packages like SPSS (used to analyse data in this study) that routinely provide estimates of Cronbach α (discussed below).

A reliable measure is measuring something consistently i.e. the process of measurement must yield values that are consistent or remain similar under constant conditions even in an extended series of repeated assessments (Testa and Simonson, 1996). The reliability of an instrument is defined as the extent to which it is free from random error/variance in the construct; as reliability increases or decreases, scores are more or less consistent (Cortina, 1993). In keeping with this definition, reliability co-efficients estimate the proportion of total score variance that is due to true score variance. In practice, the evaluation of reliability is in terms of two different aspects of a measure: internal consistency and reproducibility (Lohr et. al. 1996). Internal consistency is the extent to which items are interrelated. The most commonly used index of reliability is Cronbach α which is equivalent to the mean of all possible split-half coefficients (correlating performance on two halves of a test). Cronbach α provides an estimate of reliability based on all possible correlations between two sets of items within scale (Lohr et. al. 1996). The formula for α takes into account the number of items; the more items, the more reliable a scale will be. Most scales have acceptable levels of reliability above 0.7 and the majority are above 0.9 (Garratt et. al. 2002; Cortina, 1993). Alpha co-efficients exceeding 0.80 are considered acceptable for scales used to make group comparisons whereas the more stringent criterion of 0.90 – 0.95 is required for scales used to make individual comparisons (Lohr et. al. 1996).

Reproducibility evaluates whether an instrument yields the same results on repeated assessments upon the assumption that respondents have not changed on the domain being measured (Spearman, 1904). An example of reproducibility is test-retest reproducibility. This is thought to be the most relevant form of reproducibility for patient based outcome measures because parallel forms of measures do not usually exist and most measures are self-completed. Test-retest reproducibility is examined by re-administering the instrument to the same respondents after a specified period. If the results from the two time points have high agreement, the instrument demonstrates high test-retest reproducibility. There

seems to be no rule about the length of the test re-test interval but it does makes sense for it to be sufficiently long enough to ensure that respondents are unlikely to recall their previous answers and not so long so that changes in health have occurred; a recommended range of interval is between 2 and 14 days in accordance with the nature of the research. Correlation co-efficients are frequently used to measure test-retest reproducibility although critics recommend a measure of agreement named intraclass correlation co-efficient (ICC) as high correlations can be due to systematic errors (Bland and Altman, 1986). Intraclass correlation co-efficient (ICC), is a statistic that determines inter-rater reliability and attempts to determine how much of the total variability in the scores is due to true differences between individuals and how much to variability in measurement; the minimum standards for reproducibility are 0.80 for individual comparisons and 0.90-0.95 for group comparisons (Shrout and Fleiss, 1979).

4.2.5 Validity

There are three types of validity: content, criterion and construct.

Content validity is simply a demonstration that the items of a test are drawn from the domain/construct being measured. For example, in this research BTM patients are the expert opinion as they were asked about the way thalassaemia impacts upon their life. By involving large samples of patients in research, omission of important domains is reduced and good content validity likely.

Criterion validity examines the degree to which a measure correlates with gold- standard measures, or criterion measures, (well-established and well-validated measures), obtained at a similar point in time as the measure being validated (concurrent validity), or at a later time (predictive validity). As no 'gold standard' measure of health status exists (Guyatt, Kirschner, Jaeschke, 1992), other approaches are recommended to evaluate validity (Patrick and Erickson, 1993).

Construct validity takes place when an investigator believes that his/her instrument reflects a particular construct to which are attached certain meanings; the proposed interpretation generates specific testable hypotheses which are means of confirming or disconfirming the claim (Cronbach and Meehl, 1955) i.e. a measure has construct validity if it is related to other variables as required by theory; it involves testing hypothesis about how the

instrument is expected to perform and to examine the extent to which empirical data support these hypotheses. If testing shows negative evidence, the investigator may conclude that the test itself does not measure the construct variable and/or the theoretical network which generated the hypothesis. Cronbach and Meehl (1955) have stated that many types of evidence are relevant to construct validity including content validity and more importantly criterion (concurrent) validity; high correlations may constitute either favourable or unfavourable evidence for the proposed interpretation depending on the theory surrounding the construct, and that construct validity cannot generally be expressed in the form of a single correlation co-efficient. The authors conclude that *"construct validity cannot be an entirely quantitative process" (p300)* (Cronbach and Meehl, 1955). Two dominant ways of determining construct validity have been identified: internal and external validity (Bohrnstedt, 1983). In the absence of gold standard measures of health status both types of validity should be evaluated as they are independent, complementary and on their own insufficient (Bohrnstedt, 1983). Internal construct validity involves statistical analyses of scale scores to determine whether hypotheses concerning the theoretical structure of the instrument are supported. These analyses can include PCA. Factor analysis can confirm whether the instrument consists of distinct scales that have items consistent with those hypothesised and if item discrimination is supported (Bohrnstedt, 1983). Further evidence for construct validity is provided if correlations between scales of an instrument conform to hypotheses about the magnitude and pattern of correlations. External construct validity/clinical tests of validity examine the relationships between the score on a given scale and external variables measured simultaneously. This is an attempt to demonstrate that the instrument measures what it is supposed to measure (convergent validity), does not measure what it is not designed to measure (discriminant validity) and produces results consistent with theoretical expectations/hypothesis testing.

4.2.6 Responsiveness (Sensitivity)

Responsiveness is the ability of an instrument to measure clinically important change over time. While reliability and validity are the major determinants of the scientific robustness of a measure the ability of an instrument to detect clinically significant change is also essential when evaluating the relative benefits of different intervention (Hadorn and Uerbersax, 1995). This is particularly important when treatments are associated with small but significant benefits which may be undetected by measures that are unresponsive. In such cases, a clinically appropriate, reliable and valid but unresponsive instrument is of

limited value. A psychometric property useful for evaluating clinical significance is demonstrated validity including sensitivity or responsiveness to clinically relevant change (Hadorn and Uerbersax, 1995). Conventional validity testing does not provide an evaluation of the significance of change i.e. whether or not the change is minimally important to the decision of the patient or the decision maker (Wyrwich, Bullinger, Aaronson, Hays, Patrick, Symonds et. al. 2005). Responsiveness is a measure of the association between the change in the observed score and the change in the value of health outcome. Since health outcome is intangible, a change in health outcome is not observable. Therefore, responsiveness is often assessed by changing a criterion variable when there is evidence to support a causal link between a criterion variable and an 'observable' change e.g. clinical status measures or patient perceived transitions or changes (Wyrwich et. al. 2005). A health outcome scale should be constructed to be responsive, that is objective clinical treatments produce anticipated change or differences in the scale (Testa and Simonson, 1996). The responsiveness of a measure may be influenced by baseline health status and the magnitude of change may depend on the patient's initial health status (Lydick, 2000). Although a measure may be responsive to changes in QoL, graduations in the metric of the observed score may not be adequate to reflect these changes; sensitivity refers to the ability of the measurement to reflect true changes or differences in QoL (Testa and Simonson, 1996). Problems such as an inadequate range or the existence of ceiling and floor effects in QoL scales can mask important and therapeutically meaningful change in health outcome (Testa and Simonson, 1996). In addition, meaningful changes for a single patient are typically much smaller than differences between patients therefore intervention studies require a greater sensitivity of measurement (Testa and Simonson, 1996). For example, on the SF-36, the physical functioning (PF) scale has a mean of 94 for men 18-24 years of age and a mean of 80 for men aged 55-64 years of age (Ware et. al. 1995); the PF scale ranges from 0-100 with higher values indicating better functioning. Aging by 40 years is associated with a 14% decline on the absolute scale.

The most common method of determining responsiveness is to examine the change of scores following an intervention of known efficacy; results are reported as an effect size (a standardised change score). Responsiveness measures using effect sizes are termed prospective methods (Norman, Stratford, Regehr, 1997).

4.3 Theoretical Approach, Psychometric Considerations, Assessment of Health Outcomes and Key concepts

The health outcome literature advocates a robust and rigorous programme of instrument development and testing and most health outcome measures are developed within the psychometric tradition (Juniper, Guyatt and Jaeschke, 1996; McDowell and Newell, 1987). However, it has been argued that scales developed within the psychometric tradition often omit items important to the beliefs and values of individual patients (Gill, 1995; Hunt, McEwan and McKenna, 1985) therefore the psychometric aim of internal reliability is in conflict with the goals of achieving comprehensiveness and content validity (Brazier and Deverill, 1999) (discussed in section 4.2.5). These arguments have brought forth individualised, patient-tailored QoL assessment techniques like the Quality of Life Assessment Schedule (QOLAS) (Selai, Trimble, Rossor and Harvey, 2001).

4.3.1 Factor Analysis

Factor analysis, a type of EFA originates in, and is traditionally linked to psychometrics and is used in applied sciences that deal with large quantities of data and can assess the validity of an instrument developed by finding if the instrument measures the hypothesised factors. It is a statistical method used to describe variability among observed variables in terms of fewer unobserved variables called factors. In psychology, factor analysis is used to group items into subscales identifying 'factors' that explain a variety of results on different tests. Items analysed in an EFA determine the underlying dimensions (factors) of an instrument. Factors are extracted in a decreasing magnitude. As EFA is used to reduce the number of items to develop scales, it is a technique where a number of decisions undertaken can have a substantial impact on the results and their interpretation: the resulting item structure of the instrument depends on choices regarding the factor model e.g. principal components analysis (PCA) (discussed below), the number of factors that are appropriate, the rotation method selected i.e. orthogonal or oblique (discussed below) and the other items that are included in the analysis (Preacher and MacCallum, 2003). In addition, the interrelationship of variables is left unspecified and it is impossible to test directly alternative theoretical structures underlying the data (deVet, Ader, Terwee and Pouwer, 2005).

Principal component analysis (PCA) involves a mathematical procedure that transforms a number of possibly correlated variables into a smaller number of uncorrelated variables

called principal components (Pearson, 1901). The first principal component accounts for as much of the variability in the data as possible and each succeeding component accounts for as much of the remaining variability as possible. Principal component analysis (PCA) is mostly used as a tool in EFA and for making predictive models and involves the calculation of the eigenvalue decomposition of the data covariance/dispersion matrix. The results of a PCA are usually discussed in terms of component scores and loadings and they reveal the internal structure of the data in a way which best explains the variance in the data. It analyses all variance in the items. This method of extraction is usually preferred when trying to reduce the items to some composite scores for subsequent analysis.

Rotation is used to adjust and fine-tune the factor loadings so that the factors are more interpretable. Commonly and traditionally, varimax or orthogonal factor rotation is applied when developing and validating health outcome measures e.g. Younossi, Guyatt, Kiwi and Boparai and King (1999) (chronic liver disease (CLD)), Gee, Abbott, Conway, Etherington and Webb (2000) (CF) and Burroughs, Desikan, Waterman, Gilin and McGill (2004) (diabetes). Orthogonal rotation assumes that the factors are at right angles to each other; the factors are not correlated i.e. factor loadings from a set of variables are plotted on a two dimensional set of axes, the variables that load on one factor would lie along one axis and the variables that load on the other factor would lie along the other. Each factor is independent of, or orthogonal to, all other factors i.e. no correlation between factors. The correlation between the factors is determined to be zero. The aim of this type of rotation is to minimise the number of variables that load highly on a factor. Alternatively, oblique or oblimin factor rotation relaxes the assumption that the extracted factors must be orthogonal/correlated (over 0.3). Researchers that have used this type of rotation when developing and validating health outcome measures include, Hays, Kallich, Mapes, Coons and Carter (1994) (kidney disease), Chren, Lasek, Sahay and Sands (2001) (skin diseases), and Smith (2002) (inflammatory bowel disease (IBD)). An advantage of orthogonal factor rotation over oblique (oblimin) factor rotation is that factor loadings, which are product moment correlations between scales and factors, can be squared and summed across factors to estimate the amount of variance in each scale accounted for by each factor and the amount of variance in each scale is explained by all factors i.e. this maximises the variance of the squared elements in the columns of a factor matrix. As a result, factor content and implications for the interpretation of each scale are more straightforward. However, the advantage of oblique (oblimin) rotation over orthogonal rotation is that one

set of variables may lie along an axis, while the other set may lie along a 45 degree angle to the axes. Rather than arbitrarily constraining and maintaining the factor rotation to an orthogonal (90 degree angle/axes) the oblique solution allows for correlations between the factors and can therefore identify the extent to which each of the factors are correlated. This often simplifies the factor solution since many attitudinal dimensions are in fact likely to be correlated. Unlike orthogonal rotation, the pattern matrix and the structure matrix are not equal after oblique rotation (Rummel, 1970; Tabachnick and Fidell, 2001). Only the pattern matrix needs be examined since it allows for the easiest interpretation of factors; the pattern matrices found using oblique rotation are more interpretable than the orthogonal rotation solutions with fewer variables loading significantly on more than one factor (Rummel, 1970; Tabachnick and Fidell, 2001).

The main strengths of factor analysis are two-fold: variables can be reduced by combining two or more variables into a single factor and the analysis can identify groups of inter-related variables to see how they are related to each other (Thompson, 2004). However, factor analysis also has its weaknesses. Factor analysis can be only as good as the data allows i.e. rotation represents different underlying processes yet all rotations are equally valid outcomes of standard factor analysis optimisation so it may be impossible to pick the proper rotation using factor analysis alone. Interpreting factor analysis is based on using a heuristic which is a solution that is *"convenient even if not absolutely true"* (Darlington, 1973). More than one interpretation can be made of the same data factored the same way, and factor analysis cannot identify causality. One of the main deficiencies in various factor analysis is a lack of consensus in cutting points for determining the number of latent factors (Thompson, 2004). A usual procedure is to stop factoring when eigenvalues drop below one because the original sphere shrinks; the problem is more of interpretations than utilising a method.

A review by deVet et. al. (2005) focused on the appropriate use of factor analysis in the psychosocial and medical sciences where constructs like QoL are measured by means of multi-item health status questionnaires. They concluded the following. The aim of a factor analysis may be one of the following: (1) pure data reduction, (2) assessment of the factor structure (dimensions), (3) investigating whether a 'tool' shows the same dimensions across different groups (structural reliability), or (4) to determine content specific factor loadings to be used as weighing factors for the location of the physical and mental health

scores (deVet et. al. 2005). Principal component analysis (PCA) is adequate in the situation of the development of an instrument (second aim) and also to determine factor loadings for the instrument to be used in another situation (fourth aim). However, in order to investigate whether the questionnaire shows the same, known, dimensions across different cultural populations or disease groups (third aim), confirmatory factor analysis (CFA) is more appropriate than EFA (deVet et. al. 2005) therefore CFA should be performed at a later stage after an instrument has been developed to assess the underlying structure of the final instrument (deVet et. al. 2005; Kline, 1999). As stated briefly in chapter 3, (section 3.4.2.1.1.4.1), CFA is a special form of factor analysis used to assess the number of factors and the loadings of variables and allows for the explicit constraint of certain loadings to be zero (chapter 4, above section 4.4.2).

4.4 Health Outcome Measures: Patient-Reported Outcome Measures (PROMs) and Quality of Life (QoL) Scales

Patient-Reported Outcome Measures (PROMs) employ short, self-completed questionnaires which measure the patient's health status at a single point in time. These instruments can be completed by a patient or individual about themselves or by others on their behalf. They are used to derive measures of the outcomes of specific interventions (Guyatt et. al. 2002). A range of PROMs are available, some of which are generic, applicable to, and comparable across a range of treatments or conditions (Riazi et. al. 2002) while others are condition-specific and sensitive to changes in health status (Guyatt et. al. 2002). Generic and disease-specific outcome measures have been discussed at length in chapter 3, sections 3.4.2.1 through to 3.4.2.1.2. The PROMs used to collect data from patients will comprise a condition-specific instrument and/or generic instrument in addition to more general patient-specific information. The patient-specific questions comprise sociodemographic questions about the patient's general health, previous surgery for the target condition, co-morbidity and length of time with the condition.

Regular use of PROMs by health care providers in their routine practice may help to improve the quality of care. Marshall, Haywood and Fitzpatrick (2005) suggested that more evidence is needed before routine use of PROMs can be recommended. On the basis of this, they undertook a structured review to examine whether, and how regular use of PROMs might improve routine practice. The method adopted was a systematic search of Medline for the years 1976–2004. Controlled trials in English evaluating the impact of

clinical use of PROMs on routine practice were included. Data regarding study design, characteristics of PROMs feedback, patient populations and study results were extracted by three reviewers. Feedback of PROMs results to healthcare providers appears to have a substantial impact on some processes of care particularly on diagnosis of mental health conditions. However, the impact on patient health status is less consistent. Most of the published studies evaluated PROMs as a one-off screening technology and measured only provider behaviours and patient health outcomes. In conclusion, the pattern of results suggests a general lack of clarity in the field especially regarding appropriate goals for PROMs and the mechanisms by which they might achieve them. To fully evaluate their role in routine practice, studies need to use PROMs that capture issues of importance to patients and to measure impacts relating to the patient–provider relationship and patient contributions to their well-being, and until studies evaluate PROMs as a means facilitate patient-centred care, their full potential in clinical practice will remain unknown (Marshall et. al. 2005. In February 2009, guidance for the NHS by the Department of Health (DoH) reported on the collection of PROMs. According to the new guidance there are a range of potential applications and benefits to routine collection of PROMs data including assessing the quality of clinical providers of elective procedures that can be applied to the data to endure comparability by accounting for differences in risk and case-mix, to research that works and the efficacy and cost-effectiveness of different technical approaches to care that can be evaluated using PROMs in association with other measures that assess what would have happened to patients in the absence of treatment or with alternative treatment, to aid demand management. In addition, PROMs data can be used to establish whether referrals for elective procedures are appropriate by examining variation in baseline PROMs scores across the country and comparing against benchmarks. The new guidance supports the NHS to collect patient feedback on the success of their operations (Garratt, 2009).

Clinical trials and similar forms of evaluative study should incorporate the patient's perspective of outcome (Fitzpatrick, Davey, Buxton and Jones, 2001). According to Garratt (2009), the complete assessment of the benefits of an intervention must include evidence of the impact on the patient’s health status. Such measures provide a means of gaining an insight into the way patients perceive their health and the impact that treatments or adjustments to lifestyle have on their QoL (Garratt et. al. 2002). These terms refer to experiences of illness such as pain, fatigue and disability and also broader aspects of the individual's physical, emotional and social well-being (Sanders, Egger, Donovan, Tallon

and Frankel, 1998; Fitzpatrick, Davey, Buxton and Jones, 1998). Unlike conventional medical indicators, these broader impacts of illness and treatment need to be assessed and reported by the patient where possible (Garratt et. al. 2002). Several reviews have criticised researchers for their failure to use appropriate measures of patient outcome in evaluations purporting to address the impact of interventions by assessing outcomes of concern to patients in clinical trials (Fitzpatrick et. al. 1998), in critical care (Hayes, Black, Jenkinson, Young, Rowan, Daly, et. al. 2000), in epileptic patients (Baker, Hesdon, and Marson, 2000), and stroke patients (Duncan, Jorgensen and Wade, 2000). Trials may either neglect outcomes other than conventional, clinical, laboratory and radiological measures or may use limited, inappropriate or poorly validated indicators of the patient's own experiences; it is not clear whether this failure to incorporate patients' assessments of outcome arises because appropriate methods do not exist or because methods exist but have not been widely adopted (Garratt et. al. 2002). There may be practical or logistical difficulties in obtaining reliable reports of outcomes from patients and there may also be differences in the perceived importance of health outcome related constructs in different aspects of clinical and evaluative research (Garratt et. al. 2002). In recent years, enthusiasm has been expressed for the potential of questionnaires to provide evidence of outcomes from the patient's perspective and as it is not clear how well-developed these methods are and whether they are available across the full range of health problems. Garratt et. al. (2002) undertook an extensive review to describe the extent to which patient-assessed outcome measures have been developed and applied and examined whether such instruments are available for all aspects of clinical research. They concluded that (1) the huge growth in the number of patient-assessed measures of health outcome has obvious benefits in terms of the availability of measures for specific populations however potential users require guidance particularly when faced with multiple measures, (2) structured reviews together with recommendations based on patient and professional consensus are required for the effective application of measures, (3) concurrent evaluation can also help to determine the most suitable measure for a particular application and (4) researchers should undertake comprehensive literature searches to ascertain whether a suitable measure is available before they decide to develop a new one.

There are numerous health outcome measures instruments available developed using the psychometric theory model but little guidance for the selection between them (Garratt et. al. 2002) therefore researchers need to be able to select scales for themselves. As there is

no such thing as a 'best scale', scales are best suited to a particular purpose (Guyatt et. al. 1992). Authors of scales provide psychometric data of varying kinds and although these types of questionnaires should satisfy certain minimum criteria they do not form an essential part of choosing between scales. However, most scales have acceptable levels of reliability above 0.7 and the majority are above 0.9 e.g. the SF-36 (Tsai, Bayliss and Ware, 1997; McHorney et al. 1994; Ware et al., 1993), and the WHOQoL-100 (WHOQoL Group, 1998), and are capable of demonstrating validating correlations with other health outcome scales such as the SF-36 (Ware et al., 1993), (simply because all self-report measures are strongly correlated with the personality trait of negative affectivity like neuroticism, depression and anxiety so scales inter-correlate amongst themselves (Hyland, 2003)). Scales suited for longitudinal purpose/use i.e. clinical trials and audit, consider the relationship between item-set, population and treatment. For this purpose, Hyland (2003) recommends that scales need to be short with extended response options and that floor and ceiling effects must be minimal. More importantly, in the case of longitudinal research, Hyland (2003) recommends that a scale is chosen so items are appropriate for the population and type of improvement predicted from treatment. For cross-sectional purpose/use i.e. population and correlational studies and clinical use scales may have a wide range of items and could be longer; response options can be simpler to allow a larger set of items (Hyland, 2003). In the case of cross-sectional research, the important factor is to choose a scale that has a full and varied range of items which apply to the kind of discrimination needed (Hyland, 2003). In summary, the psychometric properties of a scale influence its use (Hyland, 2003).

4.4.1 Examples of Health Outcome Measurement Tools and their Psychometric Considerations

So far, this chapter has discussed psychometric theory and health outcome measures in general. What follows are examples of such measures from the literature. Some of these measures have already been discussed in chapter 3, sections 3.4.2.1.1.1 through to 3.4.2.1.1.5.1, so there is some overlap and repetition.

4.4.1.1 The SF-36

Since the 1970s, the focus of healthcare evaluation has moved to the measurement of patient function in terms of how patients perform the daily activities of their lives and an evaluation of their own health in general (Stewart and Ware, 1992). The primary source of

this information has been identified by Ware et. al. (1987), as standardised surveys, like the SF-36, for which psychometric techniques of scale construction e.g. factor analyses, are highly appropriate (Stewart and Ware, 1992). The SF-36 (already discussed in sections 3.4.2.1.1.1 and 3.4.2.1.1.1.1.), is a multi-purpose, short-form health survey whose major objective in construction was to satisfy the minimum psychometric standards necessary for group comparisons to allow comparitability of results (Stewart & Ware, 1992) i.e. scaling and scoring assumptions, reliability and confidence intervals and validity. The eight health concepts were selected from 40 included in the MOS. Those chosen represent the most frequently measured concepts in widely-used health surveys and those most affected by disease and treatment (Ware et al. 1993; Ware, 1995). The questionnaire items selected also represent multiple operational indicators of health including behavioural function and dysfunction, distress and well-being, objective reports and subjective rating and both favourable and unfavourable self-evaluations of general health status (Ware et al. 1993).

Garratt, Ruta, Abdalla, Buckingham and Russell (1993) aimed to assess the SF-36 health survey questionnaire as an outcome measure suitable for routine use within the NHS. They assessed its validity, reliability, and acceptability as a measure of patient outcome in a broad sample of patients suffering from four common clinical conditions: low back pain, menorrhagia (abnormally heavy and prolonged menstrual period at regular intervals) (BMA, 2002), suspected peptic ulcer, or varicose veins, and a comparison sample of 900 members of the general population. The SF-36 was found to satisfy rigorous psychometric criteria for validity and internal consistency. Clinical validity was shown by the distinctive profiles generated for each condition, each of which differed from that in the general population in a predictable manner. These results provide support for the SF-36 as a potential measure of patient outcome within the NHS. Whilst the SF-36 appeared to be acceptable to patients, internally consistent and a valid measure of the health status of a wide range of patients before it could be used in the NHS its sensitivity to changes in health status over time needed to be tested. The first evidence of the responsiveness (sensitivity to clinical change), of the SF-36 questionnaire to changes in perceived health status in a patient population with one of four conditions, (low back pain, menorrhagia suspected peptic ulcer, or varicose veins), in the UK was undertaken by Garratt, Ruta, Abdalla and Russell (1994). Changes across the SF-36 questionnaire were associated with self-reported changes in health as measured by the transition question. The questionnaire

identified significant improvements in health status for all four clinical conditions in referred or non-referred patients.

The reliability of the eight scales and two summary measures in the SF-36 has been estimated using both internal consistency (0.68-0.93) and test-retest methods. With rare exceptions, published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons in more than 25 studies (Tsai, Bayliss and Ware, 1997); most have exceeded 0.80 in tests of reliability across diverse patient groups (McHorney et. al. 1994). Reliability estimates for physical and mental summary scores usually exceed 0.90 (Ware, Kosinski and Keller, 1994). All items have been shown to correlate substantially (greater than 0.40) with their hypothesised scales. The SF-36 has proven to be both reliable and valid in the assessment of QoL. Internal consistency reliabilities for each of the instrument's eight scales were 0.78 or greater in the MOS (Hays, Sherbourne and Mazel, 1993). Multitrait scaling analyses, (a straightforward yet well-designed methodology for scale analysis; the procedure involves examining item frequencies, item and scale descriptive statistics like the mean, standard deviation and variance, scale internal consistency estimates, item-scale correlations and correlations among scales (Hays and Hayashi, 1990)), supported item discrimination across scales (Ware, Snow and Kosinki, 1993). The trends in reliability coefficients for the SF-36 scales and summary measures summarised above have also been replicated across 24 patient groups differing in sociodemographic characteristics and diagnoses (McHorney et. al. 1994). Studies to date have yielded content, concurrent, criterion and predictive evidence of validity e.g. Ware et al. (1993) and Ware et al. (1994). Multiple empirical studies have provided support for the construct validity of the SF-36 e.g. McHorney, Ware, Rogers et. al. (1992), McHorney et. al. (1994). It should be noted that the SF-36 may not be adequately sensitive to the specific QoL concerns of patients groups like those with end stage renal disease (ESRD) therefore disease-specific instruments are more likely to be relevant and responsive to clinically important changes in QoL (Edgell, Coons, Carter, Kallich, Mapes, Damush and Hays, 1996).

The validity and the interpretation of each of the eight scales and the two summary measures has been shown to differ in factor analytic studies of their construct validity e.g. the mental health, role limitations due to emotional problems and social functioning scales have been shown to be the most valid of the SF-36 scales as mental health measures and

the physical functioning, role limitations due to physical problems and bodily pain scales have been shown to be the most valid SF-36 scales for measuring physical health (McHorney, Ware and Raczek, 1993; Ware, Kosinski, Bayliss, McHorney, Rogers and Raczek, 1995). Relative to other published measures, SF-36 scales have performed well in most tests published to date e.g. Brazier, Harper, Jones, O'Cathain, Thomas, Usherwood and Westlake, (1992) (in primary care) and Krousel-Wood, McCune, Abdoh, and Re, (1994) (back pain). As cited in the SF-36 bibliography (Turner-Bowker, Bartley, and Ware, 2002), studies have compared the SF-36 with over 225 other measures.

The usefulness of the SF-36 in comparing general and specific population groups relative to longer surveys was examined. Some of the SF-36 scales have been shown to have 10-20% less precision than the long-form MOS measures that SF-36 scales were constructed to reproduce (McHorney, Ware, Rogers, Raczek and Lu, 1992). McHorney et. al. (1992) note the ceiling and floor effects in the original Version 1.0 and suggest that it may be a limitation of the scale when used in some generic populations. However, the SF-36 scales appear to be increasingly accepted as valid health measures for the purpose of documenting disease burden.

Publications have reported descriptive data for patients with hypertension and cardiac disease e.g. Krousel-Wood and Re (1994) and Jette and Downing (1994), epilepsy e.g. Vickrey, Hays, Graber, Rausch, Engel, Brook (1992) and Wagner, Keller, Kosinski, Baker, Jacoby, Chadwick and Ware (1995), diabetes mellitus I and II e.g. Nerenz, Repasky, Whitehouse and Kahkonen (1992) and Jacobson, deGroot and Samson (1994), lung disease e.g. Viramontes and O'Brien (1994), and for renal disease e.g. Kurtin, Davies, Meyer, DeGiacomo and Kantz (1992) and Meyer, Espindle, DeGiacomo, Jenuleson, Kurtin and Davies (1994). Population and large-group descriptive studies and clinical trials to date demonstrate that the SF-36 is useful for descriptive purposes such as documenting differences between sick and well patients and for estimating the relative burden of different medical conditions (Turner-Bowker et. al. 2002). Although its usefulness in capturing differences in health outcomes in clinical trials was doubted by many, experience to date from nearly 400 randomised controlled clinical trials suggests that the SF-36 is also a useful tool for evaluating the benefits of alternative treatments (Turner-Bowker et. al. 2002).

4.4.1.2 The WHOQOL-100

The World Health Organisation Quality of Life assessment (WHOQOL-100) (Power, Bullinger, Harper and The WHO Quality of Life Group (WHOQoL Group), (1999), (already discussed in sections 3.4.2.1.1.4 and 3.4.2.1.1.4.1), was developed simultaneously in 15 international centres (stated in section 3.4.2.1.1.4). A hundred items were grouped into one facet examining overall QoL and general health perceptions and 24 QoL facets. Internal reliabilities of the 25 facets, as measured by Cronbach α,, range from 0.65 to 0.93. The universality of the WHOQOL-100 was examined in several ways and was found to be remarkably adept at identifying facets of QoL which are cross-culturally important (WHOQOL Group 1998, Power et. al. 1999). Unpublished data show that test-retest reliability is very good (Power et. al. 1999). In a separate survey of the general population in Britain, the WHOQOL-100 was shown to have excellent internal reliability (Skevington, 1999). The scores discriminate well between sick and well people and concur with reported health status. Subsequent studies have been conducted. Skevington, Carse and Williams (2001a) report that the WHOQOL-100 is a reliable and valid measure of the effects of a pain management program in patients suffering from chronic pain. The WHOQOL-100 is also an excellent instrument for measuring QoL in depressed patients e.g. Skevington and Wright (2001b); Bonicatto, Dew, Zarateigui, Lorenzo and Pecina (2001). The WHOQOL-100 proved to be a more sensitive measure of change in QoL following liver transplantation than the SF-36 (O'Carroll, Cossar, Couston and Hayes, 2000). Struttmann, Fabro, Romieu, de Roquefeuil, Touchon, Dandekar, and Ritchie (1999) used the WHOQOL-100 to assess QoL in patients with either dementia or cancer. They concluded that the instrument is a powerful tool for assessing QoL in these diseases. The WHOQOL-100 has become one of the standard and most useful QoL measures in existence due to its international and multicultural aspects and demonstrated reliability and validity (Skevington et. al. 2001a).

4.4.1.3 The Health Utilities Index (HUI)

The HUI (Horsman, Furlong, Feeny and Torrance, 2003) is a family of generic health profiles and preference based systems for the purposes of measuring health status, reporting QoL and producing utility scores. The index evolved in response to the need for a standardised system to measure health status to describe the experience of patients undergoing therapy, long-term outcomes associated with disease or therapy, the efficacy, effectiveness and efficacy of healthcare interventions and the health status of general

populations. The HUI has been used in hundreds of clinical studies veering a wide range of health problems and in numerous large general population surveys since 1990 (Horsman et. al. 2003). The HUI measures have been found to have strong theoretical foundations, are reliable e.g. Boyle, Furlong, Feeny, Torrance and Hatcher (1995) and are well accepted by patients and professionals (Horsman et. al. 2003). Hundreds of studies worldwide annotate the evidence of HUI validity namely construct validity e.g. Grima, Torrance, Francis, Rice, Rosner and LaFortune (2000) (MS), Supina, Feeny, Carroll and Johnson, (2006) (type I diabetes) and predictive validity e.g. Kaplan, Berthelot, Feeny, McFarland, and Khan (2007) (mortality study). The HUI has been shown to be responsive to changes in health status over time in clinical studies for a wide variety of conditions in a large number of countries e.g. Barr, Saleh, Furlong, Horsman, Sek, Pai and Walker (2002) (haemophilia, a blood condition in which an essential clotting factor is either partly or completely missing (BMA, 2002)), Kaplan, Groessl, Sengupta, Sieber, Ganiats (2005) (rheumatoid arthritis).

4.4.1.4 Examples of Disease Specific Measures

Until the work of Grootscholten et. al. (2003) reliable and sensitive measures for the evaluation of QoL in patients with SLE (discussed in section 3.4.2.1.2), did not exist. Their study describes the development and validation of such a disease-specific questionnaire (SLE Symptom Checklist (SSC)), which assesses the presence and burden of 38 disease and treatment-related symptom. The psychometric technique of scale construction was EFA, oblique minus rotation. Reliability and reproducibility were tested. The internal consistency was high (Cronbach α coefficients 0.89) and test-retest reliability (Pearson product-moment correlation coefficient between 0.67 and 0.87) were satisfactory. Although discriminant validity was not demonstrated by the data, concurrent validity was supported by the finding that significant but moderate correlations with other measures of subjective well-being and functional status like the SF-36, underscoring the fact that the SSC provides unique information. The SSC was also shown to demonstrate short-term stability (1 month interval) (reproducibility). Sensitivity to change needs to be studied in a larger group of patients as responsiveness was measured in 17 patients; a significant change in number of symptoms and total distress level was found. It is concluded that the SSC has satisfactory psychometric properties and appears suitable for both clinical and research purposes.

Patient–generated dermatology quality of life scales (DQOLS) (Morgan, McCreedy, Simpson and Hay, 1997), were developed to assess the impact of skin conditions on patients' psychosocial state and everyday activities. The items were derived from the self-reported impacts of their skin condition by 50 dermatology out-patients. The resulting 17 psychosocial items and 12 activities items were assigned five-point scales and self-completed by 118 out-patients. Factor analysis using varimax rotation grouped the items into four psychosocial subscales (embarrassment, despair, irritableness, distress), and four activities subscales (everyday, summer, social, sexual). Tests of the psychometric properties indicated that the internal consistency of responses was high with Cronbach α coefficients of 0.92 for the 17 psychosocial items and 0.83 for the 12 activity items. Construct validity was confirmed by the ability of the scales to identify clinically expected differences and their greater sensitivity to the impacts of skin problems compared with a widely used generic health status measure, the SF-36. The DQOLS thus forms a robust measure of patient–perceived impact.

Gee et. al. (2000) developed and validated a disease-specific QoL measure for adults and adolescents with cystic fibrosis, the Cystic Fibrosis Quality of Life questionnaire (CFQoL). Areas of concern to adults and adolescents with CF were identified by unstructured interviews, self-administered questionnaires, consultation with multidisciplinary specialist staff, a review of the relevant literature and examination of other HRQoL measures. Items for the questionnaire were generated on the basis of this process. The full testing and validation of the CFQoL questionnaire took place over four phases: (1) initial item generation and testing of a preliminary questionnaire, (2) testing and validation of the second version of the questionnaire, (3) test-retest reliability of a third and final version of the questionnaire and (4) sensitivity testing of the final version of the questionnaire. Nine domains of functioning were identified using PCA with varimax rotation. Internal reliability of the identified 9 domains was demonstrated using Cronbach α coefficients (0.72-0.92) and item to total domain score correlations were strong. Concurrent validity (0.64-0.74), discriminatory ability between different levels of disease severity, sensitivity across short-lived changes in patients' health (effect size range, moderate d = 0.56 to large d = 1.95) and test-retest reliability (0.74-0.96) were also found to be robust therefore this measure may be useful in clinical trials and longitudinal studies.

4.5 Conclusions

Similar to the majority of psychological variables, health outcome cannot be measured directly; it may only be measured by asking a series of questions to identified groups of participants (Testa and Simonson, 1996). According to Ware (1995) and Gill and Feinstein (1994) consensus advice by researchers is that instruments developed must be formally evaluated to ensure that they measure the outcome of interest in a manner that is psychometrically sound. There is a host of outcome measures in the literature from the last 15-20 years each pertaining their own psychometric properties. Researchers are invited to choose the most appropriate tool(s) for their work.

4.6 Study Aims and Objectives

Disease-specific measures of health outcome have important implications, yet to date, no such measure has been developed for patients with BTM. Medical care for patients with BTM has improved (Porter and Davis, 2002) but little is known about the impact of thalassaemia on patients' QoL although it appears to be one of the ultimate outcomes for patients with chronic illness in general (Jenkins, 1992).

The general aim and objective of this project is to develop and validate a suitable patient-based health outcome measure for adults with BTM. The measure will be disease-specific and patients will self-report on the impact of BTM. Evidence has shown that the availability of a reliable, valid and responsive patient-based outcome measure is important to an improved understanding of the impact of the illness in general e.g. Telfer et. al. (2005). The instrument shall attempt to be short, multidimensional, sensitive to the major features and changes of BTM that affect patients' lives on a daily basis and applicable in a range of cultural and social settings.

This chapter has given a synopsis of psychometric theory. Chapter 5 now discusses the first stage of the development of the Thalassaemia Adult Life Index **(**THALI-35).

Chapter 5
Development of the Thalassaemia Adult Life Index (THALI-35)
Stage 1: Item Generation
Chapter Overview

This chapter presents the methods and results of stage 1 of 3 of the development of the Thalassaemia Adult Life Index **(**THALI-35), a 35-item questionnaire designed to assess the impact of BTM on adult patient's lives. The THALI-35 was developed and tested in three stages. In stage 1 (item generation), a 63-item questionnaire was generated from 16 patient interviews which were guided by an interview schedule that was devised from previous health outcome measurement and development research, multidisciplinary expert opinion and a comprehensive review of the literature. In stage 2 (item reduction), the questionnaire was administered by postal survey to a community sample of 381 adult members from the UKTS. Item reduction techniques were used to develop the 35-item measure (THALI) that essentially covers the physical, psychological and social impact of BTM. In stage 3 (validation), an initial evaluation of the psychometric properties of the THALI-35 were assessed in a clinical sample of 35 adult patients with BTM. Chapters 6 and 7 present the methods and results of stages 2 and 3 of the THALI-35, respectively.

5.1 Introduction

5.1.1 Background

Quality of Life (QoL) consists of physical and psychosocial characteristics that have become very important in healthcare as health problems place significant restrictions on patients' lives (Hart, Bilo, Redekop, Stolk, Assink and Meyboom-de Jong, 2003). Chapter 2, sections 2.1.2 and 2.2 have considered the psychosocial impact of BTM and chronic illness on patients' lives; chapter 3, sections 3.1.1 and 3.5.1 have considered QoL as an outcome variable for healthcare intervention and research in chronic illness in general and the examination of the role of QoL in BTM patients in particular. The increasing interest in measures reflecting the personal viewpoint of patients' health (Panepinto, 2008) has led to a demand for reliable, valid and standardised questionnaires for assessing QoL (Patrick and Erickson, 1993). Although the use of QoL instruments is more common in clinical research than in clinical practice, their use in clinical research can help clinicians to obtain information on the impact of illness and its treatment on patients' QoL, as well as obtaining information not accessible using traditional clinical measures; the assessment of

QoL could be of great use in clinical decision-making (Spilker, 1996; Badia, Webb, Prieto and Lara, 2004). It makes sense that disease-specific instruments rather than generic QoL assessment tools, consisting of items and domains of health that are specific to a particular illness, are more relevant, sensitive and important to patients and clinicians and consequently are more likely to tap patient areas that clinicians wish to monitor (Guyatt et. al. 2002).

Beta thalassaemia major (BTM), is a genetic disorder of Hb production (BMA, 2002). When the UK Thalassaemia Register closed at the end of 2003, the total number of living thalassaemia patients was 857 (Modell et. al. 2003). In the UK, BTM is more or less restricted to ethnic minority populations, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi (Modell et. al. 2000). Profound anaemia, failure to thrive, recurrent infections and progressive enlargement of the abdomen due to liver enlargement and the spleen, are uniformly the pre-clinical profile at 6 months of age (Nick et. al. 2002). Recommended reference treatment includes demanding regular blood transfusions and chelation therapy (Porter and Davis, 2002; UKTS, 2005). Complications such as diabetes, toxicity of the most vulnerable organs (the heart, liver and endocrine glands) can arise hence the overall prognosis is currently open-ended (Ward et. al. 2002). As discussed before, much research has also shown that thalassaemia has underlying psychosocial impact upon patients (see chapter 2, section 2.1.2). These physical and psychosocial factors make BTM an illness with considerable impact on QoL (Telfer et. al. 2005). Furthermore, the correlation between clinical severity and impact of disease on patients' lives has been shown to be weak thus it is important to include QoL as an outcome measure (Badia et. al. 2004). Patient concerns such as physical appearance, pubertal growth, sexual development and body image e.g. Georganda (1990), tiredness and energy e.g. Borgna-Pignatti et. al. (2004), and psychosocial burden for instance social integration within the education system and work environments, establishing personal relationships, getting married and raising a family e.g. Politis (1998), have been described by patients and clinicians in the literature as some of the most important personal matters within this illness. An instrument to assess QoL in people suffering with BTM may be an effective means for clinicians to assess patients' self-perceived and self-reported health status as well as screening patients who require further evaluation (Bowling and Windsor, 2001).

5.1.2 Objective

In accordance with psychometric theory (Nunnally and Bernstein, 1994), a preliminary outcome instrument was developed from the analyses of items generated from the standard technique of (patient) interviews. The instrument includes domains and a response scale that has been determined by the patients therefore given meaning.

5.2 Method: Item Generation

5.2.1 Study Design

Semi-structured interviews were conducted in this study. This method affords the interviewees the freedom to provide their own account of a topic rather than restricting their input to discrete categories pre-determined by the researcher as in the case in questionnaire-elicited responses. Qualitative analysis was subsequently used to capture the fullness of the interviewees' responses. The content of the interviews was analysed. Content analysis is a methodology, often included under the general rubric of qualitative analysis used in the social sciences for studying the content of communication; it is most commonly used by researchers in the social sciences to analyse recorded transcripts of interviews with participants (Babbie, 2004). The purpose is to describe and draw inferences/conclusions (patterns/trends) about the characteristics of communications. House (1978) and Stufflebeam and Webster, (1980) have stated that content analysis is an objective, quasi-evaluation, highly respected disciplined inquiry approach. Content analysis is considered quasi-evaluation because content analysis judgments need not be based on value statements if the research objective is aimed at presenting subjective experiences thus they can be based on knowledge of everyday lived experiences; such content analyses are not evaluations (House, 1978; Stufflebeam and Webster, 1980). On the other hand, when content analysis judgments are based on values such studies are evaluations (Frisbie, 1986). The method of content analysis enables the researcher to analyse large amounts of textual information and systematically identify its properties e.g. the frequencies of most used keywords and/or phrases by detecting the more important structures of its communication content (Babbie, 2004). Such amounts of textual information must be categorised analysis, providing at the end a meaningful reading of content under scrutiny (Babbie, 2004). In content analysis, the assumption is that words and phrases mentioned most often are those reflecting important concerns in every communication (Weber, 1990). Qualitatively, content analysis can involve any kind of analysis where communication content e.g. written text, interviews, is categorised (Weber,

1990). Normally, content analysis can only be applied on manifest content, that is, the words, sentences etc. themselves, rather than their (latent) meanings (Weber, 1990). In such prescriptive analysis, the context is a closely-defined set of communication parameters e.g. subject matter, rather than identifying the dominant messages and subject matter within the text (open analysis) (McKeone, 1995).

There are two general categories of content analysis: conceptual analysis and relational analysis (Neuendorf, 2002). Conceptual analysis can be thought of as establishing the existence and frequency of concepts in a text whilst relational analysis builds on conceptual analysis by examining the relationships among concepts in a text (Neuendorf, 2002). The latter analysis was adopted in this study. As with other sorts of inquiry, initial choices with regard to what is being studied and/or coded for often determines the possibilities of that particular study (Neuendorf, 2002). Too many categories may obscure your results and too few can lead to unreliable and potentially invalid conclusions (Krippendorff, 2004) therefore it is important to allow the context and necessities of your research to guide your coding procedures (Weber, 1990). Perhaps the strongest claim that can be made for relational analysis is that it maintains a high degree of statistical rigor without losing the richness of detail apparent in even more qualitative methods (Neuendorf, 2002). The focus of relational analysis is to look for semantic or meaningful relationships; individual concepts are viewed as having no inherent meaning, rather, meaning is a product of the relationships among concepts in a text (Neuendorf, 2002).

5.2.2 Participants/Sample

The item generation stage of the THALI-35 was conducted at University College London Hospital (UCLH) in Euston, London, the Whittington Hospital, Islington, London and Luton and Dunstable Hospital, Luton, Bedfordshire**.**

Sixteen patients with BTM who were invited for interview by either their clinical nurse specialist (CNS) and/or consultant haematologist agreed and consented to participate in the semi-structured interview. They were selected to represent as much of the diversity of the illness as possible in terms of age, treatment and management, illness complications, educational level, marital status and family circumstance, occupational level and ethnic origin. Generally, 15 – 20 patients are sufficient to provide an exhaustive list of items as more interviewees were likely to duplicate items as patients diagnosed with the same

illness and given the same treatment do report similar experiences (Riazi et. al. 2002). A similar number of male (56%) and female (44%) patients were enrolled to take part in the semi-structured interview. Inclusion criteria for the study was that BTM patients were aged 18 years or above, and being treated, managed and cared for in the UK. Exclusion criteria for the study was difficulty with the command of the English language as the questionnaire was developed in the English (UK) language. Table 4 presents the characteristics of the sample of patients who participated in the semi-structured interviews.

5.2.3 Procedure and Measures

An initial pool of 61 items concerning the health impact of thalassaemia was generated from the 16 semi-structured interviews of patients with BTM. An interview schedule (see Figure 1), served as a guide for each interview. The schedule was devised from (i) an interview schedule template from work undertaken with adult patients with MS (Hobart et. al. 2004) to develop the MSIS-29 (a new patient based outcome measure), (ii) multidisciplinary expert opinion and informal discussions with experts in the field, (a health psychology lecturer with expertise in developing disease-specific health outcome measures, an Emeritus Professor of Community Genetics and a consultant clinical psychologist with a great deal experience of working with people with thalassaemia who identified areas of concerns in such patients) and subsequently (iii) a comprehensive review of the literature. Keywords 'thalassaemia', 'BTM', 'QoL, 'HRQoL', 'psychosocial functioning', 'chronic illness', 'haematology', 'haemoglobinopathy', all likely to be associated with thalassaemia and QoL were searched within journals including Quality of Life Research, Health and Quality of Life Outcomes, Health Trends, Medical Care, Quality of Healthcare, Journal of Health Services Research and Policy, British Medical Journal (BMJ), Journal of Chronic Diseases, Haematologica, Psychology Bulletin, Journal of Health Psychology, Blood, The Lancet, Social Science and Medicine and Psychological Medicine. Relevant books on topics such as the conceptualisation and measurement of QoL were also reviewed e.g. Anderson, K. L. and Burckhardt, C.S. (1999). Internet search engines Pub Med, Science Direct, Medline, Psychlit and the Web of Knowledge were also used to identify relevant literature surrounding the key words. The aim of the literature and critical review was to identify the issues, dimensions/domains and conceptual theories/models of QoL as well as the generic and disease-specific measures of QoL and/or HRQoL primarily for thalassaemia. It is noteworthy that 'expert' discussion identified areas of concerns of patients that were underpined by the literature.

Table 4: Interview Sample Patient Characteristics

Variable	Value n
Age	
Mean (SD)	**32.60** (7.37)
(Range)	(24-47)
Ethnicity	
Greek Cypriot	**7**
Greek	**2**
Turkish Cypriot	**2**
Indian	**3**
Pakistani	**2**
Educational status*	
No qualifications	**1**
G.C.S.E. 's or equivalent	**3**
University entry or equivalent	**8**
Degree	**2**
Higher degree	**2**
Employment status**	
Employed	**6**
Self-employed	**1**
Unemployed due to illness	**1**
Unemployed	**5**
Other (student/housewife)	**2/1**
Marital status	
Single	**5**
Married	**10**
Living together as married	**1**
Dependents***	
Mean (SD)	**0.70** (1.01)
(Range)	(0-3)
Siblings****	
Mean (SD)	**2.10** (2.22)
Treatment type	
'Pump'	**8**
Oral chelator drug	**5**
Combination	**3**
Illness complication(s)	
Osteoporosis	**9**
Diabetes	**5**
More than one stated complication	**6**

*e.g. BA in Health Care, BA in Media Studies, BSc in Psychology, HND in Business and Administration, MSc in Biochemical Engineering, National Diploma in beauty therapy, National Diploma in Computing, NNEB, PhD in Air Transport Engineering.
** e.g. air transport engineering consultant, carer/outreach worker, I.T. project co-ordinator, massage therapist, mechanical engineer, nursery nurse, retail operations manager.
*** 2 patients had donor sperm, 2 patients adopted children, 1 patient stepchild, 3 patients had fertility treatment (IVF) (1 unsuccessful).
**** 3 patients had twin siblings, 2 patients had no siblings.

Figure 1: Interview Schedule

Interviewee No.
Date of interview:

Preliminary procedures

Step 1: Before we begin you have the opportunity to ask questions regarding this interview and its surrounding research. Do you have any questions?

Step 2: Patient information sheet read? Questions? Gain informed consent via interview consent form plus completed ethnic origin and ABOUT YOU form.

Patient interview

First half (unstructured): Patients to describe in detail how the illness impacts on their health

Introduction: There are no right or wrong answers to questions asked in this interview. It is based on what you think about thalassaemia. As I am not medically trained could you describe for me the illness of beta-thalassaemia major?

Can you describe to me the impact of this illness on your day-to-day life? For example, can you please talk about your typical day from the time you wake up? What do you do? What does thalassaemia make it difficult for you to do? Do you need other people's help to do day to day activities?

Are you able to do the leisure activities that you enjoy doing?

What impact does thalassaemia have on (a) family life, (b) friends/social activities/hobbies, (c) work/colleagues, (d) education?

How has your thalassaemia change over the years?

Second half (semi-structured): based on expert opinion and literature review

Ask about any of the following topics not spontaneously mentioned by the interviewee:

- general self-care - do you need other people's help to do this activity?
- physical functioning e.g. pain/osteoporosis, fatigue, medical complications, management
- psychological functioning e.g. self-esteem, body image
- chelation therapy e.g. sleep/sexual relationships, relationships with health professionals
- emotional functioning e.g. depression, anxiety
- social functioning e.g. planning ahead/future expectations like family life/fertility, marriage
- acceptance, disclosure, stigma

Upon finishing

What next? Pre-testing summary: we shall be contacting 10 BTM patients to fill in a newly-developed questionnaire based upon interviews such as this one and once they have completed it, to give us their opinion on it e.g. how easy it was to complete, whether there were any questions they did not understand.

Do you have any questions you would like to ask before the termination of this interview or have anything to add?

Thank you for your time.

Interviewees' details were passed onto the investigator so that a mutually convenient appointment for interview could be made. Prior to interview, patients were sent a patient invitation letter (see Appendix II) and the patient information sheet (PIS) (see Appendix III). Patients had the opportunity to ask questions and/or discuss any queries they had prior to being interviewed. Informed consent was obtained prior to interview by means of the 'interview' consent form (see Appendix IV). Note: if patients agreed to their G.P. being informed of their participation in the study, the G.P. information sheet for the interview stage (see Appendix V), was sent to their G.P. Patients were also asked to complete the ethnic origin form (see Appendix VI as well as the form entitled 'ABOUT YOU' which asks patients about their sociodemographic status and their treatment for BTM (see Appendix VII).

All the interviews were conducted on a one-to-one basis and lasted for an average of 1 – 1.5 hours. The interviews were carried out by a single investigator at a place convenient to the patients, at either the patients' homes or in a consultation room at the hospital in which they are treated, managed and cared for. As previously stated, a standardised interview schedule (see Figure 1) devised from multidisciplinary expert opinion and a review of the literature, served as a guide to the interviewer, and to ensure consistency of questioning.

According to Wolcott (1994) there are two main types of interview: subject area-centred, where the interviewer wants to obtain information from persons because they possess knowledge and information about a certain subject or area of activity, and person-centred, where persons may be interviewed in order to obtain information of a personal nature i.e. the person is the subject of the interview. The semi-structured patient interviews contained elements of both types of interview as information was obtained about the patients as a disease group and at the same time information of a personal nature was gathered e.g. their feelings, activities, background. The interview fundamentally incorporated open and exploratory questioning. Each interviewee was asked the same main set of questions; prompts were used as needed. The questions were carefully worded so as not to offend. If patients did not appear to understand the question, it was rephrased and the information sought in another way. Good rapport with the interviewer resulted in interviewees being very forthcoming with their experiences and at no time did they refuse to answer questions.

5.2.4 Analyses of Interviews, Rationale for Item Selection and Results

All interviews were tape recorded, transcribed and then content analysed. The interviews were transcribed verbatim including repetitions, hesitations, pauses, emphases and emotional expressions such as laughter and sighing. Patient anonymity and confidentiality was maintained at all times with identifiers i.e. interview number + page number + line number. All transcripts were read several times and brief notes were made whilst reading. On occasion, tape recordings were listened to during this phase. The interview transcripts were processed and the content analysis was organised by the qualitative analytical software tool WINMAX 97 Professional. The extraction process involved highlighting any phrase and/or a sentence made by the patients that referred to the health impact of

Table 5: Themes: Health Impact Statement Organisation

Scale category	**Facets incorporated within domains (themes emerged during the extraction process)**	**Definition of scale category**
General Physical Health (GPH)	- Overall quality of life (QoL) and general health - Energy, fatigue/tiredness - Pain and discomfort - Sleep	Self-evaluation of personal physical health status
Psychological health and personal beliefs		
A Coping (C)	- Feelings/emotions - Thinking and Concentration - Planning ahead	Self- evaluation of psychological upset and/or well-being in relation to purpose drive coping.
B Body Image, Appearance and Confidence (BIAC)	- Bodily image - Self-esteem and confidence	Self-evaluation and feelings about physical self
Social Relationships (SR)	- Relationships and support network - Leisure/social activities - Stigma	Self-evaluation of limitations in social activities from physical and emotional difficulties.
Autonomy (A)	- Mobility - Achievements/normality - Education and work - Activities of daily living	Self-evaluation of feelings of dependency and control in usual physical role activities

BTM on their lives. No parallel content analyses and/or statement extraction took place. Inductive themes emerged (n=16), and were captured using key words. See Table 5 for these themes.

Redundant statements within and between patients on a particular theme were eliminated. That is, statements made by the same and/or different individual with a high degree of overlap were discarded until only one relevant statement was retained.

Examples:

Redundant quote(s) discarded: *I don't sleep very well (15, 56)*
Quote retained: *I am unable to sleep (9, 1279)*
Category/Theme: General Physical Health (GPH)/ Sleep

Redundant quote(s) discarded*:Keeps you youthful in your appearance in comparison to your peers (13, 1301), I look young (10, 1917), I look very young (12, 1019)*
Quote retained: *You always end up looking younger than your counterparts (8, 1290)* (became item, I look younger than my age/peers item for simplicity).
Category/Theme: Body Image, Appearance and Confidence (BIAC)/Bodily image

Redundant quote(s) discarded: *Don't go shopping on my own because of carrying bags (4, 297)*
Quote retained: *I can't do the shopping on my own (15, 165)*
Category/Theme: Autonomy (A)/ Activities of daily living

Redundant quote(s) discarded: *Feeling run down (2, 60)*
Quote retained: *Feel run down (10, 166)*
Category/Theme: General Physical Health (GPH)/Overall quality of life (QoL) and general health

Redundant quote(s) discarded: *You do get like bruising and stuff and scars (16,690)*
Quote retained: *I tend to bruise quite a lot (9, 647)*
Category/Theme: General Physical Health (GPH)/ Pain and discomfort

Redundant quote(s) discarded: *Eating is not brilliant either (11, 70-72)*
Quote retained: *Lose my appetite (9, 354)*
Category/Theme: General Physical Health (GPH)/ Overall quality of life (QoL) and general health

Redundant quote(s) discarded: *Sometimes you just lose your temper, really easy and get emotional (6, 1130-1) – temper item already developed, I would probably say that you are probably more of an emotional person (2, 606)*
Quote retained: *You get emotional (8, 1703)*
Category/Theme: Coping (C)/ Feelings/emotions

Redundant quote(s) discarded: *I don't like feeling sorry for myself (13, 1386)*
Quote retained: *You feel a bit down or more stressed (7, 54)*
Category/Theme: Coping (C)/ Feelings/emotions

Redundant quote(s) discarded: *More irritable really (7, 204)*
Quote retained: *You're irritable all the time (13, 168)*
Category/Theme: Coping (C)/ Feelings/emotions

Redundant quote(s) discarded: *Having anxiety attacks (9, 1304-5).*
Quote retained: *Always anxious (1, 819)*
Category/Theme: Coping (C)/ Feelings/emotions

Redundant quote(s) discarded: *Don't go shopping on my own because of carrying bags (4, 297).*
Quote retained: *I can't do the shopping on my own (15, 165)*
Category/Theme: Autonomy (A)/ Activities of daily living

Redundant quote(s) discarded: *I cannot do bending, lifting (2, 226)* – see below for lifting item.
Quote retained: *Bending over is difficult (11, 123-4)*
Category/Theme: Autonomy (A)/ Mobility

Redundant quote(s) discarded: *I cannot do bending, lifting (2, 226), I am not in a position to be able to lift heavy things, I don't have the strength (3, 78-9), I really do not lift anything too heavy (2, 189-190), Lifting things is bad (4, 296).*
Quote retained: *I can't lift heavy things (6, 68)*
Category/Theme: Autonomy (A)/ Mobility

Redundant quote(s) discarded: *It's a bit of a struggle really sometimes (12, 111), I wouldn't say that thalassaemia interferes with my life (3, 34), It's been a huge struggle to get to where I am (5, 525), At the moment it is having more impact than it did (10, 94)*
Quote retained: *Struggling to fit everything into my routine life (9, 841).*
Category/Theme: Autonomy (A)/Activities of daily living

Some phrases and/or sentences extracted from the interviews were separated to cover more than one item within a theme. For example, the statement, "*Very angry, very frustrated, very depressed, having no sense of motivation, feeling life was pointless"(12, 715-7),* was split into 4 items: depression, anger and frustrated, motivation, and sense of pointlessness, for two reasons. Firstly, it was a very revealing and detailed phrase that encompassed more than one feeling/emotion and secondly each part of the phrase was re-iterated (redundancy), by another phrase in the interviews.

Examples,

Depression item
Redundant quote(s) discarded: *I got depressed (1, 856), Depression physically destroyed me (11, 1514)*
Quote retained: Been depressed.
Category/Theme: Coping (C)/ Feelings/emotions

Anger and frustration item
Redundant quote(s) discarded: *There's a lot of anger (11, 1358), Big explosions, very huge amounts of anger, frustration (12, 687)*
Quote retained: Angry and frustrated
Category/Theme: Coping (C)/ Feelings/emotions

Motivation item
Redundant quote(s) discarded: *Hard to motivate myself to get up and do the things that I am supposed to do (5, 82-3)*
Quote retained: It has been difficult to motivate myself
Category/Theme: Autonomy (A)/ Activities of daily living

Sense of pointlessness item
Redundant quote(s) discarded: *Sense of pointlessness (12, 972)*
Quote retained: Had a sense of pointlessness
Category/Theme: Coping (C)/ Feelings/emotions

The statement, *"Introspective, it makes them shy, it makes them lack initiative, it makes them very passive" (12, 651-2),* was split into three items: Been very shy, Lacked initiative, Been very passive, under the Autonomy and Coping categories.

The items, Lacked energy and Felt tired, were developed from the following redundancy of quotes.

Redundant quote(s) discarded: *I was more energetic (6, 244), Tired did not have the energy to keep up with it all (2, 86-7), Feel drained (11, 345-6), A lot of days that I actually took off sick simply because I could not make it because I just did not have the energy (2, 157-9) - Generic statement therefore discarded.*
Quote retained: *I always have lack of energy (4, 267)*
Category/Theme: General Physical Health (GPH)/ Energy

Redundant quote(s) discarded: *Fatigue goes along with having thalassaemia (2, 503) , Can't be bothered to do nothing (6, 39) , I start feeling really really tired (6, 41), Very lethargic (11, 70-72), I get really knackered.. (10, 224), I feel a bit lethargic (12, 110)*
Quote retained: *Always going to feel tired and lethargic (13, 929)*
Category/Theme: General Physical Health (GPH)/Tiredness/fatigue

Statements that were broader in content than specific in content and which captured that particular category/theme succinctly were retained. Items were also chosen to avoid idiosyncratic and highly specific responses and if required items were developed to better suit the generic content of the specific statements.

Examples,

Specific content quote(s): *I can't do most of my housework (6, 68), I can't hoover (11, 140), I can just about make the children's bed (11, 141)*
Broader content quote(s) retained: *Chores around the house are limited (11, 203-4)*
Category/Theme: Autonomy (A)/ Activities of daily living

Specific content quote(s): *I do things that I have wanted to do in my life and go on holidays and get married which is always one girl's dream to do, have children, try and live a normal life and do everything else that everybody does (6, 25-28), I think you should still plan everything just like someone who is healthy (15, 227-8), Plan to get married and have children (5, 748)*
Broader content quote(s) retained: *I always plan ahead (1, 871)*
Category/Theme: Coping (C)/Planning ahead

Specific content quote(s): *I worry about my ferritin levels (15, 900-1), I get a little worried when we have new staff (15, 926-7), I worry about having thalassaemia (11, 445-6).*
Broader content quote(s) retained: These statements were developed into the 'worry' item, Been worried.
Category/Theme: Coping (C)/Feelings/emotions

Specific content quote(s): *Sometimes you just lose your temper, really easy and get emotional (6, 1130-1)*
Any little thing triggers it (temper) off (6, 1165),
Broader content quote(s) retained: These statements were developed into, *Lost my temper on a number of occasions,* item.
Category/Theme: Coping (C)/ Feelings/emotions

Specific content quote(s): *I used to lose my temper with everyone and you know people at home and people at work (8, 212-3),*
Broader content quote(s) retained: This particular item also helped develop the, *I have been really short with my family,* item
Category/Theme: Coping (C)/ Feelings/emotions

Specific content quote(s): *I get really short with the children (13, 208)*
Broader content quote(s) retained: This particular item became, *I have been really short with my family.*
Category/Theme: Social Relationships (SR)/ Relationships and support network

Specific content quote(s): *I can't go to the gym or swimming (5, 190), I just like jogging (8, 353-4)*
Broader content quote(s) retained: *I don't do any leisure activities (4, 408)*
Category/Theme: Social Relationships (SR)/ Leisure/social activities

Specific content quote(s): *I know the fascism about an illness (11, 771), If people know about an illness in Greece they marginalise you or they will show pity on you (12, 561-562), People pre-judge you all the time (13, 1359), Employers might look at you as a liability for having thalassaemia (13, 1921)*
Broader content quote(s) retained: *We are penalised because we have this illness (11, 1311-2)*
Category/Theme: Social Relationships (SR)/ Stigma

Specific content quote(s): *Taking advantage of me because I was little and I was ill (10, 1161), I didn't want to expose myself to anyone and basically to seem vulnerable to other people (5, 464-5)*
Broader content quote(s) retained: These statements were developed into the vulnerability item, *Been vulnerable.*
Category/Theme: Body Image, Appearance and Confidence (BIAC)/ Self-esteem and confidence

Specific content quote(s): *Well I hate the fact that I am so small. It upsets me a lot that I am very short (11, 1291), I suppose everyone was always a bit taller than me (8, 1289)*
Broader content quote(s) retained: These statements were developed into, *I am short in height*
Category/Theme: Body Image, Appearance and Confidence (BIAC)/ Bodily image

Specific content quote(s): *My body image is probably my most conscious aspect that I have to deal with because I am different (1, 603-4), It impacts I'm trying to be a normal human being. I'm comparing myself to a normal person (13, 982-3), The way you look, the way you are, you are just different (8, 1281), Through puberty I was self-conscious of my body not being the same as their body (13, 1236-7), When people don't know it's better because it doesn't make me different to them, but if they know then maybe they see me differently (16, 391-3)*
Broader content quote(s) retained: The statement, *Everything was difficult. I was comparing myself to others (12, 768),* was retained but adapted to be, *I am different to others and am conscious of this.*
Category/Theme: Body Image, Appearance and Confidence (BIAC)/ Bodily image

Specific content quote(s): *I prefer to be alone (11, 604), I don't think I need anyone to like support me that much (16, 1090), They are my lifeline. They are the people I have faith in. I trust them (11, 1161), People whether they are normal or thalassaemic are reluctant to have a relationship with a thalassaemic (1, 632-4), Socially picked on and bullied at school (1, 27)*
Broader content quote(s) retained: These statements were developed into the item, *I have not been able to successfully form relationships with others,* and item, *My social life has been affected by my illness.*
Category/Theme: Social Relationships (SR)/Relationships and support network

Specific content quote(s): *I wasn't good enough (7, 1068), Family absolutely hated me because of the thalassaemia and I had such stress (7, 903-4), I've got nothing to hide and I am not ashamed any more (13, 1665-6).*
Broader content quote(s) retained: These statements were developed into the item, *I have been rejected in some way because I have thalassaemia.*
Category/Theme: Social Relationships (SR)/ Stigma

Specific content quote(s): *I am not as active as I used to be, I have given up all the things I used to do just so that I can manage work and a home life (15, 100), I think you really have to think about organising your life differently (9, 231-2), I just about have enough energy to look after the kids (6, 114)*
Broader content quote(s) retained: These statements were developed into the item, *I have been unable to manage my work and home/family life as usual.*
Category/Theme: Autonomy (A)/ Activities of daily living
Specific content quote(s): *It's a hinderance, it's a pain (13, 2018-9), You have successes but they are limited (1, 621), Thalassaemia continues to impact on my education (1, 422), School was disrupted immensely (1, 24), I spent so little time at school (9, 1006-7), I missed a lot of school (1, 25), My education has suffered a lot (5, 636)*
Broader content quote(s) retained: *Statements developed into item, Having thalassaemia has made most things difficult.*
Category/Theme: Autonomy (A)/ Achievements/normality and Education/Work

Statements regarding the positive impact of BTM and coping with BTM were excluded as the intention was for the health outcome questionnaire to focus on the negative impact of BTM on patients' daily lives. As discussed in chapter 3, sections 3.3.6.1 and 3.3.6.2, the concept of QoL is generally defined in positive terms (see Tables 1, 2 and 3) but it is generally measured e.g. SF-36 (Ware and Sherbourne, 1992) and SIP (Gilson and Bergner, 1976) in negative terms i.e. what people have lost e.g. loss of health rather than what people have (Brown et. al. 2004). The functionalist model of QoL taps the individual's difficulties in the performance of activities which are essential for their continuing functioning in society; this approach has led to a negative rather than a positive focus in measurement therefore scales have been developed to measure levels of functional disabilities rather than balanced scales (Brown et. al. 2004).

Examples,

Quote(s): (Tiredness) *It's not really a huge problem (16, 149)*
Category/theme: General Physical Health (GPH)/ Energy, fatigue, tiredness

Quote(s): *I am quite a confident person (3, 697),* (In body image) *Full confidence (12, 1202), I feel confident and that helps me towards my treatment (1, 1493-4)*
Category/theme: Body Image, Appearance and Confidence (BIAC)/ Bodily image

Quote(s): *I've got great friends (6, 1111), I've got lots of good friends (6, 731)*
Category/theme: Social Relationships (SR)/ Relationships and support network

Quote(s): *I wouldn't say that thalassaemia interferes with my life (3, 34), I do what all my friends do, so I don't think it makes me different (16, 430), I still think you can live your life normally I have. I don't see myself as any different to anyone else (16, 1175-6), I think my life is normal (16, 1196), My family never treat me different (7, 646), I've got nothing to hide and I am not ashamed any more (13, 1665-6)*
Category/theme: Autonomy (A)/ Achievements/normality

It should be noted that no attempt was made to eliminate gender biased questions from the THALI therefore the index can aspire to identify disparities in QoL between male and female patients should they exist. If items had been eliminated on the basis of gender differences, important issues based on gender group membership may have been missed such as household chores. It is important that gender is considered in health as there is a wealth of literature that suggests that males and females respond differently to poor health (Ruiz and Verbrugge, 1997; Gee, Abbott, Conway Etherington and Webb, 2000). Women generally report higher physical disease (Merril, Seeman, Kasl and Berkman, 1997), more pain (Unruh, 1996), more subjective or emotional symptoms than men (Piccinelli and Simon, 1997) and more use of health services (Mechanic, 1978). Based on these results, Gee et. al. (2000) suggest that an initial analyses on the basis of gender should always be conducted although where gender differences are not observed investigators should proceed with a global analysis of the data.

5.2.4.1 Key themes

A total of 158 health impact statements relating to the health impact of BTM on patients' lives were extracted from all interviews, (see Appendix VIII).

All 16 interviews were reviewed. It is noteworthy that no new inductive themes appeared after the first 10 interviews. Statements concerning the health impact of BTM were extracted from the interview and grouped into themes with no pre-conceived ideas. In total, 97 items were identified as irrelevant and/or redundant (see Appendix IX).

The inductive themes that emerged during the extraction process were captured using key words. Emergent themes (see Table 5) were classified into 5 broad categories to facilitate presentation and readability, (general physical health (GPH), coping (C), body image,

appearance and confidence (BIAC), social relationships (SR) and autonomy (A)). Thus, these were the emergent themes of the interviews; these categories came about by putting the statements into a more manageable format. In each category, statements were further organised into subcategories i.e. the themes that emerged during the extraction process e.g. the broad category of GPH included subcategories such as overall quality of life (QoL) and general health, energy, fatigue/tiredness, pain and discomfort and sleep. Each scale category once identified was defined.

The broad categories naturally formed/grouped. They were clear from (a) the content of the items/statements that were extracted from the interviews e.g. the General Physical Health (GPH) category incorporated physical symptoms of BTM like tiredness and the Body Image, Appearance and Confidence (BIAC) category incorporated items like physical appearance, self-esteem and confidence, and (b) from the content and categories identified in other health outcome measures. For example, the GPH category was noted to have similar content to the SF-36 sub-scales GHP, PF, RLPH, PAIN and E/F (Ware and Sherbourne, 1992), the EQ-5D dimensions of pain/discomfort (EuroQol Group, 1990) and the WHOQoL-100 (Power et. al. 1999) physical domain. The SR category was noted to have similar content to the SF sub-scale of the SF-36, (Ware and Sherbourne, 1992), the categories of the psychosocial domain of the SIP (Gilson and Bergner, 1976) (social interaction and recreation and pastimes), and the WHOQoL-100 (Power et. al. 1999) social domain. The A category had similar content to a self-efficacy scale for adults with SCD, the Sickle Cell Self-Efficacy Scale (SCES) (Edwards, Telfair, Cecil and Lenoci, 2000), the home management and work categories of the SIP (Gilson and Bergner, 1976), the EQ-5D (EuroQol Group, 1990) dimension of self-care and usual activities and the WHOQoL-100 (Power et. al. 1999) level of independence domain. The C category encompassed similar content to the BRIEF COPE (Carver, 1997), the EWB sub-scale of the SF-36 (Ware and Sherbourne, 1992), the emotional behaviour of the SIP (Gilson and Bergner, 1976) and the EQ-5D (EuroQol Group, 1990) dimension of anxiety/depression. The BIAC category contains items similar to those in the Body Image Quality of Life Index (BIQLI) (Cash and Fleming, 2002) which rates a person's confidence and self-esteem with regard to their body image and appearance.

A preliminary 61-item questionnaire was developed (see Appendix X*) consisting of sections of questions that relate to physical items, psychological items, body image items,

activities of daily living and social items (see Figure 2). These five sections were based on the most appropriate way to group the items without changing patients' words. All the items referred to the present and were written correspondingly. They were written in one direction to maintain clarity and no items were presented in reverse format. All items were written in the first person using words deemed familiar to all adults. The time frame specified for all of the items was the preceding 4 weeks before the completion of the questionnaire. Although the choice of time frame could be judged as being arbitrary, 4 weeks was chosen for a specific reason. Beta thalassaemia major (BTM) patients have a blood transfusion on a monthly basis so it would be a clinically suitable and significant time frame based upon BTM treatment and management.

5.2.4.2 Item-Stems and Response options

Examination of the content and wording, (for clinical appropriateness), of the pool of 61 items indicated that two distinct question stems and one response scale format was required for the questionnaire. The majority of the items (n=33) were best represented by the stem, 'In the past four weeks, I have'… with the most widely used standard psychometric response option scale in survey research, the Likert scale (Likert, 1932). A Likert scale, named after Rensis Likert, who published a report describing its use, is a psychometric scale commonly used in questionnaires and is the most widely used scale in survey research (Babbie, 2005) hence its use in this study. When responding to a Likert questionnaire item/statement respondents indicate their level of agreement or disagreement to a statement. The Likert scale is the sum of responses on several Likert items within a scale. Likert items are often accompanied by a visual analog scale, usually a horizontal line, on which a subject indicates their response by circling or checking tick-marks like in main generic measures of health outcome e.g. EQ – 5D (EuroQol Group, 1990). Likert scaling is a bipolar scaling method i.e. measures either positive or negative response to a statement in a scale. Typically five ordered response levels are used like in this study. For example, the WHOQoL-100 (Power et. al. 1999) items are scored on a 5-point Likert scale with only the anchor points being specified (never-always) (discussed in section 3.4.2.1.1.4, the COOP (Nelson et. al. 1987) where patients rate their QoL on a 5 point Likert scale on six dimensions of health status (discussed in section 3.5.1) and the MSIS-29 (Hobart et. al. 2001) where patients rate the physical and psychological impact of MS on a 5 point Likert scale.

Figure 2: Preliminary 61 item questionnaire item derivation

Scale category*	Facets incorporated within domains (themes emerged during the extraction process)	Items Derived from Content Analysis
General Physical Health (GPH) n = 15	- Overall quality of life (QoL) and general health - Energy, fatigue/tiredness - Pain and discomfort - Sleep	Lacked energy Felt tired Lacked stamina Been unable to shift a cold and/or sore throat Felt run down Felt bloated Had nausea Had headaches Been bruised Had some swelling Felt dizzy Been full of aches and pains Had a poor appetite Needed to rest more often Been unable to sleep
Psychological health and personal beliefs A Coping (C) n = 18	- Feelings/emotions - Thinking and Concentration - Planning ahead	Been depressed Been worried Been angry and frustrated Lost my temper on a number of occasions Been emotional Been a bit down or stressed Been irritable Been aggressive towards others Been generally short-tempered Had a sense of pointlessness Been very sensitive Been anxious Been suicidal on a few occasions Had trouble concentrating I have not planned ahead Been very shy Been vulnerable Been very passive
B Body Image, Appearance and Confidence (BIAC) n = 8	- Bodily image - Self-esteem and confidence	I have a shortened body I look younger than my age/peers I have a pale complexion I am short in height My arms are short I am different to others and am conscious of this I have no self-confidence I feel a bit inferior to others

Scale category*	**Facets incorporated within domains (themes emerged during the extraction process)**	**Items Derived from Content Analysis**
Social Relationships (SR) n = 7	- Relationships and support network - Leisure/social activities - Stigma	I have not been able to successfully form relationships with others I have been rejected in some way because I have thalassaemia I have been penalised in some way because I have thalassaemia My social life has been affected by my illness I have not done any leisure activities I have been really short with my family There are lots of things that I would have liked to have done with my family that I could not do.
Autonomy (A) n = 13	- Mobility - Achievements/normality - Education and work - Activities of daily living	I have had difficulty doing the shopping on my own Travelling has been difficult Doing chores around the house has been limited. I have been unable to manage my work and home/family life as usual Mobility is difficult I could not bend with ease I could not do alot of walking I have been unable to lift heavy things I have struggled to fit everything into my routine life Having thalassaemia has made most things difficult Lacked initiative It has been difficult to motivate myself It has been an effort for me to get myself ready in the morning.

*It should be noted that after the pre-testing phase the number of items within the Psychological health and personal beliefs category was increased. Within the C category the item, Been angry and frustrated was split, making that 19 items within that category and within the BIAC category the item, My arms are long was added making that 9 items within that category.

The 'classic' format of a five-level Likert item is 1. Strongly disagree, 2. Disagree, 3. Neither agree or disagree, 4. Agree, 5. Strongly Agree (Likert, 1932). In this instance, the typical format was not adopted. Examination of the content of the items/statements, the

response options of the questionnaire are on a five point scale anchored from 1 (not at all) to 5 (extremely); 2 being 'too little', 3 being 'moderately' and 4 being 'quite a bit'.

Essentially, the majority of the questionnaire items describe the general physical health of patients (n=15) and psychological health and personal beliefs (n=18). Eight items describe other aspects of patients' psychological health and personal beliefs i.e. body image, and were best represented by the stem, 'In the past four weeks, it has bothered me that…'. The remaining items (n=20) are statements relating to social relationships and autonomy and were best represented by the stem, In the past four weeks…'.

5.3 Objective: Pre-testing Phase

In accordance with the development of an outcome measure, at the item generation stage, (Nunnally and Bernstein, 1994), the preliminary 61 item questionnaire (see Appendix X, column 3) including its instructions, item-stems, items and response options, was reviewed for content, wording and clinical appropriateness by patients and clinicians. Pre-testing is crucial for identifying problems with a questionnaire such as the question content which can cause confusion with the overall meaning of an item as well as the misinterpretation of individual terms or concepts (Kaplan and Saccuzzo, 1993).

5.4 Method: Pre-testing Phase

5.4.1 Participants/Sample

A sample of 10 patients with BTM, were invited to take part in the pre-testing phase. The sample included 5 very responsive interviewees, as well as a small, independent, clinical, (opportunity) sample of 5 heterogeneous patients with BTM who are treated at UCLH or at the Whittington Hospital. These patients were selected to be representative of the general BTM population. It is noted that the same number of male and female patients participated in this phase of the development of the questionnaire. See Table 6 for a breakdown of the patient characteristics. Two clinicians, an Emeritus Professor of Community Genetics and a consultant clinical psychologist were invited to, and agreed to review the questionnaire for clinical appropriateness.

Table 6: Pre-testing Sample Patient Characteristics

			Patients (value)		
Gender					
Male	Female		5	5	
Age					
Mean	(SD)	Range	35.4o	(6.64)	19-45
Ethnicity					
Greek Cypriot			3		
Greek			2		
Turkish Cypriot			2		
Indian			1		
Pakistani			1		
Other			1		
Educational status					
No qualifications			1		
G.C.S.E. 's or equivalent			2		
University entry or equivalent			4		
Degree			3		
Employment status					
Employed			5		
Self-employed			1		
Unemployed			3		
Other (student/housewife)			1		
Marital status					
Single			4		
Married			4		
Living together as married			1		
Separated			1		
Dependents					
Mean	Range		1.1	0-3	
Treatment type					
'Pump'	Oral chelator drug	Combination	5	4	1
Illness complication(s)					
Osteoporosis			7		
Diabetes			2		
More than one stated complication			4		

5.4.2 Measures, Procedure and Design

Preceding pre-testing, patients were given (at their hospital visit) or sent, a letter of invitation (see Appendix XI) and the pre-testing PIS (see Appendix XII). Patients were given the opportunity to ask questions before reviewing the questionnaire. Half of the patients reviewed the questionnaire over the telephone and the other half within a clinical setting. Informed consent was obtained prior to pre-testing (see Appendix XIII). Patients were also asked to complete the ethnic origin and the 'ABOUT YOU' forms to obtain patient sociodemographic details (see appendices VI and VII). Patients who had already been interviewed for the generation of the item pool were asked to complete the 'ABOUT YOU' form once again due to potential change of personal and/or clinical circumstance; their consent to being part of the pre-testing phase was also obtained (see Appendix XIII). As in the interview phase of stage 1, if patients agreed to their G.P. being informed of their participation in the study, the G.P. information sheet for the pre-testing stage (see Appendix XIV) was sent to their G.P.

Patients were asked to complete the preliminary 61-item questionnaire in the presence of the study investigator and to comment on it by identifying items, item stems and instructions including the response options, that were unclear, ambiguous, irrelevant, misleading or offensive and to make suggestions for alterations to the questionnaire. A one-to-one, (cognitive), mini, informal, unstructured interview/discussion using the 'think aloud' approach was adopted. This approach asks respondents to describe their thoughts while answering the questions (Van Someren, Barnard and Sandberg, 1994). The think-aloud method avoids interpretation by the subject and only assumes a very simple verbalisation process and verbal discussion are considered as objective data, (Van Someren, Barnard and Sandberg, 1994, *p30*). *"Currently the think-aloud method is accepted as a useful method by a large part of the scientific community in psychology"* (Van Someren, Barnard and Sandberg, 1994, *p32*).

5.5 Results: Pre-testing Phase

Overall, patient comments were very positive. All the patients stated that the instructions were easy to follow; 50% found it easy to complete. Twenty percent mentioned that the layout was good; 20% stated that it had good readability and 30% found it straightforward and precise. Twenty percent of the patients commented that the questionnaire was all encompassing. A verbatim comment worthy of note, *"True reflection of thalassaemia*

especially feelings stuff'. Thirty percent stated that the questionnaire was much needed. Seventy percent remarked that the content was fine and 60% percent found it interesting.

Patient suggestions included removing the word 'impact' from the first line of instructions, replacing the word aggressive with hostile in item 23, "In the past four weeks, I have…. been aggressive", adding the word 'generally' to item 24, "In the past four weeks, I have….been short-tempered", and adding 'in some way' after the 'word' rejected in item 51, "In the past four weeks….. I have been rejected because I have thalassaemia". Fifty percent of patients commented that item 18, "In the past four weeks, I have….. been angry and frustrated", should be split, 30% of patients commented that item 37, "In the past four weeks, it has bothered me that….. I am small", should be re-worded, 40% of patients commented that item 47, "In the past four weeks….. there are lots of things that I would have liked to have done with my family that I could not do", should be reworded.

The word 'impact' was not removed from the first line of instructions as it sets the scene of the questionnaire. Item 18 was split, to avoid offending patients and became items 18 and 19. Item 23 was re-worded to "Been hostile towards others" and became item 24. The word 'generally' was added to item 24 which became item 25 due to the split of item 18. Item 37 was reworded as "I am short in height" to avoid offending patients. Due to the split of item 18, item 37 became item 38. Item 47 was re-worded to, "I have been restricted in doing things that I would have liked to have done with my family", for readability and clarity. It became number 49. 'In some way' was added after the word 'rejected' in item 51 to avoid offending patients and became item 53. The expert clinicians added the item, 'My arms are long". This was placed after item 39, "My arms are short" and became item 40. The clinicians' decision was rationalised as follows; older patients who have had growth hormone treatment as adolescents may have longer limbs which could potentially affect their body image. After pre-testing, the preliminary 61 item questionnaire consisted of 63 items (see Appendix XV).

5.6 Discussion

Thalassaemia is no longer considered a fatal illness and advances in medical treatment and management have greatly increased the life expectancy of these patients (Bush et. al. 1998). This has highlighted the importance of the disease specificity of QoL measurement (Telfer et. al. 2005) which thus far has not been developed.

5.6.1 Overall Results

The aim of this stage was to develop a preliminary BTM, patient-based outcome measure. Items were generated from in-depth patient interviews and the pre-testing of a preliminary instrument. The THALI was developed on the basis that QoL is multidimensional. The results of stage 1 champion investigators like Beckie and Hayduk (1997) and Cummins (2005) who have suggested that subjective health status is multidimensional thus the focus of multidimensionality on measurement. (Correlations between the scales of the THALI and other measures that encompass multidimensionality are described in chapter 7 that outlines the psychometric evaluation of the THALI-35, stage 3 of 3 (validation)). Five broad categories with incorporated facets were identified from the content analysis of patient interviews. Within each domain are sets of items, each of which tap into specific areas of QoL issues/concerns of importance to adults with BTM. The outcome of this is that these issues/concerns can be assessed on a domain-by-domain basis or more specifically on an item by item basis if individual issues are to be evaluated in a therapeutic context.

The THALI has been identified by the author as a measure of the multidimensional impact of BTM from the patients' perspective. Terms like QoL, HRQoL, health status and well-being, are often used interchangeably (Bergner, 1989) or without specific reference to what they measure (Ware, 1995). As measures intended to assess these concepts are collectively referred to as 'patient-based outcome measures' (Fitzpatrick, Davey, Buxton and Jones, 1998), the author specifically chose not to describe the THALI as a QoL measure, as this term is ambiguous and can mislead investigators and/or clinicians when they are selecting measures for clinical research and/or practice (Badia et. al. 2004).

5.6.2 Evaluation of Stage 1

It is important to consider the potential limitations of this stage. This study represents the first step in developing a psychometrically sound, patient-based health outcome measure for adult BTM patients and sought to present initial issues and/or concerns of patients. Even so, other important concerns/issues of patients may have been omitted and pertaining issues/concerns may not be all-encompassing. Whilst it is common practice in qualitative research to use small patient samples, the author is aware that the issues/concerns of these patients may not be representative of the patient population as a whole therefore this limits generalisability where application of theory to a general population is a desired endpoint

i.e. the domains of health impact upon patients could possibly be limited to the interview sample from which the data were collected.

The THALI hopes to be sensitive to the impact of thalassaemia upon patients therefore patients who were selected for interview were chosen to represent the diversity of the illness. Additionally, the THALI endeavours to be used to assess the benefits of new medications and treatments from the patients' perspective, and to understand the natural course and progression of the illness in terms of its effects on the domains identified by the interview sample. Intensive interviewing of patients, thorough discussions with clinicians and a comprehensive literature review warranted face validity i.e. the measure *"looks like it is going to measure what it is supposed to measure"* (Anastasi, 1988, p144), and content validity.

Analysis of content has theoretical and procedural drawbacks. In particular, content analysis can be time consuming and is inherently reductive when dealing with complex texts like in-depth interviews (Wolcott, 1994). In addition, the text being analysed may be 'unrepresentative' with regard to the subject matter and/or aim of the study yet overwhelming in volume (Babbie, 2004). Content analysis can often be devoid of a theoretical base and can be difficult to computerise (Bohrnstedt, 1983) and the design itself may often be overly simplistic for the research question (Babbie, 2004).

The advantage of qualitative research is clear. Such research examines complex phenomena like health outcome that would be impossible to examine quantitatively. Nevertheless, subjectivity leads to procedural problems. The validity of content analysis refers to the correspondence of the categories to the conclusions. For example, the relevance of questionnaire domains to the patient group, and the generalisability of results to a theory i.e. the multidimensionality and disease-specificity of QoL in BTM patients (Hobart et. al. 2004). Internal validity in qualitative research equates to credibility (Wolcott, 1994) i.e. the right setting and informants, accurate reflection of situation and informant perceptions. External validity in qualitative research equates transferability/generalisability (Wolcott, 1994). To seek validity in interview data researchers need to listen and observe carefully, be candid and record accurately. This is difficult when one researcher is responsible. The reliability of content analysis in a study refers to its stability or the tendency for coders to consistently re-code the same data in the

same way over a period of time (reproducibility) (Bryman, 2001). The data that led to the 63-item THALI was collected by, and based upon the abilities and interpretations of a sole interviewer; reliability is very difficult and research bias is built in and often unavoidable (Oppenheim, 1992). The validity, inter-coder reliability and intra-coder reliability are subject to many methodological research efforts (Krippendorf, 2004) but were not tested in this study.

Interviews are a social situation and are dependent upon how the interviewer and interviewee interact (Oppenheim, 1992). In addition, what patients say in interviews may not necessarily be a guide to what they do outside interviews (Bryman, 2001) therefore the information upon which the 63-item measure is based upon could be inaccurate. Aspects of interviewees' accounts may have been based upon the acceptability or desirability of the interviewer and/or acceptability to some image of society in general i.e. social desirability.

Although the 'think-aloud method' used in the pre-testing phase of the item generation stage is accepted *"as a useful method by a large part of the scientific community in psychology"* (Van Someren, Barnard and Sandberg, 1994, *p32*), certain factors may threaten the validity and completeness of verbal data, for example, validity due to the disturbance of the cognitive process i.e. does the additional task of thinking aloud change the cognitive process? Will a different process take place than without thinking aloud? (Van Someren et. al. 1994). Emotional and motivational factors can also result in a cognitive process that is different from the process that would take place during task performance without thinking aloud, and incompleteness due to synchronisation problems i.e. thinking aloud takes place concurrently with the cognitive process and such a process takes longer when 'the think-aloud method' is used, so potentially people are able to slow down the normal process to synchronise it with verbalisation (Van Someren et. al. 1994). However, interviewees frequently report that sometimes verbalization does not keep up with the cognitive process and that their report is incomplete; this is consistent with the observation that occasionally reports contain holes of which it is almost necessary to assume that an intermediate thought occurred (Van Someren et. al. 1994).

Chapter 6 presents stage 2 of 3 of the development of the THALI-35.

5.7 Acknowledgements

Ethical approval was obtained from the Northern and Yorkshire Research Ethics Committee as well as the ethics committee at Brunel University, Uxbridge (see Appendices XVI and XVII respectively). It should be noted that although 'the examination of the relationship between HRQoL, adherence and psychosocial factors' was approved this was not undertaken due to time constraints. The official sponsor for this research was Brunel University (see Appendix XVIII) who had in place non-indemnity insurance (see Appendix XIX) and data protection registration policy (see Appendix XX for this project. It should be known that the relevant Research and Development Departments of the hospitals/universities also gave their approval for this research to commence (see Appendices XXI through to XXIII). Site specific assessment was not needed (see Appendix XXIV) but gained in some instances i.e. Luton and Dunstable Hospital, The Whittington Hospital (see Appendix XXV). Departmental honorary contracts were obtained where stated as required by the hospital(s), Trust(s) and/or department(s) (see Appendices XXVI and XXVII). A notification of amendment application was sent to the Northern and Yorkshire Research Ethics Committee, and approved to include the ABOUT YOU form (see Appendix XXVIII). In addition, a typing error on the ethics approval letter was amended by the Ethics Committee (see Appendix XXIX where marked by x x).

It should be noted that for administrative purposes Dr. Anna Mandeville, Consultant Clinical Health Psychologist (UCLH) is the named principal investigator of this research.

Chapter 6

Development of the Thalassaemia Adult Life Index (THALI-35)
Stage 2: Item Reduction

Chapter Overview

This chapter outlines stage 2 of 3 of the development of the Thalassaemia Adult Life Index **(**THALI-35). In stage 2 (item reduction), the preliminary 63-item questionnaire was administered by postal survey to a community sample of 381 adult members from the UKTS. Item reduction techniques were utilised to develop the 35-item measure (THALI) that covers the physical, psychological and social impact of BTM.

6.1 Introduction

6.1.1 Background

An instrument to assess QoL in people suffering from BTM may well be an effective means for HCPs to assess patients' self-perceived and self-reported health status as well as screening patients who require further evaluation (Bowling and Windsor, 2001). The development of such an outcome measurement instrument involves two stages. Chapter 5 described the first stage, the generation of an item pool; this stage is followed by the reduction of the item pool to form the final instrument (Hobart et. al. 2004). The purpose of this is to reduce the number of items and to develop scales. The instrument is administered to a large sample of patients and results are analysed using psychometric techniques of item analysis (Streiner and Norman, 1995).

6.1.2 Objective

In accordance with psychometric theory (Nunnally and Bernstein, 1994) the preliminary outcome instrument was administered by postal survey to a community sample of adults with BTM. Item reduction techniques were adopted to develop the 35-item, 5 domain instrument that measures the physical, psychological and social impact of BTM.

6.2 Method: Item Reduction

6.2.1 Participants/Sample

The item reduction stage of the THALI-35 was conducted with an adult community sample (n=381) from the UKTS membership database. A similar number of male (47%) and

female (53%) patients were enrolled. Inclusion criteria for the study was that BTM patients were aged 18 years or above and being treated, managed and cared for in the UK. Participants ages ranged from 19-68 (M=33.74; SD = 9.63). Though the exclusion criterion for the study was difficulty with the command of the English language, as the questionnaire was developed in the English (UK) language, this was difficult to identify by the UKTS membership database. Table 7 presents the characteristics of this sample of patients.

6.2.2 Procedure/Item Reduction and Measures

The 63-item questionnaire (see Appendix XV) was administered by postal survey to the community sample.

The UKTS supported this research but understandably do not allow people who do not work for the charity to have access to their membership database. To protect the anonymity of the sample, the prepared packs of questionnaires and other relevant research documents i.e. the postal survey letter of invitation (see Appendix XXX), the postal survey 1 PIS (see Appendix XXXI), the postal survey 1 consent form (see Appendix XXXII), the ethnic origin form, (see Appendix VI) and the ABOUT YOU form (see Appendix VII), were given to the UKTS administrator who attached member address labels and then posted them with a pre-paid, stamped addressed envelope inside. To avoid extra workload for the UKTS administrator, the questionnaires and other relevant documents were returned to the researcher's place of work. It is common practice that questionnaires and other relevant documents are re-sent to the sample with postcard/letter reminders within a three week period if they have not been received in the first instance (Dillman, 2000). However, the UKTS did not think that it was appropriate to adopt this practice. In their experience, 'pestering' members for information has been to their detriment as they have lost members. It should be noted that although the prepared packs of questionnaires and other documents were sent via the UKTS, the PIS (see Appendix XXXI), clearly stated that this study was independent to UKTS projects. The researcher asked people who received the packs who did not have BTM to return the questionnaires etc. Blank. No blank questionnaires were returned.

Table 7: Community Sample Characteristics

Variable	Value in % or n
Ethnicity	
Greek Cypriot	36%
Indian	25%
Greek	10%
Middle Eastern	10%
Chinese	8%
White British	5%
Turkish Cypriot	3%
Pakistani	3%
Educational status	
No qualifications	7%
G.C.S.E. 's or equivalent	34%
University entry or equivalent	13%
Degree	38%
Higher degree	8%
Employment status	
Employed	69%
Self-employed	3%
Unemployed	10%
Other (student/housewife)	18%
Marital status	
Single	58%
Married	35%
Living together as married	7%
Dependents	
Mean (SD)	0.47 (0.99)
(Range)	(0-5)
Treatment type	
'Pump'	32%
Oral chelator drug	34%
Combination	34%
Illness complication(s)	
Osteoporosis/Osteoarthritis*	28%
Diabetes	22%
Cardiac problems	10%
Hypothyroidism**	8%
Impaired glucose tolerance	6%
Asthma	4%
Other (not stated)	4%
Hepatitis C***	4%
Insensitivity to pain	4%
Eczema	4%
Coeliac disease****	2%
Hormonal Imbalance	2%

*Loss of bone tissue causing the bone to become brittle and fracture easily/a common joint disease characterized by degeneration of the cartilage that lines joints or by formation of an outgrowth of bone at the boundary of a joint (osteophyte), leading to pain, stiffness and occasionally loss of function (BMA, 2002).

**The underproduction of thyroid hormones by an underactive thyroid gland (BMA, 200).

***Infection often transmitted through sharing needles and/or blood transfusions; can progress to cirrhosis (long term damage to liver cells) and/or hepatoma (a type of liver cancer) (BMA, 2002)

****The lining of the small intestine gets damaged due to hypersentivity to gluten (protein found in wheat, rye and other cereals) (BMA, 2002).

As in stage 1, if patients agreed to their G.P. being informed of their participation in the study, the G.P. information sheet for postal survey 1 (see Appendix XXXIII) was sent to their G.P.

6.2.3 Results

6.2.3.1 Rationale

It is anticipated that the THALI measure may be used in both research and clinical practice therefore it was required that the resulting scale be reasonably short for quick completion during a research and/or consulting session. The typical length of a clinic session could be approximately 30-60 minutes and face-to-face clinical research interviews tend towards this length (Dillman, 2000). For an instrument to be considered for use within these settings it should be easily administered and completed within this period of time as where administration and completion times exceed this limit they can be viewed as too disruptive and time-consuming for inclusion (Eiser, 2000). In addition, a short scale should allow for the calculation of scale scores immediately after its completion and the information could then be used from that time (Millar and Shevlin, 2007). Furthermore, if each subscale contained the same number of items then each subscale will have the same potential minimum and maximum score thereby making subscale scores directly comparable like in the General Health Questionnaire-28 (GHQ-28) by Goldberg and Hillier (1979) (Millar and Shevlin, 2007). The GHQ-28 is the most well-known and popular version of the GHQ (Goldberg and Williams, 1988). The GHQ-28 is used to detect psychiatric disorder in the general population and within community or non-psychiatric clinical settings such as primary care or general medical out-patients (Goldberg, 1997). It assesses the respondent's current state and asks if that differs from his or her usual state; it is therefore sensitive to short-term psychiatric disorders but not for long-standing attributes of the respondent (Goldberg, 1997). It is often of interest to be able to examine a profile of scores rather than a single score, making this version of the GHQ particularly useful; the GHQ contains 28 items that, through factor analysis, have been divided into four sub-scales: A – somatic symptoms (items 1-7), B – anxiety/insomnia (items 8-14), C – social dysfunction (items 15-21) and D – severe depression (items 22-28). (This self-administered questionnaire focuses on two major areas: the inability to carry out normal functions and the appearance of new and distressing psychological phenomena). There are

no thresholds for individual sub-scales as individual sub-scales are used for providing individual diagnostic or profile information (Goldberg and Williams, 1988).

The need for a brief scale needs to be considered in terms of the necessity to have enough items to generate adequate scale variability (Millar and Shevlin, 2007). The choice of using 7 items per subscale allows a possible range of scores from 7 – 35 for each dimension and from 35-105 for the entire scale and can be quickly and easily completed. The development of scales based on pre-determined number of items to retain has been used frequently to facilitate scale comparisons as in the well-known and widely used GHQ-28 (Goldberg and Hillier, 1979). The GHQ -28 was used as a precedent in this study.

The aim of this research was to develop an outcome measure that was short, for quick completion, that was simple and quick to score and that has little burden on the patient(s) to complete. The decision to have 7 items per subscale prior to EFA was made so that there would be an appropriate balance between the scale being short and having poor/low reliability and being too long and putting a greater demand on the patient(s). Seven items were chosen only if they loaded on the factor > 0.40 as per 'rule of thumb'. Quick scoring on a balanced scale i.e. equal number of items per scale, leads to easy comparison between sub-scales. The EFA was not truly 'exploratory as a one-factor model was requested (refer to section 6.2.3.3).

6.2.3.2 Missing Data

Data were missing on all items although the percentage of missing data was small on items 1 through to 61 (range 2.2-7.8%; mean 3.8; SD = 1.20). There was a larger amount of missing data for items 62, *(I have struggled to fit everything into my routine life),* and 63 *(Having thalassaemia has made most things difficult),* (24.4%). Missing data were successfully imputed using the expectation-maximization (EM) algorithm which has been demonstrated to be an effective method of dealing with missing data (Bunting, Adamson and Mulhall, 2002). Ninety one (100%) valid cases were included; likewise deletion was based on all variables. The EM algorithm is used in statistics for finding maximum likelihood estimates of parameters in probabilistic models, where the model depends on unobserved latent variables (Bunting, et. al. 2002). Expectation-maximization (EM) methods are available for randomly missing data and form a missing data correlation

matrix by assuming the shape of a distribution for the partially missing data and basing inferences about missing values on the likelihood under that distribution. It is an iterative process with two steps: (1) the E step finds the conditional expectation of the missing data given the observed values and current estimate of the parameters such as the correlations; (2) the M step performs maximum likelihood estimation as though the missing data had been filled in. After convergence is achieved the filled in data are saved in the data set. The EM algorithm is an alternative to the psychometrically sound method of imputing data of replacing missing items with a person-specific mean score i.e. the average score across completed items for that respondent (Ware et. al. 1993). Whilst the person-specific mean score reduces the variability of the data, the EM algorithm presents the likelihood or value that would be the most likely i.e. maximum likelihood, drawn from the given population (Bunting, et. al. 2002). The descriptive statistics and response data of the 5 subscales of the THALI are reported in Tables 8a, 8b and 8c.

Item discriminant validity, which simply tests that each item is correctly placed in a subscale was assessed by correlating each item with the total subscale across all subscales. If the item was correctly classified in a subscale it produced higher correlations with that subscale compared to the other 4 subscales. Within all the sub-scales most correlations were significant at the 0.01 level (two tailed) (see Appendix XXXIV).

Table 8a: THALI (5 sub-scales) - Scaling Assumptions

Psychometric Properties	**General**	**Coping**	**Body**	**Social**	**Autonomy**
Item Mean Score Range	1.46 – 2.78	1.73 – 2.38	1.34 – 1.72	1.31 – 2.10	-0.77 – 2.20
Item SD Range	2.61 – 3.22	2.55 -3.12	2.15 – 3.06	2.08 – 2.65	2.62 – 5.51
Item Skewness Range	-3.95 – 2.79	-3.47 – -3.08	-3.32 – -2.63	-3.41 – -2.90	-3.30 – -1.02
Item correlation with Hypothesised Scale Range (See Appendix XXXIVfor more detail*)	*r* =0.72– 0.88	*r* =0.83– 0.91	*r* =0.63– 0.77	*r* =0.62– 0.83	*r* =0.79– 0.90

* Reported item correlation range is inclusive of all correlations (significant and non-significant).

Table 8b: THALI (5 sub-scales) - Missing Data

Psychometric Properties	General	Coping	Body	Social	Autonomy
Number of respondents	91	91	91	91	91
No. of Respondents Missing Data on 1 item only	4	1	2	3	1
No. of Respondents Missing Data on 2 items only	0	0	2	1	20
No. of Respondents Missing Data on 3 items or more	3	4	3	2	3
No. of respondents with complete data	83	85	83	84	66

Table 8c: THALI (5 sub-scales) - Acceptability

Psychometric Properties	General	Coping	Body	Social	Autonomy
Total Possible Score Range	7-35	7-35	7-35	7-35	7-35
Total Observed Score Range	9 - 34	7 -34	7 - 32	7 - 31	7 - 35
Mean Observed Score (SD)	19.13	17.45	13.42	13.93	16.14
Floor/Ceiling Effect *	No	No	Floor (19.27%)	Floor (15.48%)	No
Skewness	.39	.50	.98	.88	.76

*Floor or Ceiling effects were calculated by assessing the proportion of participants with the lowest or highest possible score. Floor or ceiling effects are considered to be present if more than 15% of the respondents achieved the lowest or highest possible score respectively
(Terwee, Bot, de Boer, van der Windt, Knol, Dekker. et. al. 2007).

6.2.3.3 Exploratory Factor Analysis (EFA): Purpose and Methods

The purpose of EFA is to identify the factor structure for a set of variables (Tabachnick and Fidell, 2001) as in this instance. Exploratory factor analysis (EFA) involved determining how many factors existed as well as the pattern of the factor loadings. Exploratory factor analysis (EFA) is generally considered to be more of a theory-generating than a theory-testing procedure (Tabachnick and Fidell, 2001).

Although the measure was designed to be multidimensional, each subscale is intended to be unidimensional. Unidimensional subscales were created using maximum likelihood EFA. Each group of items, representing each subscale, was separately subjected to a maximum likelihood factor analysis with a forced one-factor solution, so that all the items loaded on the factor they were designed to, and the 7 items with the highest factor loadings were retained for inclusion in the final scale. This resulted in five separate factor analyses. There were 4 reasons for conducting the analysis in this fashion. First, Anderson and Gerbing (1988) advocate this two-step approach to scale construction which emphasizes the importance of unidimensionality of subscales. Similarly, Comrey (1988) supports the use of unidimensional subscales based on factor analysis. Second, this approach maximises the power of the analyses as the ratio of participants-to-variables is higher than when all the variables are analysed together. Third, maximum likelihood has much better statistical properties than other methods of estimation in factor analysis such as principal components, specifically (1) they become minimum variance unbiased estimators as the sample size increases i.e. the average value of the parameter estimates will be theoretically exactly equal to the population value if a very large number of random samples is replaced from a population so the estimator has the smallest variance and thus the narrowest confidence interval of all estimators of that type, and (2) they have approximate normal distributions and approximate sample variances that can be used to generate confidence bounds and hypothesis tests for the parameters (Bollen, 1989). Forth, maximum likelihood factor analysis is preferred to the common use of (1) PCA, (2) the retention of factors with eigenvalues greater than one and (3) varimax rotation. This approach has been shown to be poor at explaining the underlying structure of data and has been *"...shown to have potentially serious negative consequences" (p13)*, in terms of producing inconsistent results as a number of decisions undertaken can have a substantial impact on the results and their interpretation (Preacher and MacCallum, 2003). In addition, the interrelationship

of variables is left unspecified and it is impossible to test directly alternative theoretical structures underlying the data (deVet et. al. 2005).

Factor analysis was primarily used as a tool for reducing the number of variables, a candid exploration of the data collected. Exploratory factor analysis (EFA) was used to identify a group of items that appeared to measure the domains of general physical health (GPH) (n=15), psychological health and personal beliefs – coping (C) (n=19), psychological health and personal beliefs – body image, appearance and confidence (BIAC) (n=9), social relationships (SR) (n=7) and autonomy (A) (n=13). Although the THALI measure is multidimensional each subscale is intended to be unidimensional. Unidimensional subscales were created using maximum likelihood factor analysis. Comrey (1988) supported the use of unidimensional subscales based on factor analysis. Data from the returned 91 questionnaires were used for the analysis that aimed to create five unidimensional subscales i.e. 5 domains identified from content analysis. Each group of items within the domains were designed and written to measure only one aspect of the impact of BTM on adult patients. This was represented in the factor analysis by forcing a one-factor solution so that all the items loaded on the factor they were designed to. Each group of items was separately subjected to a maximum likelihood factor analysis with a forced one-factor solution and the 7 items with the highest factor loadings were retained for inclusion in the final scale. The factor loadings for the items that were retained were all adequate ranging from 0.66 – 0.86 for GPH, 0.80 – 0.88 for C, 0.53 – 0.78 for BIAC, 0.41 – 0.86 for SR and 0.73 – 0.88 for A. Bar 1 loading on the SR scale (0.41), all the loadings exceeded, or were equal to, the conservative criteria for item retention by being greater than 0.45 (Tabachnick and Fidell, 2001). Table 9 shows the order in which variables contribute to factors by size of loadings. It should be noted that the scale SR had 7 items therefore all items were chosen as per rationale (see section 6.2.3.1).

6.2.3.4 Variance

The total variance explained is reported. Eigenvalues greater than 1, the default value (Tabachnick and Fidell, 2001) are given. Extracted factor 1 for GPH explained 44.41% of the variance (eigenvalue 6.66). Together with factors 2 (eigenvalue 1.26), 3

Table 9: Order (by size of loadings) in which Variables Contribute to Factors

Factor 1 (GPH)		Factor 2 (C)		Factor 3 (BIAC)		Factor 4 (SR)		Factor 5 (A)	
Item	**Loading**	**Item**	**Loading**	**Item**	**Loading**	**Item**	**Loading**	**Item**	**Loading**
Tired	0.86	*Frust. 1*	0.88	*Body*	0.78	*Rejected*	0.86	*Mobility*	0.88
Run down	0.85	*Angry*	0.84	*Height*	0.77	*Penalised*	0.79	*Lift 10*	0.87
Energy	0.78	*Irritable*	0.82	*Age/peers 2*	0.66	*Social 6*	0.79	*Walk*	0.86
Rest	0.74	*Emotion*	0.81	*Diff. 3*	0.66	*Rel. 7*	0.56	*Things 11*	0.82
Stamina	0.73	*Anxious*	0.81	*Complexion*	0.58	*Leisure*	0.53	*Bend*	0.82
Aches	0.67	*Stressed*	0.80	*Inferior 4*	0.58	*Family 8*	0.51	*Fit life 12*	0.77
Dizzy	0.66	*Worried*	0.80	*Self-con. 5*	0.53	*Short f. 9*	**0.41**	*Chores*	0.73

Key for items:

Frustrated (1) Look younger than age/peers (2) Different to others (3)
Inferior to others (4) Self-confidence (5) Social life affected by illness (6)
Inability to form successful relationships (7) Restricted in doing things with family (8) Short with my family (9)
Unable to lift heavy things (10) Thalassaemia makes most things difficult (11) Struggled to fit everything into routine life (12)

(eigenvalue 1.16) and 4 (eigenvalue 1.01), the cumulative % was 67.24. Extracted factor 1 for C explained 55.70% of the variance (eigenvalue 10.58). Together with factors 2 (eigenvalue 2.05) and 3 (eigenvalue 1.09), the cumulative % was 72.23. Extracted factor 1 for BIAC explained 46.04% of the variance (eigenvalue 4.14). Together with factors 2 (eigenvalue 1.40) and 3 (eigenvalue 1.11), the cumulative % was 73.93. Extracted factor 1 for SR explained 50.94% of the variance (eigenvalue 3.57). Together with factor 2 (eigenvalue 1.11), the cumulative % was 66.84. Extracted factor 1 for A explained 57.72% of the variance (eigenvalue 7.50). Together with factor 2 (eigenvalue 1.14), the cumulative % was 65.71.

6.2.3.5 Reliability and Internal Consistency

The internal consistency for the 5 sub-scales was tested using Cronbach's α (Cronbach, 1951). Internal reliability is generally acceptable for factors with a Cronbach α of 0.70 or above (Nunnally, 1996). Analysis of internal consistency was evaluated with Cronbach's

α for each group of five items; all the estimates were high (0.83-0.94). Table 10 shows the 5 health profiles, their description, number of items, items and Cronbach α. No α's were higher than the total alpha if an item was deleted for all subscales (see Appendix XXXV).

6.2.3.6 Descriptive Statistics and Response Data for the Thalassaemia Adult Life Index (THALI)

The stated 35 items (see Table 9) constituted the THALI scale. The descriptive statistics and response data for each subscale are presented in Tables 8a (scaling assumptions), 8b (missing data), 8c (acceptability) and 10 (internal consistency). Each of the subscales generated score variability of between 13.42 and 19.13 out of a possible 35. The mean scores on subscales GPH (19.13) and C (17.45) reflect the average responses above the subscale midpoint (17.5).

6.2.3.7 Convergent Validity

Table 11 shows the (Pearson) correlations between the 5 subscales. A good correlation was taken to be between 0.3 – 0.8 (Lohr et. al. 1996). As per 'rule of thumb', a lower correlation would indicate that the sub-scales are measuring two conceptually different/distinct constructs and a higher correlation would indicate that the sub-scales are measuring conceptually very similar constructs. All of the correlations are positive and significant seemingly due to the subscale measurement of a broader global outcome of QoL

6.3 Discussion

6.3.1 Overall Results

The THALI was developed on the principles of domain specificity, multidimensionality and expectations for the future. Data from a community sample of adult patients were used for the purposes of item selection for a short scale and to identify a factor structure. During the process of item selection, the 7 items selected to measure each of the 5 domains were found to have desirable properties. Firstly, each item loaded positively with high factor loadings extracted by maximum likelihood. Secondly, each group of items was found to be internally consistent and highly reliable (>0.80) in terms of Cronbach's α per scale. (The estimates for α were satisfactory). Thirdly, each group of items generated adequate score variability suggesting that the measure may be useful in quantifying individual differences on each of the 5 domains.

Table 10: Internal Consistency of the Thalassaemia Adult Life Index (THALI)

Scale	No. of items	Items	Definition of scale	Internal consistency (Cronbach's α)
General physical health (GPH)	7 items	*Lacked energy* *Felt tired* *Lacked stamina* *Felt run down* *Felt dizzy* *Been full of aches and pains* *Needed to rest more often*	Self-evaluation of personal physical health status	α=0.90
Psychological health and personal beliefs (PHP) A Coping (C)	14 items total 7 items	*Been worried* *Been angry* *Been frustrated* *Been emotional* *Been a bit run down or stressed* *Been irritable* *Been very anxious*	Self-evaluation of psychological upset and/or well-being	α=0.94
B Bodily image, appearance and confidence (BIAC)	7 items	*I have a shortened body* *I look younger than my age/peers* *I have a pale complexion* *I am short in height* *I am different to others and am conscious of this* *I have no self-confidence* *I feel a bit inferior to others*	Self-evaluation of physical appearance and self-confidence	α=0.83
Social relationships (SR)	7 items	*Been restricted in doing things that I would have liked to have done with my family* *Been really short with my family* *Not been able to successfully form relationships with others* *Been rejected in some way because I have thalassaemia* *Been penalised because of my illness* *Felt that my social life has been affected by my illness* *Not done any leisure activities*	Self-evaluation of limitations in social activities from physical and emotional difficulties	α=0.83
Autonomy (A)	7 items	*Been limited in doing chores around the house* *Had difficulty with my mobility* *Not been able to bend with ease* *Not been able to do a lot of walking* *Been unable to lift heavy things* *Struggled to fit everything into my routine life* *Felt that having thalassaemia has made most things difficult*	Self-evaluation of limitations in usual physical role activities	α=0.94

(100% of valid cases were included (n=91); likewise deletion was based on all variables)

Table 11: Subscale Correlation Matrix

	GPH	C	BIAC	SR	A
GPH	1.00	0.58(**)	0.36(**)	0.55(**)	0.61(**)
C	0.58(**)	1.00	0.49(**)	0.54(**)	0.61(**)
BIAC	0.36(**)	0.49(**)	1.00	0.60(**)	0.52(**)
SR	0.55(**)	0.54(**)	0.60(**)	1.00	0.78(**)
A	0.61(**)	0.61(**)	0.52(**)	0.78(**)	1.00

** Correlation is significant at the 0.01 level (2-tailed); N=91 for all correlations

Key for THALI-35 sub-scales

General physical health (GPH) Coping (C) Bodily image, appearance and confidence (BIAC)
Social relationships (SR) Autonomy (A)

Note: With the exception of the items on body image, the 35-items remaining after item refduction were ordered in a way so that they were mixed i.e. item 1 of GPH, then item 1 of C, item 1 of BIAC, item 1 of SR, item 1 of A, item 2 of GPH, item 2 of C, to avoid response set, bias and order effects (Wolcott, 1994). The stem, In the past four weeks, it has bothered me that…', best represented the body image items so they were grouped together. All the other items were best represented by the stem, In the past four weeks, I have…'.

6.3.2 Evaluation of Stage 2

6.3.2.1 Practical Considerations

The sampling frame adopted in this stage has the main advantage of being representative of people with thalassaemia (Hobart et. al. 2004). Additionally, it has the largest numbers of geographically disparate patients that can be accessed by postal survey thus reducing selection bias and minimising research staff involvement (Hobart et. al. 2004). A disadvantage of using the UKTS membership database to define the sampling frame is that the representativeness of people who join charitable groups is unknown; those who join such groups may be the most affected by their condition and/or least able to cope with illnesses (Eiser, 2000). A further disadvantage is that not all members have thalassaemia or BTM specifically (Hobart et. al. 2004). It is known that many members of the UKTS are partners, friends or relatives of people with thalassaemia although the percentages of each have not been determined by the UKTS. Due to the sampling frame and its limitations a response rate was difficult to calculate. Even so, what is known is that the preliminary 63-item questionnaire was administered by postal survey to a community

sample of 381 adult members from the UKTS and 91 questionnaires were returned i.e. 24% response rate.

According to Modell et. al. (2003) in 2003 there were over 500 adults with thalassaemia alive and on treatment in the UK (although the exact type of diagnosis of these patients was not deciphered). It is noteworthy that it would be difficult to generalise the findings of 91 patients to a potential BTM adult population of over 500 (17%) however, like the UK Thalassaemia Register this study incorporated age, gender and ethnicity of patients therefore there may be some generalisation. For example, Modell et. al. (2000) identified that BTM is more or less restricted to ethnic minority populations, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi. In this patient sample, 36% were Greek Cypriot, 25% Indian, 10% Greek, 10% Middle Eastern and 3% were Pakistani.

Advocates of quantitative methods argue that only by using such methods can the social sciences become truly scientific (Sanchez, 2006). This systematic scientific investigation reaches many people, in the community in this instance and the contact with questionnaire respondents is quick (Sanchez, 2006). Psychometrics is the field of study concerned with the theory and technique for measuring social and psychological attributes and phenomena and this field is central to much quantitative research that is undertaken within the social sciences; by using quantitative methods it is possible to give precise and testable expression to qualitative ideas (Sanchez, 2006). Associations may be examined between variables using methods of statistics therefore is suited for EFA as per psychometric theory (Nunnally and Bernstein, 1994). However, a fundamental principle in quantitative research is that correlation does not imply causation; this principle follows from the fact that it is always possible a spurious relationship exists for variables between which covariance is found in some degree (Sanchez, 2006).

6.3.2.2 Theoretical Considerations

Missing data were effectively imputed using the EM algorithm**.** This procedure has the advantage of avoiding impossible matrices, avoiding over-fitting i.e. making the solution better than it actually is and producing realistic estimates of variance (Tabachnick and Fidell, 2001).

In this study, EFA was adopted for item reduction. Most applications of factor analysis are exploratory in nature (Tabachnick and Fidell, 2001). Although EFA is not based on theoretical criteria (Tabachnick and Fidell, 2001) domains of interest/importance can be identified by researchers even though there was no statistical basis. This was the case in this research. In using EFA, the researcher identified a sample that exhibited a spread in scores (see Tables 8a, 8b and 8c). Correlation coefficients tend to be less reliable when estimated from small samples therefore it is important that the sample size be large enough that correlations are reliably estimated (Tabachnick and Fidell, 2001). As a guide upto 100 is poor; 300 cases is the least necessary for factor analysis (Comrey and Lee, 1992). Although the sample size was small (n=91) 60% of correlations were strong (> 0.75), all were reliable and a few (5) domains were shown. The UK adult thalassaemia population is small (Modell et. al. 2003) therefore this sample size was sufficient (Tabachnick and Fidell, 2001). Although the size of the sample may be deemed adequate for the purpose of this preliminary research, further sampling would be essential to estimate the generalisability of the measure for use with people with thalassaemia in general.

Reproducibility evaluates whether an instrument yields the same results on repeated assessments assuming that respondents have not changed on the domain being measured (Spearman, 1904). An example of reproducibility is test-retest reproducibility and is the most relevant form of reproducibility for patient-based outcome measures because parallel forms of measures do not usually exist and most measures are self-completed (Hobart et. al. 2004). In this study, test-retest reproducibility was to be examined by re-administering the instrument to the same respondents after a specified period. However, this was not accomplished as the UKTS did not consent to their members being contacted for questionnaire completion on more than one occasion for any one study. (If the results from the two time points had high agreement the instrument would have demonstrated high test-retest reproducibility). Although there is no rule about the length of the test-retest interval, it needs to be long enough to ensure that respondents are unlikely to recall their previous answers but not so long that changes in health have occurred (Nunnally and Bernstein, 1994). Although the recommended that the range of the test-retest interval is between 2-14 days (Streiner and Norman, 1995) this must be influenced by the nature of the study; in this study the interval may have been between 2-27 day (the time between the patient having their next blood transfusion).

Health outcome experts have argued that measures like the THAkLI may fundamentally be a list of medical symptoms (physical parts) and not aspects of QoL (Cummins, 2005). Thalassaemia is all-encompassing and affects life on a daily basis; it does not go away hence its chronicity (CDC, 2007). Therefore, the QoL assessment of such persons shall need to include their health (CDC, 2007). Like in other chronic illness, QoL is one of the most important outcomes for people with thalassaemia and it is important to assess the degree of illness intrusion (Jenkins, 1992). What needs to be established is whether the THALI includes symptoms of circumstance, or causes and consequences (Cummins, 2005). As no consensus exists about what QoL is or how it should be measured (Anderson and Burckhardt, 1999) it may not be obvious what the THALI is actually measuring therefore the THALI is described as a patient-based outcome measure.

Chapter 7 presents the initial evaluation of the psychometric properties of the THALI-35.

6.4 Acknowledgements

It should be known that the UKTS gave their full consent and support of this study (see Appendix XXXVI) for the letter of support from the UKTS).

Chapter 6 Addendum

An Alternative Exploratory Factor Analysis (EFA) of Stage 2 (Item Reduction) data in the Development of the Thalassaemia Adult Life Index (THALI)

Chapter 6 Addendum Overview

The EFA was re-done with no preconceived ideas about the content and structure of the health outcome questionnaire for BTM adults. A number of factor analyses have been considered and an explanation of the one chosen to be the most appropriate has been given. Full methods and results are provided.

6A.1 Method

6A.1.1 Principal Component Analysis (PCA)

As discussed by Fayers and Machin (2000), PCA is adequate in the situation of the development of an instrument. It is the mostly used tool in EFA and for making predictive models and determines underlying domains (factors) of instruments.

Scales were to be developed using an iterative process. To determine the factor structure (structural validity) for the data collected on the 63 items generated in stage 1 (see Chapter 5), EFA was carried out using PCA with oblimin (oblique rotation) with Kaiser Normalization rotation. Cases with missing data were deleted listwise.

6A.1.2 Rotation

Commonly and traditionally, varimax or orthogonal factor rotation is applied when developing and validating health outcome measures e.g. Gee et. al. (2000) (CF) and Burroughs et. al. (2004) (diabetes). However, in this instance, factor solutions were examined using oblimin (oblique rotation) with Kaiser Normalization rotations of the factor loading matrix (Kaiser, 1960). A discussion on the rationale for this decision now follows.

Orthogonal rotation assumes that the factors are not correlated therefore each factor is independent of, or orthogonal to all other factors so that no correlation exists between the factors therefore determined to be zero (Nunnally and Bernstein, 1994). The aim of this type of rotation is to minimise the number of variables that load highly on a factor

(Nunnally and Bernstein, 1994). Alternatively, oblique or oblimin factor rotation relaxes the assumption that the extracted factors must be orthogonal/correlated (over 0.3) (Nunnally and Bernstein, 1994). Researchers that have used this type of rotation when developing and validating health outcome measures include Hays et. al. (1994) (kidney disease) and Smith (2002) (IBD). The advantage of orthogonal factor rotation over oblique (oblimin) factor rotation is that factor loadings can be squared and summed across factors to estimate the amount of variance in each scale accounted for by each factor and the amount of variance in each scale is explained by all factors i.e. this maximises the variance, and as a result factor content and implications for the interpretation of each scale are more straightforward (Nunnally and Bernstein, 1994) whereas in oblique (oblimin) rotation one set of variables may lie along an axis, while the other set may lie along a 45 degree angle to the axes so rather than arbitrarily constraining and maintaining the factor rotation to an orthogonal (90 degree angle/axes), the oblique solution allows for correlations between the factors and can therefore identify the extent to which each of the factors are correlated (Nunnally and Bernstein, 1994). This often simplifies the factor solution since many attitudinal dimensions are in fact likely to be correlated (Rummel, 1970; Tabachnick and Fidell, 2001). Unlike orthogonal rotation, the pattern matrix and the structure matrix are not equal after oblique rotation (Rummel, 1970; Tabachnick and Fidell, 2001) so only the pattern matrix needs be examined since it allows for the easiest interpretation of factors; the pattern matrices found using oblique rotation are more interpretable than the orthogonal rotation solutions with fewer variables loading significantly on more than one factor (Rummel, 1970; Tabachnick and Fidell, 2001).

In summary, oblimin (oblique rotation) was adopted to allow the factors to be correlated and to provide the best defined item structure.

6A.2 Results

6A.2.1 Data Screening

The data was screened for univariate outliers; there were none. Ninety one (91) (100%) valid cases were included; likewise deletion was based on all variables. User-defined missing values were treated as missing. Statistics were based on cases with no missing values for any variable used. Data were missing on all items although the percentage of missing data was small on items 1 through to 61 (range 2.2-7.8%; mean 3.8; SD = 1.20). There was a larger amount of missing data (24.4%) for items 62 *(I have struggled to fit*

everything into my routine life) and 63 *(Having thalassaemia has made most things difficult*). No items were eliminated prior to factor analysis.

6A.2.2 Selection of Factors

Eigenvalues over 1.00 are used as a basis for determining factor retention (Kaiser, 1960; Field, 2003). This is considered more appropriate than selection by scree plot and communalities (a figure between 0 and 1 that represents the proportion of common variance of greater than 0.70) (Field, 2003).

Initially, the factorability of the items was examined (factor analysis). Two well-recognised criteria for the factorability of a correlation were used (Nunnally and Bernstein, 1994). Firstly, all of the 63 items correlated with at least 0.3 with at least one other item suggesting factorability and secondly the communalities were all above 0.3 ranging from 0.70 to 0.93 further confirming that each item shared a common variance with other items i.e. there was a high degree of homogeneity as each item correlated highly with the rest of the scale (see Appendix XXXVII for communalities). Given these overall indicators, factor analysis, which describes the variability among observed variables in terms of fewer unobserved variables called factors used to group items into subscales, was conducted with all 63 items.

All items were entered into a PCA and the initial eigenvalues showed that the first factor explained nearly 40% (39.55) of the variance, the second factor 7% (7.25) of the variance and the third factor nearly 6% (5.82) of the variance. The fourth to the thirteenth factors had eigenvalues of just over one to just over three, each factor explaining between 1.7% (1.69) - 5% (5.12) of the variance. The first 13 factors (with all eigenvalues over 1) explain 82.49% of the total variance. The first 15 factors (where factors 14 and 15 have eigenvalues less than 1) explain 85.30% of the total variance. See Appendix XXXVIII for the extraction statistics.

The data suggested one, four and thirteen factor solutions. The four factor solution (four principal components) was favoured accounted for the following reasons: it accounted for nearly 58% of the variance, (all factors had eigenvalues over 1 (Kaiser, 1960; Field, 2003)), 'leveling' off of eigen values (Cattell, 1966) (see Appendix XXXIX for scree plot), the 'rule of thumb' 5% variance cut off (Guertin and Bailey, 1970), and the difficulty of

interpreting fifth and subsequent factors. Of the 16 primary loadings on factor 1, 50% were over 0.5 with particularly strong loadings ranging from 0.61 – 0.85. See Appendix XXXX for the pattern matrix.

6A.2.3 Sample Size

Guadagnoli and Velicer (1998) suggest that if a factor has four loadings greater than 0.6 it should be reliable regardless of sample size. MacCallum, Widaman, Zhang and Hong (1999) suggest that with communalities greater than 0.6, sample sizes of less than 100 should be adequate.

6A.2.4 Internal Reliability

The internal consistency for the scale and each of its subscales was examined using Cronbach's α, with a score equal to, or greater than 0.7 considered satisfactory (Huck and Cormer, 1996). The alphas varied from 0.73 to 0.96 (see Appendix XXXXI) therefore the subscales have high internal reliability. Alphas higher than the total alpha if an item deleted occurred in the Problems with Physical Health and Difference domain (0.76; scale alpha was 0.73) and the Body Image domain (0.86; scale alpha was 0.81) (see Appendix XXXXI). Overall, these analyses indicate that four factors underlie BTM adult patients' health outcome.

6A.3 Scale Identification and Refinement

Four components were identified and named. The criteria for item selection and deletion after entering the raw data into a PCA were two-fold: 1) statistical criteria loading of > 0.3 and 2) theoretical criteria with regard to items being meaningful clinically and based on literature (discussed in chapter 2 - the psychology of BTM and other chronic illnesses).

All potential factor solutions were examined for cross loadings. Two cross loadings were identified: cross loadings met the minimum criteria of cross loadings of 0.3 or above (Ferguson and Cox, 1993): item 29 (0.37 factor 1 and 0.48 factor 4) and item 48 (factor 1 0.32 and factor 3 -0.62). Some of the items were conceptually difficult to retain within their respective factors. See Appendix XV for the items mentioned forthwith. In component 1, named Feelings and Emotions, there were 16 items. Item 48 cross loaded in component 3; its suitability was held in component 3. Items 7 and 13 were conceptually difficult to retain in component 1. Thirteen items remain in component 13. In component

2, named Problems with Physical Health and Difference, there were 9 items. Items 42, 45 and 52 were conceptually difficult to retain in this component. In addition, the general content of item 50 is already covered by items in component 1. Five items remain in component 2. It should be noted that 3 of the 5 retained items have negative loadings. Negative loadings on components mean that the factor name should indicate that it is negative. This also explains the negative correlation of factors. In component 3, named Problems with Daily Activities and Routine, there were 14 items. Items 28, 31 and 63 were eliminated as they were conceptually difficult to retain within this component. The content of item 3 is covered by an item in factor 2. Ten items, all with negative loadings, remain in component 3. Component 4, named Body Image, had 5 items. Item 29 cross loaded with another item in component 1 and was deemed better suited to that component. Four items remain in component 4.

Thirty two items were retained. The content of the overall scale concerns the physical and psychological impact of BTM.

6A.2.4 Distributional Shape and Descriptive Statistics (Factors)

Descriptive statistics for the subscales are presented in Table 12. Data are generally normally distributed if the kurtosis and skewness indices are not more than 1 away from 0 (Huck and Cormer, 1996). Nunnally and Bernstein (1994) also stated that absolute values of skewness indices greater than 0.30 seem to be extremely skewed and that kurtosis indices greater than 0.10 may be a problem. Thus, all four factors may not be regarded as normally distributed.

It is noteworthy that response data for the 63-items can be found in Tables 8a, 8b and 8c.

6A.2.5 Inter-correlations between the THALI Subscales

Correlations between the factors were investigated. Item reduction produced four scales supporting the multidimensionality of health outcome in BTM adult patients. The scales seemed to measure distinct constructs but there was an expectation that stronger correlations would exist between the components although no clear delineation between the components was apparent. Very low strength relationships between the factors were found (see Table 13).

Table 12: Descriptive Statistics for each Factor

Statistic		Factor 1 Feelings and Emotions	Factor 2 Physical Health and Difference	Factor 3 Daily Routine	Factor 4 Body Image
N	Valid (Valid listwise = 75)	81	85	83	84
	Missing	10	6	8	7
No. of Items		13	5	10	4
Mean		30.11	12.73	21.58	7.31
Std. Error of Mean		1.43	0.45	1.21	0.45
Std. Deviation		12.89	4.13	10.22	4.13
Variance		166.25	17.03	104.44	17.08
Skewness		0.66	0.38	0.70	1.26
Std. Error of Skewness		0.27	0.26	0.26	0.26
Kurtois		-0.64	-0.79	-0.54	0.55
Std. Error of Kurtois		0.53	0.52	0.52	0.52
Floor/Ceiling effect(s)*		Ceiling (27.4%)	No	No	Ceiling (23%)
Total Possible Score Range		13-65	5-25	10-50	4-20
Range		48	16	39	16
Minimum		13	6	10	4
Maximum		61	22	49	20
Sum Statistic		2439	1082	1791	614
Item Inter-correlation Range (mean)**		0.41-0.85 (0.62)	-0.02-0.78 (0.35)	0.38-0.82 (0.58)	0.26-0.84 (0.50)

*Floor/ceiling effects were calculated by assessing the proportion of participants with the lowest or highest possible score. Floor/ceiling effects are considered to be present if more than 15% of the respondents achieved the lowest or highest possible score respectively Terwee, Bot et. al. (2007). The average maximum endorsement frequency (calculated as the mean of the most frequently endorsed response category for each question) was 42.01% with the highest maximum endorsement frequency being 74.4% for question 39.
**Reported item correlation range is inclusive of all correlations (significant and non-significant) (Pearson Correlation statistic). Correlations among items should not be greater than 0.70 (Juniper, Guyatt, Streiner and King, 1997).

Table 13: Component Correlation Matrix

Component	1	2	3	4
1	1.00	0.01	-0.32	0.11
2	0.01	1.00	-0.07	0.11
3	-.032	-0.07	1.00	-0.05
4	0.11	0.11	.05	1.00

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

The four summary scores are generated by summing individual items and then transformed to a scale; a high score indicates worse health.

In summary, 63 questionnaire items generated from interviews with 16 adults with BTM were grouped into scales using factor analysis and then refined to form the THALI that contains 32 items, an instrument that measures the biopsychosocial impact of BTM. Psychometric properties of the scale (data quality, assumptions, acceptability, reliability), were good. Missing data was essentially very low. There was excellent communality amongst the items and item inter-correlation was sound. The subscales showed very good variability, moderate ceiling effects (on factors 1 and 4) and high internal consistency (Cronbach's alpha 0.73-0.96). However, very low strength relationships between the factors were evident. These results indicate that the THALI may become a useful tool in health outcome research in this patient group but must first undergo further rigorous psychometric evaluation.

Chapter 7

Psychometric Evaluation of the Thalassaemia Adult Life Index (THALI-35) Stage 3: Validation

Chapter Overview

This chapter outlines the psychometric evaluation of the Thalassaemia Adult Life Index **(**THALI-35). In stage 3 of 3 (validation), the 35-item reduction questionnaire was administered 'face-to-face' and by postal survey to a clinical sample of 35 adults with thalassaemia. In addition, these patients were sent several other questionnaires to assess the validity of the THALI-35.

7.1 Introduction

7.1.1 Background

The lack of validated BTM specific measures has led to the use of generic measures such as the SF-36 (Ware et. al. 1993) which have the advantage of enabling comparisons across diseases (Hobart et. al. 2001). However, psychometric limitations of the use of the SF-36 with other chronic illnesses like MS include significant floor and ceiling effects, limited responsiveness and under-estimation of mental health problems (Freeman, Hobart, Langdon and Thompson, 2000). Whichever health outcome instrument is used to assess the QoL of patients within clinical practice and/or research, it should satisfy the criteria for validity; instruments should have a strong psychometric property base (Hobart et. al. 2004). Quality of Life (QoL) scales especially those that are disease-specific, should have predictive validity so that they can be sensitive to real changes in real clinical conditions therefore have social and clinical validity (Hobart et. al. 2004). Eiser (2000) stated that QoL measures should tap areas of social importance to patients and be responsive to the different stages of conditions and their treatment.

7.1.2 Objective

In accordance with psychometric theory (Nunnally and Bernstein, 1994) the THALI-35, along with several other instruments, were administered to a clinical sample of adults with BTM. In this way, an initial evaluation of some of the psychometric properties of the THALI-35, (a 35-item, 5 domain instrument that measures the physical, psychological and social impact of BTM), were investigated.

7.2 Method: Validation

7.2.1 Participants/Sample

The validation stage of the THALI-35 was conducted with an adult clinical sample (n=35) from 6 hospitals around the UK (UCLH, The Whittington Hospital, Manchester Royal Infirmary, the Royal Hallamshire Hospital in Sheffield, Leicester Royal Infirmary and Birmingham City Hospital). A power analysis was conducted, using g-power, in order to estimate the sample size needed at this stage. The effect size was specified at 0.50, alpha at 0.05 and power at 0.90. The sample size was estimated at 31. To accommodate missing data and attrition an additional 10% was to be recruited, making a total sample of at least 34. Full details of the power analysis protocol are presented in Appendix XXXXI.

Seventy one percent of female patients and 29% of male patients were enrolled. Inclusion criteria for the study was that BTM patients were aged 18 years or above and being treated, managed and cared for in the UK. Participants ages ranged from 18-55 (M=30; SD = 8.56). The exclusion criterion for the study was difficulty with the command of the English language as the questionnaire was developed in the English (UK) language (this was difficult to identify by the patient records within the relevant departments of the hospital(s) by the administrators).

The majority of the patients (83%) were being treated, managed and cared for by the London hospitals. Fourteen percent of the patients did not state which hospital they attended; 0.03% of patients attend the Royal Hallamshire Hospital. Table 14 presents the characteristics of this clinical sample of patients.

Table 14: Clinical Sample Patient Characteristics

Variable	Value n
Ethnicity	
White British	12
White other	7
Indian	4
Pakistani	3
Bangladeshi	3
Asian/Asian British	1
Chinese	1
Other	1
Refused	3
Educational status	
No qualifications	4
G.C.S.E. 's or equivalent	12
University entry or equivalent	7
Degree	6
Higher degree	5
Employment status	
Employed	13
Self-employed	2
Unemployed due to TM	1
Unemployed	2
Other (student/housewife)	3
Marital status	
Single	18
Married	13
Separated	1
Divorced	1
Dependents	
Mean (SD)	1.40 (0.42)
(Range)	(0-2)
Treatment type	11
'Pump'	16
Oral chelator drug	5
Combination	3
Not stated	
Illness complications	
Diabetes	9
Osteoporosis/Osteoarthritis*	4
Hormonal problems	4
Cardiac problems	3
Hepatitis C**	3
Kidney disease	1
Asthma	1

*Loss of bone tissue causing the bone to become brittle and fracture easily/a common joint disease characterized by degeneration of the cartilage that lines joints or by formation of an outgrowth of bone at the boundary of a joint (osteophyte), leading to pain, stiffness and occasionally loss of function (BMA, 2002).

**Infection often transmitted through sharing needles and/or blood transfusions; can progress to cirrhosis (long term damage to liver cells) and/or hepatoma (a type of liver cancer) (BMA, 2002)

7.2.2 Procedure

The 35-item questionnaire was administered by postal survey to the clinical sample from the 6 most accessed hospitals in the UK by thalassaemia patients (UKTS, 2005).

Patients being cared for at the London hospitals i.e. The Whittington Hospital and UCLH were approached directly by the researcher over a four week period, in the outpatient departments (OPDs). These patients were identified for representativeness, and approached by their CNS asked if they would be interested in participating in the research. If they were interested, their contact details were given to the researcher with the view that relevant research documents and questionnaires would be sent to them within a week. A total of 77 patients expressed an interest in taking part in this stage of the research from these hospitals collectively. Two people who were asked to participate, refused (from UCLH). Via post, each patient was sent the documents relevant to this stage of the study i.e. a letter of invitation (see Appendix XXXXII), the PIS (see Appendix XXXXIII), the consent form (see Appendix XXXXIV), the ethnic origin form (see Appendix VI), the ABOUT YOU form (see Appendix VII) and a pack of 6 questionnaires. The pack of questionnaires included the THALI-35 (see XXXXV), the SF-36 (Ware and Sherbourne, 1992) (see Appendix XXXXVI), the BRIEF COPE (Carver, 1997) (see Appendix XXXXVII), the Rosenberg Self-Esteem scale (RSE) (Rosenberg, 1965) (see XXXXVIII), the Sickle Cell Self-Efficacy Scale (SCSES) (Edwards et. al. 2000) (see Appendix XXXXIX), and the Body Image Quality of Life Inventory (BIQLI) (Cash and Fleming, 2002) (see Appendix XXXXX). These questionnaires are discussed below in section 7.2.3. The questionnaires were not to be completed in any particular order and there was no time limit.

As in stages 1 and 2, if patients agreed to their G.P. being informed of their participation in the study, the G.P. information sheet for postal survey 2 (see Appendix XXXXXI) was sent to their G.P.

Due to logistics i.e. the researcher being based in London, patients being cared for at Manchester Royal Infirmary (n=10), the Royal Hallamshire Hospital in Sheffield (n=4), Leicester Royal Infirmary (n=10) and Birmingham City Hospital (n=10), were sent the relevant documents by the administrators within the relevant departments at the relevant sites. The prepared packs of questionnaires and other relevant research documents (stated

above), were sent to the administrators who then attached patient address labels and then posted them with a pre-paid, stamped addressed envelope inside.

Whilst it is common practice that questionnaires and other relevant documents are re-sent to patient samples with postcard/letter reminders within a three week period if they have not been received in the first instance (Dillman, 2000), in this study the patients were sent the questionnaires on only one occasion. Although it would have been possible to adopt this practice for the London based clinical sample, the clinicians at the other 4 hospitals thought this would add to the workload of the administrators and 'pester' their patients, to their detriment for subsequent departmental clinical trials and research, so for consistency this practice was not carried out at any site. In addition, to avoid extra workload for the administrators at these sites, the questionnaires and other relevant documents were returned to the researcher's place of work.

The researcher asked patients who did not want to participate to return the questionnaires blank; no blank questionnaires were returned. The response rate was 32%.

7.2.3 Measures

In addition to the THALI-35, the following self-report questionnaires were administered to the clinical sample to assess the patients on the 5 domains of the THALI.

7.2.3.1 General Physical Health and Social Relationships

The SF-36 (version 1) (Ware and Sherbourne, 1992) consists of 36 items and 8 independent dimensions and incorporates physical functioning, social functioning and role limitations (emotional) scales. As already discussed in chapter 3, sections 3.4.2.1.1.1 and 3.4.2.1.1.2, the SF-36 is a well-standardised and well-validated measure of assessing generic QoL in a general adult patient population (Ware et. al. 1996) and is clinically and socially relevant (Stewart, Greenfield, Hays, Wells, Rogers, Berry et. al. 1989). The SF-36 was designed for research and it easy to complete and score. A higher score indicates less limitation, better functioning or less pain. See chapter 4, section 4.4.1.1 for a discussion on the psychometric properties of the SF-36.

7.2.3.2 Self-esteem and Body Image (Body Image, Appearance and Confidence THALI Domain)

The RSE (Rosenberg, 1965) was administered to indicate adults' global feelings of self-worth. Responses to each of the 10 Likert scale items range from 'strongly disagree' to 'strongly agree'. Total scores on the RSE can range from 10 to 40 with higher scores representing greater levels of self-worth/self-acceptance. The RSE has repeatedly demonstrated good psychometric properties e.g. reliability 0.80 (total scale alpha), construct and convergent validity (Blascovich and Tomaka, 1991). The RSE can be completed in less than 5 minutes.

The BIQLI (Cash and Fleming, 2002) is designed to quantify the impact of body image on aspects of one's life. The item content reflects domains and/or contexts in which body image has been found to be consequential (Cash and Fleming, 2002). Participants rate the impact of their own body image on 19 areas using a 7-point bipolar scale from -3 to +3 that report negative, positive or no impact. The BIQLI is internally consistent (0.95) and there is strong initial support of the reliability of the impact of body image on QoL experiences e.g. in males and females (Cronbach alpha's 0.95 and 0.95 respectively), and validity established with other relevant measures of body image (evaluation, investment, affect, and body image QoL), as well as with measures of psychosocial functioning like self-esteem, anxiety, depression, eating disturbance (Cash, Jakatdar and Williams, 2003).

7.2.3.3 Coping

The BRIEF COPE (Carver, 1997) is a 28-item coping inventory of 14 subscales. Each sub-scale has two items. Carver (1997) reported the reliability and validity data with Cronbach's alphas ranging from 0.50 to 0.90. The widely used COPE was developed upon the review of existing scales and critical analysis of coping scales and is based upon the theoretical literature around functional coping strategies (Carver, Scheier and Weintraub, 1989). The BRIEF COPE is a brief measure modified from the COPE of coping, assessing several responses known to be relevant to effective and ineffective coping; it is useful in minimising time demands of participants. The BRIEF COPE has no overall score; each separate scale is to be looked at in relation to the other scales.

7.2.3.4 Autonomy

The SCSES (Edwards et. al. 2000) is a 9-item scale developed specifically for the SCD patient population. The SCES assesses adult patients' self-appraisals of their ability to engage in daily functional activities, (despite having SCD), on a 5-point Likert scale. Response choices range from 'not at all sure' to 'very sure'. Like thalassaemia, SCD is an inherited haemoglobinopathy so items on this scale are also relevant to BTM adult patients. The items in the scale are few and their administration quick, so useful in clinical practice and research (Edwards et. al. 2000). The SCSES demonstrates good internal consistency, (Cronbach's alpha = 0.89), discriminant, convergent and predictive validity. In this research, only 6 items from the SCSES were administered to the clinical sample as items 1, 3 and 4 relate to pain and crises in SCD and not relevant in BTM. Higher scores indicate greater self-efficacy.

7.3 Results

7.3.1 Descriptive Statistics of the Thalassaemia Adult Life Index (THALI) at Validation

Descriptive statistics and response data for each sub-scale of the THALI are presented in Table 14a (scaling assumptions), 14b (missing data) and 14c (acceptability).

Missing data statistics are also presented for each of the alternative scales i.e. BRIEF COPE, SF-36, RSE, SCSES and the BIQLI, in Table 15.

Each of the sub-scales generated score variability of between 12.71 and 19.20 out of a possible 35. The mean scores on sub-scales GPH (19.2), C (18) and A (18.09) reflect the average responses above the sub-scale midpoint (17.50). Note that there were no missing data for this sample.

Item discriminant validity was analysed. Within all the sub-scales, most correlations were significant at the 0.01 level (two tailed). See Appendix XXXXXII.

Table 14a: THALI (5 sub-scales) - Scaling Assumptions

Psychometric Properties	General	Coping	Body	Social	Autonomy
Item Mean Score Range	1.89 - 3.20	2.03 – 3.06	1.69 – 1.97	1.71 – 2.29	2.29 – 3.23
Item SD Range	1.11 – 1.53	1.18 – 1.47	1.08 – 1.34	1.16 – 1.47	1.178 – 1.64
Item Skewness Range	-0.00 - 1.49	0.11 – 1.09	1.21 – 1.88	0.84 – 1.60	-.021 – 1.01
Item correlation with Hypothesised Scale Range *(See Appendix XXXXXII)	*r* =0.66- 0.91	*r* =0.67-0.91	*r* =0.44-0.87	*r* =0.64-0.91	*r* = 0.69-0.89

* Reported item correlation range is inclusive of all correlations (significant and non-significant).

Table 14b: THALI (5 sub-scales) – Missing Data

Psychometric Properties	General	Coping	Body	Social	Autonomy
Number of respondents	35	35	35	35	35
No. of respondents missing data on 1 item only.	0	0	0	0	0
No. of respondents missing data on 2 items only.	0	0	0	0	0
No. of respondents missing data on 3 items or more	0	0	0	0	0
No. of respondents with complete data	35	35	35	34	35

Table 14c: THALI (5 sub-scales) – Acceptability

Psychometric Properties	General	Coping	Body	Social	Autonomy
Total Possible Score Range	7 - 35	7 - 35	7 - 35	7 - 35	7 - 35
Total Observed Score Range	7 - 35	7 -33	7 - 33	7 - 34	7 - 33
Mean Observed Score (SD)	19.200	18.000	12.714	14.324	18.086
Floor/Ceiling Effect **	No	No	Floor (22.86%)	No	No
Skewness	.239	.586	1.635	1.213	.335

**Floor or ceiling effects were calculated by assessing the proportion of participants with the lowest or highest possible score. Floor or ceiling effects are considered to be present if more than 15% of the respondents achieved the lowest or highest possible score respectively (Terwee et. al. 2007).

Table 15: Missing Data (Alernative Scales)

Psychometric Properties	BRIEF COPE	SF-36	RSE	SCSES	BIQLI
Number of respondents	35	35	35	35	35
No. of respondents missing data on 1 item only.	1	2	1	1	1
No. of respondents missing data on 2 items only.	0	1	0	1	1
No. of respondents missing data on 3 items or more	8	5	3	3	4
No. of respondents with complete data	26	27	31	30	29

7.3.2 Reliability and Internal Consistency

The community sample was measured on the 35 items. Analysis of internal consistency was evaluated with Cronbach's α (Cronbach, 1951) for each group of the 5 sub-scales incorporates five items. Internal reliability is generally acceptable for factors with a Cronbach α of 0.70 or above (Nunnally, 1996). All the sub-scale estimates met this criterion (GPH=0.93, C=0.93, BIAC=0.87, SR=90, A=0.92) (see Appendix XXXXXIIIa). Alphas have been shown to be higher for sub-scales C = 0.94 and BIAC = 0.91 when 1 item is deleted (see Appendix XXXXXIIIa). Cronbach's α also was also calculated for each of the alternative scales (BRIEF COPE = 0.91, SF-36 = 0.96, Rosenberg = 0.88, SCES = 0.87, BIQLI = 0.97) (see Appendix XXXXXIIIb). No α's were higher than the total alpha if an item was deleted for all alternative scales.

7.4 Validity

7.4.1 Construct and Concurrent Validity

In statistics, correlation (measured as a correlation coefficient), indicates the strength and direction of a linear relationship between two random variables (Colman, 2001). A number of different coefficients are used for different situations. The best known is the Pearson product-moment correlation coefficient (Pearson, 1901), symbolised by r, which is obtained by dividing the covariance **(**a measure of how much two variables change together), by the product of their standard deviations. Although establishing a correlation between two variables is not a sufficient condition to determine a causal relationship in either direction between variables, a correlation can be taken as evidence for a possible causal relationship but cannot indicate what the causal relationship, if any, might be (Colman, 2001). With regard to the interpretation of the size of a correlation, Cohen (1988) has stated that correlations are arbitrary and should not be observed too strictly as the interpretation of a correlation coefficient depends on the context and purposes. Nevertheless, the grid below is a guide to correlations (Cohen, 1988).

Correlation	Negative	Positive
Small	−0.3 to −0.1	0.1 to 0.3
Medium	−0.5 to −0.3	0.3 to 0.5
Large	−1.0 to −0.5	0.5 to 1.0

Taken from Cohen (1988)

7.4.1.1 Hypotheses, Results and Discussion

The validity of the THALI sub-scales was assessed by estimating the correlation between the sub-scales and other variables. Consideration of the literature discussed in chapter 2, sections 2.1.2 and 2.2, generated the following hypotheses to test for construct validity.

1. *It was hypothesised that the BIAC sub-scale will be correlated with all the sub-scales of the BRIEF COPE.* With the exception of the humour (H) sub-scale of the BRIEF COPE, the BIAC was found to be positively correlated to coping in general. The significant correlations ranged from 0.34 – 0.43 (0.05; 2-tailed). See Appendix XXXXXIV.
2. *It was hypothesised that the BIAC sub-scale will be correlated with the EWB sub-scales of the SF-36.* A significant, positive relationship was found (0.33; 0.05; 2-tailed). See Appendix XXXXXV.
3. *It was hypothesised that the BIAC sub-scale will be correlated with the BIQLI.* A significant, positive relationship was found (0.39; 0.05; 2-tailed). See Appendix XXXXXVI.

There seems to be a major psychological burden in coping with the many problems of BTM and its therapy (Politis, 1998). One of the current developments concerning psychosocial burden of thalassaemia in the present includes physical appearance, pubertal growth and sexual development (Politis, 1998). The above findings were expected as the literature has shown that one of the challenges faced, and one of the most pronounced aspects of life affected by thalassaemia for adult patients that may compromise their psychosocial functioning, is their different appearance due to physical deformities e.g. growth retardation therefore short stature, bone deformities and delayed puberty therefore delayed or absence of sexual development, that may result in body image, appearance and confidence issues. Consequently adjustment to the illness as an adolescent and adult may be problematic (Bush et. al. 1998; Canatan et. al. 2003; Georganda, 1990. Telfer et. al. (2005) identified some of the major clinical and psychological aspects of thalassaemia and its treatment expected to affect the QoL of their adult patients. The BIAC and BIQLI were correlated; it was expected that they would have been slightly higher correlated than the correlation of 0.39 (Cohen, 1988) as the two scales were essentially measuring the same construct. It may be suggested that this correlation was due to the disease-specificity of the BIAC and not the BIQLI.

4. *It was hypothesised that the BIAC sub-scale will be correlated with the RSE.* This hypothesis was not supported. See Appendix XXXXXVI.

Unmarried patients have been reported as scoring better than a control group with regard to social adjustment, self-esteem and self-description (DiPalma et. al. 1998). Patients also showed a very positive self-image with regard to self-esteem and indicated a high degree of confidence in their abilities (DiPalma et. al. 1998). Other chronically ill patient groups such as people with CF and SCD have been reported as being concerned about their appearance and having low self-esteem (Hodson and Geddes, 1995; Abbott et al. 2000). Due to such findings the expected result would have been that the self-reported data by patients on the RSE (Rosenberg, 1965) would be related to the BIAC. A possible explanation may be the disease-specificity of the BIAC and not the RSE.

5. *It was hypothesised that the SR sub-scale will be correlated with the RSE.* This hypothesis was not supported. See Appendix XXXXXVI.

Thalassaemia patients tend to report high self-esteem and also report that getting married and having children as being distant targets (DiPalma et. al. 1998). As social networks influence health-promoting or health-damaging behaviour, cognitive and emotional states such as self-esteem (Berkman et. al. 2000), it was expected that there would be a significant relationship between the patient scores of the RSE (Rosenberg, 1965) and the SR sub-scale of the THALI-35. Such a significant relationship was not observed possibly due to the disease-specificity of the SR sub-scale.

6. *It was hypothesised that the SR sub-scale will be correlated with the SF sub-scale of the SF-36.* This hypothesis was supported (0.55; 0.01; 2-tailed). See Appendix XXXXXV.
7. *It was hypothesised that the SR sub-scale will be correlated with the PF sub-scale of the SF-36.* A significant, positive relationship was found (0.46; 0.01; 2-tailed). See Appendix XXXXXV.

8. *It was hypothesised that the SR sub-scale will be correlated with the EWB sub-scale of the SF-36.* A significant, positive relationship was found (0.57; 0.01; 2-tailed). See Appendix XXXXXV.
9. *It was hypothesised that the SR sub-scale will be correlated with the PAIN sub-scale of the SF-36.* A significant, positive relationship was found (0.49; 0.01; 2-tailed). See Appendix XXXXXV.
10. *It was hypothesised that the SR sub-scale will be correlated with the GH sub-scale of the SF-36.* A significant, positive relationship was found (0.57; 0.05; 2-tailed). See Appendix XXXXXV.

Various researchers have identified and studied the issues and characteristics of the impact of thalassaemia upon patients focusing upon social integration, relationships between adults and self – esteem (Ratip et. al. 1995; Politis, 1998; Canatan et. al. 2003). Evidently, these issues are important for this patient group and the results of this study observed this importance. It is widely recognised that social relationships and affiliation can have powerful effects on physical and mental health e.g. Berkman et. al. (2000). With regard to bodily pain and SR, relevant clinical and research data are shown for altered interpersonal relationships (Edwards et. al. 2005).

11. *It was hypothesised that the C sub-scale will be correlated with the PF sub-scale of the SF-36.* A significant, positive relationship was found (0.39; 0.05; 2-tailed). See Appendix XXXXXV.
12. *It was hypothesised that the C sub-scale will be correlated with the EWB sub-scale of the SF-36.* A significant, positive relationship was found (0.66; 0.01; 2-tailed). See Appendix XXXXXV.
13. *It was hypothesised that the C sub-scale will be correlated with the SF sub-scale of the SF-36.* A significant, positive relationship was found (0.54; 0.01; 2-tailed). See Appendix XXXXXV.
14. *It was hypothesised that the C sub-scale will be correlated with the PAIN sub-scale of the SF-36.* A significant, positive relationship was found (0.44; 0.01; 2-tailed). See Appendix XXXXXV.

The source of cognitive reinforcements for health-related behaviours as internal, a matter of chance or under the control of powerful others has been documented as a variable in

health behaviours (Wallston et. al. 1978). Thalassaemia patient groups believe that they are in control of their health and that their behaviour determines their health outcomes (Bush et. al. 1998). Furthermore, Bush et. al. (1998) suggest that the positive orientation of thalassaemia patients could relate to denial and argue that these patients use denial as a coping mechanism i.e. hope not realism. Examples of challenges for people with BTM include mortality and the ever present knowledge that thalassaemia is a life-long illness and the loss of peers with thalassaemia due to complications associated with the disease (Bush et. al. 1998; Politis et. al. 1990; Georganda, 1990). These uncertainties about the future imply difficulties in long-term planning (Telfer et. al. 2005). Relevant clinical and research data are described on the relationship between psychosocial functioning and SCD; the chronicity of the illness combined with frequent hospitalisations for treatment and medical management was found to contribute significantly to impaired psychosocial functioning, altered intra-and interpersonal relationships and reduced QoL (Edwards et. al. 2005). Anie et. al. (2007) suggested that this patient group's psychosocial issues mainly result from the impact of pain and symptoms on their daily lives in relation to their physical coping mechanisms. Painful and time-consuming iron chelation treatment is also liable to lead to psychosocial problems (Politis et. al. 1990).

15. *It was hypothesised that the A sub-scale will be correlated with the SCSES.* This hypothesis was not supported. See Appendix XXXXXVI.

Research has shown that patients' self-concept is related to adequate psychosocial adjustment and that autonomy is an important issue (Moise et. al. 1987; Hodson and Geddes, 1995). A significant correlation between the self-reported patient data on the SCSES (Edwards et. al. 2000) and the autonomy sub-scale of the THALI-35 was expected as both scales were thought to be measuring similar constructs; results may have been affected by the SCD disease specificity of the scale itself.

16. *It was hypothesised that the A and GPH sub-scales will be correlated with all of the sub-scales of the SF-36.* This hypothesis was supported. Significant, positive correlations between A and the sub-scales of the SF-36 ranged from 0.43 – 0.82 (2-tailed; 0.01 with the exception of RLEP at 0.05). See Appendix XXXXV. Significant, positive correlations between GPH and the sub-scales of the SF-36

ranged from 0.38-81 (2-tailed; 0.01 with the exception of RLEP at 0.05). See Appendix XXXXV.

This result was expected as studies surrounding the psychological and social wellbeing of chronically ill and disabled people in general find the presence of high levels of emotional problems (Cadman et. al. 1987), depressive symptoms (Mikelli and Tsiantis, 2004; Pakbaz et. al. 2005; Abetz et. al. 2006), feelings of anxiety, (Canatan et. al. 2003; Pakbaz et. al. 2005), concern of overall health status and/or indications of recent deterioration in physical health (Pakbaz et. al. 2005) like fatigue, dyspnoea, physical functioning and psychological distress (Abetz et. al. 2006).

The following (theoretically) logical and reasonable hypotheses, if supported, would add to the evidence of the validity of the THALI scores and the measure itself i.e. concurrent validity.

1. *It was hypothesised that the BIAC and C sub-scales of the THALI will be correlated with all the sub-scales of the BRIEF COPE.* With the exception of the humour (H) sub-scale of the BRIEF COPE, the BIAC was found to be positively related to coping in general. The significant correlations ranged from 0.34 – 0.43 (0.05; 2-tailed). See Appendix XXXXXIV. No relationship was found between the C sub-scale of the THALI and the BRIEF COPE.
2. *It was hypothesised that the SR sub-scale of the THALI will be correlated with the BRIEF COPE sub-scales ES, SD, H, AC, IS, P and R.* No such relationship was found. See Appendix XXXXXIV.
3. *It was hypothesised that the GPH sub-scale of the THALI will be correlated with the BRIEF COPE sub-scales AC and IS.* No such relationship was found. See Appendix XXXXXIV.
4. *It was hypothesised that the A sub-scale of the THALI will be correlated with the BRIEF COPE sub-scales IS and ES.* No such relationship was found. See Appendix XXXXXIV.
5. *It was hypothesised that all the sub-scales of the THALI will be correlated with the BIQLI.* A significant, positive relationship was found (0.39; 0.05; 2-tailed). See Appendix XXXXXVI.

6. *It was hypothesised that all the sub-scales of the THALI will be correlated with the RSE.* No such relationship was found. See Appendix XXXXXVI.
7. *It was hypothesised that all the sub-scales of the THALI will be correlated with the SCSES.* No such relationship was supported. See Appendix XXXXXVI.
8. *It was hypothesised that all the THALI sub-scales will be correlated with all of the sub-scales of the SF-36.* Significant, positive correlations between A and the sub-scales of the SF-36 ranged from 0.43 – 0.82 (2-tailed; 0.01 with the exception of RLEP at 0.05). See Appendix XXXXV. Significant, positive correlations between GPH and the sub-scales of the SF-36 ranged from 0.38-81 (2-tailed; 0.01 with the exception of RLEP at 0.05). See Appendix XXXXV. Significant, positive correlations between C and the sub-scales PF, EWB, SF and PAIN of the SF-36 ranged from 0.39 – 0.66 (2-tailed; 0.01 with the exception of PF at 0.05). See Appendix XXXXV. A significant, positive correlation was found between the BIAC and the sub-scale EWB of the SF-36 (0.33; 0.05; 2-tailed). See Appendix XXXXV. Significant, positive correlations between SR and the sub-scales PF, EWB, SF, PAIN and GH of the SF-36 ranged from 0.34 – 0.57 (2-tailed; 0.01 with the exception of GH at 0.05). See Appendix XXXXV.

One may speculate that the relationships hypothesised that were not supported may have been due to the disease-specificity of the THALI sub-scales.

7.4.2 Convergent Validity

Table 16 shows the sub-scale correlations between the 5 THALI sub-scales. All the correlations, with the exception of GPH and BIAC, are positive and significant (the majority at the 0.01 level; 2-tailed). A good correlation was taken to be between 0.3 – 0.8 (Lohr et. al. 1996). All the correlations were expected to be significant and high as the sub-scales were theoretically measuring the broad, global outcome of QoL. As per 'rule of thumb', a lower or insignificant correlation would indicate that the sub-scales are measuring two conceptually different/distinct constructs i.e. GPH and BIAC and a very high correlation would indicate that the sub-scales are measuring conceptually very similar constructs i.e. correlation between the GPH and A sub-scales.

Table 16: Subscale Correlation Matrix

	GPH	C	BIAC	SR	A
GPH	1.00	0.59(**)	**0.32**	0.68(**)	**0.91(**)**
C	0.59(**)	1.00	0.57(**)	0.75(**)	0.49(**)
BIAC	**0.32**	0.57(**)	1.00	0.71(**)	0.35(*)
SR	0.68(**)	0.75(**)	0.71(**)	1.00	0.74(**)
A	**0.91(**)**	0.49(**)	0.35(*)	0.74(**)	1.00

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); N=35 for all correlations

7.5 Discussion

The present study evaluated the psychometric properties of a 35-item instrument assessing the impact of BTM on health outcome. The THALI is targeted for use in an adult BTM population. This study is a first validation in a small clinical sample of adults with thalassaemia.

Overall, the results indicate that the THALI exhibits sound internal consistency, convergent and concurrent validity. In terms of internal consistency, all the sub-scales of the THALI had high reliability. Due to the single underlying facet of the THALI-35 i.e. QoL, it was expected that the 5 domains would be related in some way. The convergent validity of the THALI-35 sub-scales was acceptable however it should be noted that the observed correlation between the GPH and A subscales of the THALI-35 may indicate that the scales may be measuring very similar constructs.

The established relationships suggest that disease-specific QoL beliefs do not overlap entirely with patients' feelings on coping, self-efficacy and self-esteem, general QoL, body image and social relationships. This finding is in accordance with Power et. al's (1999) suggestion that QoL is multidimensional and incorporates the individual's perception of the issues stated above in other aspects of their life within cultural, social and environmental contexts and it's tendency to focus on its multi-domains, comprising objective descriptors as well as subjective evaluations (Brown et. al. 2004). Each area of QoL influences the other areas thus QoL is multidimensional and its parts affect each other as well as the sum (Veenhoven, 2000).

7.6 Evaluation of Stage 3

As there is to date no objective 'gold standard' measure of QoL it has been suggested that it is frequently difficult to assess validity (Bowling, 2001). Nevertheless, this validation study represents the initial assessment of the psychometric properties of the THALI-35.

Appropriate methods of item generation and selection help to ensure content validity (Hobart et. al. 2004). Persons with BTM defined the aspects of health status affected by the disease however the sample in the item generation stage (see chapter 5) only included 16 patients consequently important domains may have been omitted thus validity compromised (Hobart et. al. 2004). In addition, the data presented were based on a small clinical sample of mostly female patients attending London hospitals. Although the size of the sample was adequate for the purposes of this initial study, (as calculated by a power calculation, see section 7.2.1), further sampling (a broader spectrum of patients) is essential to estimate the generalisability of the measure for use with adults with BTM

Although there is a debate about whether 'clinical responsiveness' is actually an aspect of validity (Hadorn and Uerbersax, 1995), it should be noted that the ability of the THALI to detect clinically significant change in patients was not undertaken in this initial evaluation. It would be beneficial for the disease-specific THALI to be able to measure clinically important change over time when evaluating the benefits of different interventions i.e. clinical trials of oral chelators. The assessment of the predictive validity of the THALI could be undertaken by reporting the THALI profile scores for patients and reported physical symptoms and/or psychosocial concerns longitudinally at different intervals. The assessment of discriminant validity could be also be undertaken by dividing a sample of patients on the basis of physical symptoms e.g. lack of mobility and/or biological markers like ferritin levels (a protein that stores iron and releases it in a controlled fashion; a buffer against iron deficiency and iron overload (BMA, 2002)), and administering the THALI and making domain comparisons.

Likert scales (Likert, 1932) may be subject to misrepresentation that may include respondents trying to portray themselves in a favorable light i.e. social desirability bias, as well as avoiding using extreme response categories i.e. central tendency bias (Babbie, 2005). Future investigations of the THALI may benefit from direct measurement of social

desirability bias as well from inclusion of multiple data sources e.g. behavioural observations, reports from family and/or friends (Edwards et. al. 2000).

Similar to stage 2 of 3 (chapter 6) this study advocated quantitative methodology. The strengths and limitations of using such methods have been addressed in chapter 6, section 6.3.2.1.

One could consider that patients who volunteered to participate in the research may have been less affected by BTM than others. With regard to the sample in this small validation study, the researcher is unable to establish if the sample was truly independent to the sample of patients in the other stages i.e. patients who participated in this stage may have been members of the UKTS therefore participated in stage 2 and/or interviewed in stage 1. All returned questionnaires were annonymised so the researcher would not have been able to identify any overlap.

In conclusion, the findings of this small validation study suggest that the THALI has produced scores that are reliable and valid. At this stage it may be premature to suggest that the THALI is useful in anything other than a research context however after further validation and the compilation of suitable normative data i.e. standardisation, the scale could be useful in a clinical guidance context as a means of ascertaining the type and level of intervention best suited to particular patients.

Chapter 8 now presents a general discussion of the study, its strengths and limitations, implications for healthcare and policy and recommendations for future research.

7.7 Acknowledgements

It should be known that the Research and Development Departments of the hospitals/universities also gave their approval for this research to commence (see Appendices XXXXXVII through to XXXXXX). Departmental honorary contracts were obtained where stated as required by the hospital(s), Trust(s) and/or department(s) (see Appendices XXXXXXI through to XXXXXXIII). A notification of amendment application was sent to the Northern and Yorkshire Research Ethics Committee and approved to include the newly developed THALI-35 in this stage (see Appendix XXXXXXIV). The researcher informed the authors' or authors' family of the use of the

measures stated in section 7.2.3 and where necessary, permission by the authors' or authors' family was sought to use the measures in this study.

Chapter 8

Discussion

"The most important thing in illness is never to lose heart"

Nikolai Lerrin

Study Overview

The aim of this study was to develop and validate a health outcome measure for adults with a BTM that combines the patient perspective, with a psychometric, scientific approach. This aim was addressed by generating items from in-depth patient interviews, using the self-report method of administration, selecting items on the basis of psychometric performance and applying psychometric assessment methods. Testing showed the THALI-35 to be a reliable measure of the biopsychosocial impact of BTM. Preliminary testing of its validity showed acceptable results. This final chapter presents a discussion of the study results, the study's strengths and limitations and the implications of the THALI-35 for healthcare; it also provides recommendations for future research.

8.1 Discussion of Results: A Summary

Results from this study suggest that the THALI-35, a health 'profile' of health outcome which records the perceived health of individuals, is a reliable measure of the bio-psychosocial impact of BTM. In addition, preliminary testing of its validity showed acceptable convergent validity and good concurrent validity. Adopting the standard psychometric model of the development and validation of health outcome measures was important because the results of studies surrounding the QoL of patients are dependent on the quality of the measures used for data collection (Hobart et. al. 2004). Furthermore, the limitations of measures cannot be overcome easily by improvements in study design and powerful statistical methods (Fleiss, 1986).

The terms QoL, HRQoL, health status and disability are often used interchangeably or without specific reference to what they measure (Anderson and Burckhardt, 1999; Bowling and Windsor, 2001). Measures that are intended to assess such concepts are collectively referred to as 'patient-based outcome measures' (Fitzpatrick et. al. 1998). The researcher specifically chose not to describe the THALI-35 as a measure of HRQoL, QoL, health

status or disablement, as these terms are ambiguous and can mislead investigators upon selection of measures to be used in their clinical research and/or clinical practice.

Section 7.4.1.1 considered many hypotheses in relation to literature and theory. All the sub-scales of the THALI-35 correlated significantly with each other, the THALI-35 sub-scale BIAC was found to be correlated to coping in general and the sub-scale emotional well-being of the SF-36 was correlated to patient scores on the BIQLI (Cash and Fleming, 2002). A relationship was observed between the SR sub-scale of the THALI-35 and the sub-scales PF, EWB, SF, PAIN and GH of the SF-36. The THALI-35 sub-scale coping was related to the SF-36 subscales PF, EWB, SF and PAIN. The autonomy and GPH sub-scales of the THALI-35 were correlated with all of the sub-scales of the SF-36. There were some unexpected results. The RSE (Rosenberg, 1965) scores were not significantly correlated with the BIAC, the SR sub-scale of the THALI-35, the SCSES (Edwards et. al. 2000) and the autonomy sub-scale of the THALI-35.

Overall, the findings support the multidimensionality of QoL (Power et. al. 1999) nevertheless each of the sub-scales belongs to the multidimensional THALI-35 and the RSE and the SSCES are one-dimensional scales thus may not have been suitable to assess the self-esteem and autonomy status of BTM patients within a multidimensional framework. Furthermore, the sub-scales of the THALI-35 are disease-specific whereas the content of the RSE and the SCSES is generic.

Previous findings suggest that a two-dimensional model, consisting of physical and psychological health, explains the construct of subjective health status (Pfennings, Cohen, Van der Ploeg, Bramsen, Polman, Lankhorst et. al. 1999; Ware, Kosinski, Keller, 1994) however psychometric analyses seemed to support a more multidimensional model (Power et. al. 1999). Dimensions of general physical health, psychological health and personal beliefs incorporating coping, body image, appearance and confidence, social relationships and autonomy appeared to underlie the diverse 63-item pool so the THALI-35 supports 3 distinct dimensions of subjective health status of these patients: (1) physical health i.e. general physical health and autonomy, (2) psychological health i.e. psychological health and personal beliefs incorporating coping, body image, appearance and confidence, and (3) ‘social health’ i.e. social relationships.

8.2 Study Strengths and Limitations

The THALI-35 was developed and validated in accordance with psychometric theory (Nunnally and Bernstein, 1994). The value of psychometric methods in assessing health outcomes was demonstrated in the HIS (Brook et. al. 1979) and MOS (Stewart et. al. 1989) studies (Hobart et. al. 2004). The studies demonstrated that psychometric methods of scale construction and data collection were good ways of measuring health status and found that psychometric methods can generate scientifically sound and clinically useful health outcome measures (Hobart et. al. 2004). Ratip (1996) did not adopt this scientific approach when developing his instrument yet despite this weakness the instrument was adopted in research e.g. Ratip and Modell (1996), Klein et. al. (1998), Canatan et. al. (2003).

A primary goal of health outcome instrument development is that patients self-report on issues deemed important by patients (Hobart et. al. 2004). The THALI-35 is a reliable and initially valid disease-specific measure consisting of 35 items across five domains of functioning which have been identified, and are of importance to adult patients with BTM. Therefore, the THALI-35 is a clinically useful patient-based outcome measure of the impact of BTM and appears suitable for clinical and research purposes. In contrast, though Ratip's (1996) research was partly patient driven, clinicians imposed their relevance on clinical parameters, scoring and weighting (Telfer et. al. 2005). In addition, ICT is not listed as a clinical burden yet the literature infers that this is a major concern in the adherence to treatment (Porter and Davies, 2002). Ratip's (1996) 'psychosocial instrument' aimed to assess psychosocial burden in patients but issues were identified from literature alone and not via patient interview (Telfer et. al. 2005).

The THALI-35 is a disease-specific instrument of health outcome. The instrument therefore has the benefit of consisting of items and domains of health that are specific to a particular disease, are therefore more relevant and important to patients and clinicians and consequently more likely to be responsive to subtle changes in outcome (Guyatt et. al. 2002). The THALI-35 is comprised of questions that address specific areas of importance such as disease-related symptoms e.g. tiredness, lack of stamina, as opposed to generic measures that target a specific age, disease or treatment group as necessary (Hobart et. al. 2004). The THALI-35 takes into account aspects of disease and treatment that are relevant to BTM which may be preferable when studying a disease longitudinally (Hobart et. al. 2004). In general, disease-specific instruments have the advantage of being more specific

and sensitive to the major features of the illness as well as the changes of the disease that affect patients' lives on a daily basis (Spilker, 1996). Disease-specific measures have been discussed in chapter 3, section 3.4.2.1.2.

Several practical limitations of the study should be noted. Like most health outcome research, this study relied upon participants' self-report. A substantial literature exists concerning the numerous problems of self-report data e.g. Some of the problems of self-report include unreliable answers for example respondents may exaggerate, may be embarrassed or forget (Brown and Moskovitz, 1998). Of particular concerns herein is the issue of social desirability which may have affected the magnitude of the results. The results (scores) may be more or less significant and/or important than reported by patients e.g. Hays et. al. (1995), Ko and Coons (2006). Imminent investigations of the THALI may benefit from direct measurement of social desirability bias as well as from inclusion of multiple data sources like behavioural observations and reports from family and/or friends (Edwards et. al. 2000).

The use of the UKTS membership database to define the sampling frame in stage 2 is another potential limitation of this study. It is known that many members of the UKTS are partners, friends or relatives of people with BTM therefore the researcher specifically asked people who did not have BTM to return the questionnaires blank. None were returned therefore it is difficult to calculate the percentage of people in the UKTS database who have BTM. In addition, the representativeness of people who join charitable groups is unknown (Hobart et. al. 2004). It is difficult for the researcher to establish whether the samples in stages 1, 2 and 3 (N=147) were truly independent to each other i.e. patients who participated in stages 1 and 3 may have been members of the UKTS. All returned questionnaires were annonymised so the researcher would not have been able to identify any overlap. Nevertheless, an estimate indicates that the research sample was from approximately 28% of the total UK population of people with thalassaemia (532) (Modell et. al. 2003).

Regardless of the mode used to administer a survey, poor response rates are a persistent problem and although there is no set standard for what constitutes an acceptable response rate, convention has indicated a poor response rate as below 60% (Kane, 2006). A survey's response rate is viewed as an important indicator of survey quality and many

researchers presume that higher response rates assure more accurate survey results (Dillman, 2000). A meta-analysis of survey response rates in published research in counselling and clinical psychology over a 20-year span by Van Horn, Green and Martinussen (2009) describes reported survey administration procedures in these fields. Results of 308 survey administrations showed a weighted average response rate of 49.6%. kAlthough the future of survey research in general may rely more heavily on Internet data collection, mail surveys dominate in this field. Studies surrounding the psychosocial aspects of thalassaemia patients e.g. Ratip et. al. (1995) and Bush et. al. (1998), as well as this study, tend to have sample sizes that are generally small and are essentially volunteer or self-selected therefore restricting the generalisation of study findings in general. In spite of this, research has shown that lower response rates may not necessarily mean poor accuracy. Visser, Krosnick, Marquette and Curtin (1996) challenged the presumption that a lower response rate means lower survey accuracy and showed that surveys with lower response rates (near 20%) yielded more accurate measurements than did surveys with higher response rates (near 60 or 70%).

There are no agreed criteria for what constitutes QoL (Lauer, 1999) and often it is difficult to know what is being measured therefore instruments may therefore lack validity (Bowling and Windsor, 2001). Nevertheless, comprehensive instrument evaluation includes the assessment of scientific properties like reproducibility and clinical responsiveness (sensitivity) neither of which were evaluated in the preliminary assessment of the THALI-35. These two types of property assessment have been discussed in sections 4.2.4 and 4.2.6 respectively. Test-retest it is the most relevant and important form of reproducibility for patient-based outcome measures; parallel forms of disease-specific measures do not exist in this instance and measures are self-completed (Hobart et. al. 2004). It would also be beneficial for the disease-specific THALI to be able to measure clinically important change over time when evaluating the benefits of different interventions. Establishing the validity of any measure is an ongoing process and impending future endeavours to validate the THALI shall assess both these important properties along with its potential predictive and discriminant validity.

8.3 Implications for Healthcare

The THALI-35 was purposely developed to be short and simple enough for routine use in a wide range of healthcare applications. It offers the opportunity to measure the impact of

BTM and evaluate treatment effectiveness from the patient's perspective. In the last year, Deferasirox or 'Exjade' the new, once-daily oral chelator has become available as a treatment of BTM. The THALI-35 provides a scientific method of evaluating the effectiveness of new interventions in relation to current treatments. It is noteworthy that there is clear consensus about the need for outcome measures to evaluate models of care e.g. Frater and Costain (1992). Fundamentally, thalassaemia is incurable, has an impact on longevity and in the majority of people complications occur over the years (Telfer et. al. 2005). It is a complex disorder with diverse effects and variable manifestations that pose unique problems to patients and their families and/or carers (Telfer et. al. 2005). Moreover, the cost of thalassaemia in the UK is estimated to be 1 million pounds sterling per patient (UKTS, 2005) and is expected to increase with new oral iron chelating drugs. In the UK, thalassaemia is certainly a concern for those in the field of haematology and beneficial interventions are welcomed by patients, their families/carers and clinicians alike. Outcomes of therapeutic interventions like the clinical trials for new iron chelating drugs must be rigorously evaluated if policy decisions and clinical practice are to be evidence-based (Hobart et. al. 2004). The need for more rigorous evaluation of treatments for thalassaemia has recently become critically important for several reasons. Firstly, new oral iron chelating treatments aimed at increasing the adherence of treatment and reducing the burden of the illness have been introduced in the last few years and the effectiveness of the most recent introduction of drugs is currently being determined (UKTS, 2005). Secondly, analyses of comparative effectiveness between drugs and patients needs to be determined and thirdly, these treatments are expensive and are required on a long-term, indefinite basis therefore there are long-term economic implications for the UK (UKTS, 2005).

Due to the disease specificity of the THALI-35 it is sensitive to the major features of BTM as well as the changes of the illness that affect patients' lives on a daily basis (Spilker, 1996). Consequently, the THALI-35 may be applicable in the range of different cultural, age and social settings to describe the impact of BTM from the patient's perspective. It may be valuable in longitudinal studies to monitor the natural history of BTM, most importantly in clinical trials, as well as in biopsychosocial interventions to evaluate therapeutic effectiveness in comparing health outcomes between clinics. Furthermore, the availability of a reliable, valid and responsive patient-based outcome measure is central to

an improved understanding of the impact of BTM and its relationships with other indicators of disease activity e.g. liver and heart scans.

The THALI-35 has been developed for use in both clinical research and evidence-based clinical practice, to monitor the progress of people with BTM. Therefore, it is highly relevant to the NHS. In light of the disease treatment-modifying drugs that will be available, the THALI-35 may provide a further valuation of the effectiveness of this type of therapy as well as of other future treatments. It may be used in routine data collection and clinical governance which is also relevant to the NHS (Hobart et. al. 2004).

8.3.1 Healthcare Policy

Traditionally, outcomes in medicine and healthcare have largely been determined by objective medical evaluations e.g. changes in health parameters, disease status and costs of care however it has become increasingly clear that the perspective of the patient is also a critical variable (Hobart et. al. 2004). As a result, it is now increasingly common to include evaluations of medical/health-related outcomes from the patient's perspective (Guyatt et al. 1993; Ware et al. 1993). These outcomes must be measured rigorously if they are to influence patient welfare and the expenditure of public funds hence health outcome is not only a primary concern of patients, their families and clinicians but also for policy interests (Hobart et. al. 2004). Estimates of the relative impact of chronic disease on QoL are needed to better plan and allocate resources for research, training and healthcare (Sprangers et. al. 2000). Quality of life (QoL) measures are usually better than more traditional, clinical measures for evaluating the social and emotional outcomes of treatments and illness processes as it gives an overall picture of how treatments and/or diseases are affecting the patient's ability to function in life (Hobart et. al. 2004). The scientific discipline of health measurement grew in response to the need to supplement clinical judgment with reliable and valid patient-based measures of health outcomes (McDowell and Jenkinson, 1996) and there has been increasing recognition of the importance of assessing more patient-relevant consequences of disease, a practice that is now considered essential in a comprehensive evaluation of healthcare (Peto et. al. 1995). As measurement of such outcomes will influence decisions that affect patient welfare, policy development and the expenditure of public funds, it is essential that rigorous measurement instruments are used in healthcare evaluation (McDowell and Newell, 1996). The importance of research around health outcome is amenable to manipulation by health,

social, economic and environmental policy (Bowling and Windsor, 2001). Quality of life (QoL) in general is attracting increasing policy interest and indeed policy decision-making (Brown et. al. 2004). It can be important to treatment decision making to maximise the likelihood of long-term survival with the highest QoL possible (Devins et. al. 1990). Quality of life (QoL) information can also enable health policy-makers to compare the impact of different chronic diseases on healthcare costs and to assess the cost-effectiveness of different interventions (Jenkins, 1992).

Given the distinct nature of subjective QoL and its lack of association with standard mental health predictor's e.g. socio-demographic and observer-rated variables, and outcomes its role in outcome assessment may be as follows. Some QoL researchers consider the individual's perception of his/her circumstances to be the central component of QoL (Brown et. al. 2004). This approach has the merit of empowering the 'consumer' and giving him/her a central role in the development of treatment services (Brown et. al. 2004). It has been argued that subjective and objective appraisals are different kinds of data and that both have a role in QoL assessment (Bowling, 2002). It has been suggested that the subjective dimension is essential in painting a complete picture of the person's life i.e. in explaining patterns of behaviour and in providing the person's interpretation of the personal impact of objective circumstances (Ruggeri et. al. 2001). It is clear that various factors make it difficult to build predictive models around subjective outcomes and these include the tendency towards psychological adaptation or 'response shift' that can occur over time in the subjective appraisal of a person's current state and the multi-factorial establishment of subjective outcomes as well as the diverse reaction of different individuals to the same circumstances. Ruggeri et. al. (2001) proposed that socio-demographic and observer-rated variables are associated with change in objective circumstances rather than in subjective QoL. A possible explanation for this is that objective measures may prove to be more suitable in detecting the effects of treatment interventions because many interventions are not targeted at improving the subjective QoL of patients therefore objective information may be more suitable for building predictive models and in the longitudinal assessment of chronic illness (Ruggeri et. al. 2001).

8.4 Recommendations for Future Research

8.4.1 Further Evaluation of the Thalassaemia Adult Life Index (THALI-35)

There are several recommendations for future research. As already stated in section 8.2, further evaluations of the THALI-35 are needed as the psychometric properties of health outcome measures are sample dependent and cannot be established in a single study (Stewart, Hays and Ware, 1988). The assessment of its reproducibility and responsiveness should be undertaken. Evaluations of the performance of the THALI-35 with different patient samples and in different settings will help to clarify its strengths and weaknesses and further define its role in clinical practice and research i.e. it's predictive and discriminant validity. Upon assessment of convergent validity, the sub-scales GPH and A were shown to highly correlate (0.91); this may indicate that the sub-scales are too similar. It would be interesting to merge these two scales (14 items) and undertake further evaluation of convergent and concurrent validity to observe the relationship between this larger itemed sub-scale with the other THALI-35 sub-scales as well as other constructs measured by relevant scales. As traditional psychometric methods were used to develop and initially evaluate the THALI-35, it is important that newer psychometric methods such as Rasch item analyses (Rasch, 1960) and IRT models (Lord and Novick, 1968) are used to evaluate the THALI-35. The specificity of the THALI-35 to BTM and applicability to other haemoglobinopathies should be tested. The THALI-35 was developed from in-depth interviews with people with BTM so it is most suitable for use with people with BTM however it may be applicable to people with other 'disabling' haematological conditions like haemophilia and SCD and this may be another area for future research. Although steps were taken to ensure that the pre-testing sample was sufficiently large and representative of the general BTM population, a larger follow-up interview survey would have been useful. Thus, further interviews should be conducted to obtain feedback especially regarding questions that are deemed irrelevant by sub-groups e.g. ethnic minority groups and older people (over 50's). The assessment of the THALI-35 by other investigators in different cohorts of patient could also be undertaken.

8.4.2 A Computerised Thalassaemia Adult Life Index (THALI-35)

In clinical practice the monitoring of QoL is mostly undertaken routinely by the 'how are you?' question (Goldbeck, Zerrer and Schmitz, 2007). The use of standardised psychometric instruments is often limited due to the lack of staff trained in applied psychometrics and limited practicality of these instruments may be responsible for the

abstinence from structured routine assessment of QoL in clinical practice (Henry, Aussage, Grosskopf and Goehrs, 2003). The feasibility of a computerised THALI (eTHALI) for measuring health outcome in clinical outpatient and/or research settings is suggested from the results of a computerised QoL measure for CF adults (Goldbeck et. al. 2007). The measure was broadly accepted by patients and staff alike and highlighted by the completeness of the collected data and by the shortness and convenience of the assessment procedure. The advantage of using computer-assisted QoL assessments include the possibility of immediate analyses and that automatic documentation of individual results can facilitate the implementation of clinical routine (Goldbeck et. al. 2007). Multiple benefits of such a procedure for the patients can be expected for example in times of downsizing healthcare budgets it becomes increasingly important for therapists to recognise the patients' situation adequately within the restricted time limits for clinical consultations (Gee et. al. 2000). Regular and standardised QoL assessment would easily provide additional information on the effects of changes in individual treatment schedules, on unexpected changes in the patients' subjective health perceptions and/or on potential special needs arising from a difficult social situation that may reduce adherence to treatment i.e. those patients who are not used to communicating their subjective health-related perceptions to their HCPs spontaneously may be enabled to report their personal situation in a more comprehensive way than when responding to the global question, 'how are you?' (Goldbeck et. al. 2007). Taking QoL into account may allow HCPs a better understanding of patients' subjective health related thought processes and this may enhance the integration of the patients' subjective perspective into the process of shared decision making (Goldbeck et. al. 2007). Despite possible limitations of computer-assisted QoL measures like inconsistent training of staff in using the computer system and inconsistent availability of hardware perhaps in relation to costs to the NHS (Goldbeck et. al. 2007), future studies with BTM patients could evaluate different methods and designs for monitoring QoL and the effect of the immediate feedback of assessment results on patient-HCP communication. The reliability and validity of a computerised THALI-35 would also need to be reported in both clinical and research samples.

8.4.3 Translation Availability

A key advantage of the THALI-35 would be its availability in several languages as in this way the measure may be used with patient populations in other countries. The THALI-35 was originally developed and validated for an English-speaking population however due to

the ethnic demographic status of BTM patients the measure could be translated into other languages following recommended standard methodology (Herdman, Fox-Rushby and Badia, 1998). The English questionnaire should be translated by two professional bilingual translators who have experience of translating similar questionnaires; both translations should then be compared with each other and with the original English version at a consensus meeting. If the translation is clear and correct no changes should be made. If there are doubts or contrasting opinions a consensus needs to be reached after in-depth discussions to produce the first version of the appropriate language questionnaire(s). This version should then be independently translated back into English (back translation) to ascertain equivalent significance in both languages. At a second meeting, a second consensus version of the new language questionnaire should be produced and presented to the language speaking English patients with BTM to assess and correct for comprehension, clarity, cultural relevance and suitable wording (cognitive debriefing) thus producing the final language version of the THALI-35.

The THALI-35 could be translated into Greek, Turkish and Urdu following the same procedure however it would be necessary to undertake validation studies per adaptation to establish the multi-lingual THALI-35. The instrument would be translated into these three languages initially as these are the main languages spoken and read in the UK by the adult thalassaemia patient group, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi (Modell et. al. 2000).

8.4.4 Identification of the Predictors/Determinants of QoL

There is a growing literature on the variables that are associated with QoL **(**Cote et. al. 2003). It is important to identify predictors of QoL in chronic illness as they may be helpful to patients and professionals in guiding counselling, as well as interventions and forming a basis for clinician–patient relationships **(**Cote et. al. 2003). In addition, identifying predictors will be significant in clinical practice as it may help professionals to target interventions relating to those predictions (Riazi et. al. 2002). Therefore, it is important to examine whether levels of adherence and psychosocial factors such as social support and self-efficacy are predictors of QoL in people with BTM.

8.4.4.1 Adherence

Non-adherence with drug therapy is a significant problem in all patient populations from children to the elderly. It applies to nearly all chronic disease states (Lacombe, Vicente, Pages and Morselli, 1996) and is well recognised to have major medical, psychological and economic consequences (Myers and Midence, 1998). Adherence to drug treatment and QoL are both related to the patient and are important to consider when assessing the impact of any type of intervention in healthcare at the patient level (Cote et. al. 2003). A positive impact on QoL as perceived by the patients is an important criterion for evaluating treatment success (Revicki et. al. 2000). Adherence and QoL are two outcomes representing different points in time following processes of care and whilst adherence is thought to be an intermediate outcome HRQoL is thought to be an ultimate outcome (Cote et. al. 2003). This implies that the impact of any type of intervention will be revealed by a change in adherence first and consequently by a change in QoL (Cote et. al. 2003). Results from studies that have attempted to measure the relationship between adherence to drug treatment and QoL have shown that QoL is not consistently associated with adherence to medication (Holzemer, Corless, Nokes, Turner, Brown, Powell-Cope et. al. 1999; Sung, Nichol, Venturini, Bailey, McCombs, and Cody, 1998). Most of the studies that did not find an association between adherence and QoL used a generic instrument to measure QoL that may have affected the results (Riazi, Thompson and Hobart, 2004). Research needs to be undertaken using a disease-specific measure of adherence e.g. liver scan. Despite the very clear benefits of ICT, it is a difficult treatment to administer and adherence to therapy has been a major issue for both clinicians and patients over the last 30 years (Porter and Davis, 2002). Assessing the impact of treatments on QoL is important for many reasons not least because an adverse impact could reduce adherence with therapy (Bradley, 2001). An examination of BTM patients' adherence should be undertaken to examine whether following the strict regimen for the treatment of BTM has an influence on their QoL as efforts to achieve excellent health may damage QoL particularly in the management of thalassaemia (Telfer et. al. 2005).

8.4.4.2 Self-efficacy

Self-efficacy refers to personal judgments concerning one's ability to engage successfully in specific behaviours that lead to specific, desired outcomes (Bandura, 1977). Self-efficacy/autonomy was shown to be a relevant domain in BTM patients as reported by in-depth patient interviews and measured by the SCSES (Edwards et. al. 2000). Research

has shown it to be an important construct in chronic illness literature e.g. Hodson and Geddes (1995). Recent studies have indicated that self-efficacy is an important factor in psychosocial and physical adjustment for persons with chronic medical conditions (Riazi et. al. 2004). Self-efficacy beliefs have been noted to play an important role as they are thought to act like a buffer (Barlow, Williams and Wright, 1996). Research has shown that enhanced self-efficacy coping beliefs at a given time point may be associated in disease symptoms and improvements in adjustment in patients with arthritis (Lorig and Gonzalez, 1992), cancer (DeBoer, Van den Borne, Pruyn, Ryckman, Volovics, Knegt et. al. 1998) and heart problems (Clark and Dodge, 1999). Self-efficacy has also been found to predict psychosocial outcomes and QoL in MS e.g. Schwartz, Coulthard-Morris, Zeng and Retzlaff, (1996), Airlie, Baker, Smith and Young (2001), Rigby, Domenech, Thornton, Tedman and Young (2003). Results from these studies suggest that higher levels of baseline levels of self-efficacy are associated with fewer physical and emotional problems at various follow-up periods however the predictive value of self-efficacy on health status in BTM has not been investigated. It has been suggested that when a person experiences a discrepancy between goal importance and attainability due to low self-efficacy it may impair their QoL (Kuijer and de Ridder, 2003). When setbacks occur, people high in self-efficacy recover more quickly and maintain more commitment to goals that those low in self-efficacy (Schwarzer, 1992). Self-efficacy health beliefs and behaviour may assist individuals in adjusting to symptoms of their illness (Kuijer and De Ridder, 2003) and is thought to predict changes in health status over a period of time in illness such as SCD (Edwards et. al. 2000). If self-efficacy is taken to be a strong predictor of QoL then it is an important area to target in clinical practice as negative beliefs may be modifiable (Riazi et al. 2004). Interventions to enhance specific self-efficacy for health behaviours have been suggested to improve QoL (Stuifbergen, Seraphine and Roberts, 2000) hence a future study could examine the predictive value of self-efficacy on BTM patients' QoL.

8.4.4.3 Social Support

The literature has long recognised that social support is an important resource available to persons with chronic illness (Amir, Roziner, Knoll and Neufeld, 1999). Social support in medical settings has received considerable attention of which the vast majority supports the positive effect of social support in chronic diseases (de Ridder and Schreurs, 1999). One may speculate that the patients see social support as a mirror image of social stigma and the quality and quantity of the social network may become evidence of social rejection or

indeed acceptance for the individuals (Amir et. al. 1999). Alternatively, lack of social support may mean a diminished self-value and less instrumental, cognitive and emotional support from fewer resources, this in turn lowers the evaluation of the individual regarding his/her ability to cope with the disease (Amir et. al. 1999). Social support has been found to predict QoL in various chronic illnesses. For example, in people with epilepsy the limitations in QoL are perceived as being mediated by personal and social characteristics especially his/her social situation (Lutgendrof, Antoni, Schneiderman and Fletcher, 1994). Similarly, significant associations between social support and QoL in human immunodeficiency virus (HIV) infected persons have been found e.g. Friedland, Renwick and McColl (1996) (HIV is a virus which is the cause of acquired immune deficiency syndrome (AIDS), which is a deficiency of the immune system (BMA, 2002)). Social support was significantly associated with all QoL domains except physical functioning and bodily pain HIV infected persons (Bastardo and Kimberlin, 2000). In addition, the role of social support has been one of the previously unexplained reasons for the association between functional limitations and poorer QoL for coronary artery disease (CAD) patients (Bosworth, Siegler, Olsen, Brummett, Barefoot, Williams et. al. 2000) (CAD is the narrowing of the coronary arteries which supply blood to the heart leading to damage or malfunction of the heart) (BMA, 2002)).

As the life expectancies of patients with chronic illness increases, understanding factors relating to QoL and how these factors like social support are associated with QoL become increasingly important (Bosworth et. al. 2000). It has been suggested that social support affects health outcomes either through its effects on the function of the immune system (Kiecolt-Glaser and Glaser, 1995) or through effects on self-care activities and other illness behaviours (Lutegendorf et. al. 1994). Several studies have examined the level of social support in TM patients as it is acknowledged that psychosocial aspects of BTM appear to play a major role in patients' lives (Porter and Davis, 2002). Much of the coping with BTM takes place in a social context with regard to self-image, time taken off work for blood transfusions, disclosing illness to new friends, work colleagues, and personal acquaintances (Georganda, 1990). In fact, the degree of social support that BTM patients experience was found to be a better predictor of adherence than the severity of the illness (Bush et. al. 1998). Compared to healthy subjects, thalassaemic groups of patients have endorsed having greater social support; people with thalassaemia were identified as having more sources of social support in general as well as greater levels of emotional support - no

significant differences were found in the levels of perceived support from other friends, family members, doctors, mental health professionals or clergy although the group with thalassaemia identified a greater amount of emotional support from nurses (Bush et. al. 1998). At the same time, maintaining adequate social support may be problematic for some people with BTM because of the stigma associated with the disease among other persons in one's support network (Georganda, 1990). As individuals experience illnesses like BTM there is potential for disruption to their social support system that may inadvertently affect their QoL (Bush et. al. 1998). To date researchers have not investigated the predictive value of social support on BTM patients' QoL. It should be noted that some of the facets of the SR sub-scale of the THALI-35 were noted in findings from Bush et. al. (1998) and Georganda (1990) e.g. rejection and being penalised due to illness.

Clearly, the levels and sources of social support of patients and their self-efficacy beliefs have important functions within chronic illness. As thalassaemia patients undergo burdensome treatment, social support networks as well as the beliefs surrounding their challenging situation are important in determining psychological health status therefore a study which examines the predictive value of social support, self-efficacy and adherence on BTM patients' QoL would be beneficial. The study would have significant importance for the following reasons: a) as the life expectancies of patients with BTM increases, the understanding of factors relating to quantity and QoL and how factors such as social support are associated with QoL become increasingly important, b) self-efficacy health beliefs and behaviour seems to be a strong predictor of health status in chronic BTM patients and c) a BTM patient's decision on whether they adhere to treatment or not may or may not be detrimental to their life quality and well- being.

8.5 Interpreting the Scores of the Thalassaemia Adult Life Index (THALI-35)

Despite the widespread use of health outcome measures there is no systematic strategy for translating scores generated by such instruments into clinical decisions (Hobart et. al. 2004). It is standard practice with any standardised measure to interpret scores in relation to normative values for the population - these are generally expressed as standard deviation units, percentiles or percentages thus enabling comparisons across samples, constructs and measures (Hobart et. al. 2004). However, norm-based interpretations are unfamiliar to clinicians and patients and may have limited clinical meaning (Hobart et. al. 2004). Some

authors have suggested a simplistic preliminary method of interpreting scores for Likert scales (Jenkinson, Fitzpatrick, Swash, Levvy, 2001). Based on this suggestion, a simple method of interpreting THALI-35 scores would be to categorise scores according to its 5-point scale i.e. 0-34 as no problems, 35-69 as few problems, 70-104 as moderate problems, 105-139 as quite a few problems and 140-175 as extreme problems. A higher score on the THALI-35 indicates poor QoL. In this way, each separate sub-scale could be looked at in relation to the other scales. Although simplistic, this method may be used until the accumulation of further data needed to enable population norms. In the interim, THALI-35 scores can be compared with mean scores from the random sample of people from the UKTS, with permission. Scores from groups of individuals with BTM can be compared with the mean scores of people from the UKTS to identify how much that group's score differs from the UKTS sample.

Several other methods have been proposed for the clinical interpretation of scores on health measures. These include relating scores or score changes to preference weightings (Hadhorn and Uerbersax, 1995) and/or equivalence with the impact of other diseases (Brook, Ware, Rogers, Keeler, Davies and Donald, 1983). These methods have their limitations e.g. the impact of other symptoms in illness is uncommon (Lydick and Epstein, 1993) and weighting it often calculated by clinicians (Ratip, 1996). Such limitations prompted Deyo, Andersson, Bombardier, Cherkin, Keller and Lee (1994) to recommend the use of a limited number of measures in research. Lydick and Yawn (1998) add that the continued collection of data concerning clinical anchors will enable clinicians, over time, to become increasingly familiar with the clinical significance of particular levels of change. The latter highlights the need for continuous collection of THALI-35 data to determine the clinical significance of change scores (Hobart et. al. 2004).

8.6 Conclusions

Measurement of health outcomes underpins clinical research and clinical practice. In chronic disorders such as BTM it is essential that outcome measures incorporate the patient's perspective. The 35-item THALLI is a new measure of the biopsychosocial impact of BTM derived from patient interview and evaluated from the patients perspective. Initial validation of the psychometric properties of the THALI-35 shows reliability and validity therefore appears to be suitable for use with adult BTM populations. Moreover, it appears to be the first available disease-specific QoL measure utilised with a BTM

population. This brief instrument could be easily administered in a community healthcare setting. Given the intimate ties between QoL and behaviour e.g. Politis (1998), identification of at-risk individuals low in QoL may provide opportunities to reduce adverse BTM impact. Assessments of QoL beliefs in this population might lead to interventions targeted toward those individuals who are at high risk from poor symptom management and decreased psychosocial adjustment. Effective, relatively low-cost interventions such as psycho-educational groups, individuals counselling or group therapies may facilitate increased QoL beliefs and improve adjustment and coping in BTM thus increasing patient and provider satisfaction. Although both positive and negative relationships were observed between QoL and coping, autonomy, general health perceptions and body image, adaptation to any chronic illness is multi-dimensional with dynamically interacting facets (Edwards et. al. 2000). Quality of life (QoL) is an important outcome (Bowling, 1995) and the results of this study indicate that QoL in a population of adults with BTM is measurable in a psychometrically sound manner. Furthermore, these data suggest that perceived QoL may play a significant role in predicting adjustment to and/or coping with BTM. Nonetheless such a conclusion awaits independent empirical verification even though the present study provides an adequate point of departure for such a programme of research.

References

Abbey, A. and Andrews, F.M. (1986). 'Modelling the psychological determinants of life quality' In: FM. Andrews (ed.) *Research on the quality of life*. Michigan, Ann Arbor, Survey Research Center, Institute for Social Research, University of Michigan.

Abeles, R.P., Gift, H.C. and Ory, M.G. (1994). *Aging and quality of life*. New York, Springer Publishing.

Abel-Smith, B. (1976). *Value for money in health services*. London, Heinemann.

Abetz, L., Baladi, J.F., Jones, P. and Rofail, D. (2006). The impact of iron overload and its treatment on quality of life: results from a literature review. *Health and Quality of Life Outcomes*, 4, 73, 1-6.

Abbott, J., Conway, S., Etherington, C., Fitzjohn, J., Gee, L., Morton, A., et. al. (2000). Perceived body image and eating behaviour in young adults with cystic fibrosis and their healthy peers. *J Behav Med*, 23, 501-17.

Achenbach, T.M. (1992). *Manual for the child behaviour checklist (2/3 profile).* University of Vermont, Department of Psychiatry, Burlington, VT.

Ahmed, S., Saleem, M., Modell, B. and Petrou, M. (2002). Screening extended families for genetic hemoglobin disorders in Pakistan. *N Engl J Med*, 347, 1162-1168.

Airlie, J., Baker, G.A., Smith, S.J. and Young, C.A. (2001). Measuring the impact of multiple sclerosis on psychosocial functioning: the development of a new self-efficacy scale. *Clin Rehabil*, 15, 259-65.

Albrecht, G.L. and Devlieger, P.J. (1999). The disability paradox: high quality of life against all odds. *Soc Sci Med*, 48, 977-988.

Allen, M.J. and Yen, W. M. (2002). *Introduction to Measurement Theory*. Long Grove, IL: Waveland Press.

al-Refaie, F.N., Hershko, C., Hoffbrand, A.V., Kosaryan, M., Olivieri, N.F., Tondury, P. and Wonke, B. (1995. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral Iron Chelators. *Br J Haematol,* 91, 224-229.

Amir, M., Roziner, I., Knoll, A. and Neufeld, M.Y. (1999). Self – efficacy and social support as mediators in the relation between disease severity and quality of life in patients with epilepsy. *Epilepsia,* 40, 216 – 24.

Anastasi, A. (1988). *Psychological testing.* New York, NY: Macmillan.

Anderson, K.L. (1995). The effect of chronic obstructive pulmonary disease on quality of life. *Research in Nursing and Health,* 18, 547 – 556.

Anderson, K.O., Bradley, L.A., Young, L.D., McDaniel, L.K. and Wise, C.M. (1985). Rheumatoid arthritis: review of psychological factors related to etiology, effects, and treatment. *Psychol Bull,* 98, 2, 358-87.

Anderson, K. L. and Burckhardt, C.S. (1999). Conceptualisation and measurement of quality of life as an outcome variable for healthcare intervention and research. *Journal of Advanced Nursing,* 29, 2, 298 – 306.

Anderson, J. C. and Gerbing, D. W. (1988). Structural equation modeling in practice: A review and recommended two-step approach. *Psychological Bulletin,* 103, 3, 411-423.

Andreou, P. et. al. (2003). *The Cypriot thalassaemics: a survey*. Paper presented at the 9th International Conference on Thalassaemia and the Haemoglobinopathies and the 11th International Conference for Parents and Thalassaemics, Palermo, Italy, October 19.

Angastiniotis, M. and Modell, B. (1998). Global epidemiology of haemoglobin disorders. *Ann N Y Acd Sci,* 850, 251-269.

Angelucci, E., Brittenham, G.M., McLaren, C.E., Ripalti, M., Baronciani, D., Giardini, C., Galimberti, M., Polchi, P. and Lucarelli, G. (2000). Hepatic iron concentration and total body iron stores in thalassaemia major. *N Engl J Med*, 343, 327-331.

Anie, K.A., Dasgupta, T., Ezenduka, P., Anarado, A. and Emodi, I. (2007). A cross-cultural study of psychosocial aspects of sickle cell disease in the UK and Nigeria. *Psychology, Health and Medicine*, 12, 3, 299-304.

Anionwu, E.N (2004). 'Sickle cell disorders and thalassaemia: the challenge for health professionals and resources available' In: Okpala, I.E. (ed) *Practical management of haemoglobinopathies,* Oxford, Blackwell Publishing Limited.

Araujo, A.S., Silva, W.A., Leao, S.A., Bandeira, F.C., Petrou, M., Modell, B., et. al. (2003). A different molecular pattern of beta-thalassaemia mutations in northeast Brazil. *Hemoglobin*, 27, 211-217.

Arboretti, R., Tognoni, G., Alberti, D., Thalassarmia, I.C.G. (2001). Pharmacosurveillance and quality of care of thalassaemic patients. A large scale epidemiological survey. *European Journal of Clinical Pharmacology*, 56, 915-922.

Arnold, R., Ranchor, A.V., Sanderman, R., Kempen, G.I.J.M., Ormel, J. and Suurmeijer, T.P.B.M. (2004). The relative contribution of domains of quality of life to overall quality of life for different chronic diseases. *Qual Life Res*, 13, 883-896.

Atkin, K. and Ahmad, W. I. U. (2001). Living a 'normal' life: young people coping with thalassaemia major or sickle cell disorder. *Soc Sci Med*, 53, 615-626.

Babbie, E.R. (2004). *The Practice of Social Research* (10th edition), Wadsworth, Thomson Learning Inc.

Babbie, E.R. (2005). *The Basics of Social Research*. Wadsworth, Thomson Learning Inc.

Badia, X., Webb, S.M., Prieto, L. and Lara, N. (2004). Acromegaly Quality of life questionnaire (AcroQol). *Health and Quality of Life Outcomes*, 2, 13, 1-6.

Baker, G.A., Hesdon, B. and Marson, A.G. (2000). Quality of life and behavioural outcome measures in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards. *Epilepsia*, 41, 1357-1363.

Baker, F. and Intagliata, J. (1982). Quality of life in the evaluation of community support systems. *Evaluation and Program Planning*, 5, 69-79.

Bandura, A. (1977). Toward a unifying theory of behavioural change. *Psychological Review*, 84, 191-215.

Barlow, J.H., Williams, B. and Wright, C. (1996). The generalized self-efficacy scale in people with arthritis. *Arthritis Care Res*, 9, 189 – 196.

Barnes, J.A. (1954). Class and committees in a Norwegian island parish. *Human Relations*, 7, 39-58.

Baron, H. (1996). Strengths and Limitations of Ipsative Measurement. *Journal of Occupational and Organizational Psychology*, 69, 49–56.

Barr, R.D., Saleh, M., Furlong, W., Horsman, J., Sek, J., Pai, M., Walker, I. (2002). Health status and health-related quality of life associated with haemophilia. *Am J Hematology*, 71, 152-160.

Barrett, D.H., Wisotzek, I.E., Abel, G.G., Rouleau, J.L, Platt, A.F., Pollard, W.E. et. al. (1988). Assessment of psychosocial functioning o patients with sickle cell disease. *Southern Medical Journal*, 81, 6, 745-750.

Bastardo, Y.M., and Kimberlin, C.L. (2000). Relationship between quality of life, social support and disease-related factors in HIV-infected persons in Venezuela. *Aids Care*, 12, 5, 673-684.

Beck, A. Ward, C. Medelson, M. Mock, J. Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry*, 4, 561 – 571.

Beckie, T.M. and Hayduk, L.A. (1997). Measuring quality of life. *Social Indicators Research*, 42, 21-39.

Bergner, M. (1989). Quality of life, health status, and clinical research. *Med Care*, 27 (3 Suppl), S148–56.

Berkman, L.F. and Glass, T. (2000). 'Social integration, social networks, social support and health' In: L.F. Berkman and I. Kawachi (eds.) *Social Epidemiology*, Oxford: Oxford University Press.

Berkman, L.F., Glass, T., Brissette, I. and Seeman, T.E. (2000). From social integration to health: Durkheim into the new Millennium. *Soc Sci Med*, 51, 6, 843-857.

Bigelow, D.A, Brodsky, G., Stewart, L. and Olson, M. (1982). 'The concept and measurement of quality of life as a dependent variable in evaluation of mental health services' In: W. Tash and G. Stahler (eds.) *Innovative approaches to mental health evaluation*, New York, Academic Press.

Bland, J.M. and Altman, D.G. (1986). Statistical methods for assessing the agreemtn between two methods of clinical measurement. *Lancet*, i, 307-310.

Blascovich, J. and Tomaka, J. (1991). 'Measures of self-esteem' In: J.P. Robinson, P.R. Shaver and L.S. Wrightsman, Measures of personality and social psychological attitudes, 291-371, In: *Measures of social psychological attitudes*, Volume 1. San Diego, CA, Academic Press.

Bohrnstedt, G.W. (1983). 'Measurement' In: Rossi, P.H., Wright, J.D and Anderson, A.B, (eds.) *Handbook of survey research*, 69–121, New York: Academic Press.

Bollen, K.A. (1989). *Structural Equations with Latent Variables*. New York: Wiley.

Bonnicatto, S.C., Dew, M. A., Zarateigui, R., Lorenzo, L., Pecina, P. (2001). Adult outpatients with depression: Worse quality of life than in other chronic medical diseases in Argentina. *Soc. Sci. Med*., 52, 6, 911-919.

Borgna-Pignatti, C., Rugolotto, S., De Stefano, P., Zhao, H., Cappellini, M.D., Del Vecchio, G.C., et. al. (2004). Survival and complications in patients with thalassaemia major treated with transfusion and deferoxamine. *Haematologica,* 89, 1187-1193.

Bosworth, H.B., Siegler, I.C., Olsen, M.K., Brummett, B.H., Barefoot, J.C., Williams, R.B., et. al. (2000). Social support and quality of life in patients with coronary artery disease. *Qual Life Res*, 9, 829-839.

Bott, E. (1957). *Family and social network*. Tavistock Press, London.

Bowling, A. (1995). 'Respiratory conditions' In: A. Bowling (ed.) *Measuring Disease: a review of disease specific quality of life measurement scales,* Open University Press.

Bowling, A. (1995a). What things are important in people's lives? *Soc Sci Med*, 41, 1447-1462.

Bowling, A. (1995b). The most important things in life. Comparisons between older and younger population age groups by gender. *Int. J. Health Sciences*, 6, 169-175.

Bowling, A. (2002). *Research methods in health: Investigating health and health services* (2nd ed.), Open University Press, Buckingham, Philadelphia.

Bowling, A., Gabriel, Z., Dykes, J., Marriott-Dowding, L., Fleissig, A., Evans, O., Banister, D. And Sutton, S. (2003). Let's ask them: a national survey of definitions of quality of life and its enhancement among people aged 65 and over. *International Journal of Aging and Human Development*, 56, 269-306.

Bowling, A. and Windsor, J. (2001). Towards the good life. A population survey of dimensions of quality of life. *Journal of Happiness Studies*, 2, 55-81.

Boyle, M. H., Furlong, W., Feeny, D., Torrance, G. and Hatcher, J. (1995). Reliability of the Health Utilities Index - Mark III Used in the 1991 Cycle 6 General Social Survey Health Questionnaire. *Quality of Life Research*, 4, 3, 249-257.

Boyle, I., diSant'Agnese, P. and Sack, P. (1976). Emotional adjustment of adolescents and young adults with cystic fibrosis. *J Pediat*, 88, 2, 318-26

Bradley, C. (2001). Importance of differentiating health status from quality of life. *The Lancet*, 357, 9249, 7-8.

Brazier, J. and Deverill, M. (1999). A checklist for judging preference based measures of health related quality of life: learning from psychometrics. *Health Economics*, 8, 41-51.

Brazier, J.E., Harper, R., Jones, N.M.B., O'Cathain, A., Thomas, K.J., Usherwood, T., Westlake, L. (1992). Validating the SF-36® Health Survey Questionnaire: new outcome measure for primary care. *British Medical Journal*, 305, 1, 60-4.

Brissette, I., Cohen, S. and Seeman, T.E. (2000). 'Measuring social integration and social networks' In: S. Cohen, L.G. Underwood and B. H. Gottlieb (eds.) *Social support measurement and intervention: A guide for health and social scientists*, 53-85, Oxford University Press.

Brissette, I., Scheier, M.F. and Carver, C.S. (2002). The role of optimism in social network development, coping, and psychological adjustment during a life transition. *Journal of Personality and Social Psychology*, 82, 102-11.

British Medical Association (BMA) (2002). *Illustrated Medical Dictionary*. London, New York, Munich, Melbourne, Delhi: Dorling Kindersley.

Brittenham, G.M., Griffith, P.M., Nienhuis, A.W., McLaren, C.E., Young, N.S., Tucker, E.E., et. al. (1994). Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassaemia major. *N Engl J Med*, 331, 567-573.

Brook, R.H., Ware, J.E. Jr., Davies-Avery, A., Stewart, A.L., Donald, C.A., Rogers, W.H., et al. (1979). Overview of adult health status measures fielded in Rand's Health Insurance Study. *Med Care*, 17 (7 Suppl), S1–131.

Brook, R.H., Ware, J.E. Jr., Rogers, W.H., Keeler, E.B., Davies, A.R., Donald, C.A. (1983). Does free care improve adult health? Results from a randomized controlled trial. *N Engl J Med*, 309, 1426–34.

Brosseau, L. (1994). The inter-rater reliability and construct validity of the Functional Independence Measure for multiple sclerosis subjects. *Clin Rehabil*, 8, 107–15.

Brown, J., Bowling, A. and Flynn, T. (2004). *Models of Quality of Life: A Taxonomy, Overview and Systematic Review of the Literature.* European Forum on Population Ageing Research, European Group on Quality of Life Extending quality of life in old age (EQUAL), University of Bristol, University College London.

Brown, R., MacCarthy, B., Jahanshahi, M. and Marsden, C. (1989). Accuracy of self-reported disability in patients with Parkinsonism. *Arch Neurol*, 46, 955–9.

Brown, K.W. and Moskovitz, D.S. (1998). It's a function of time: a review of the process approach to behavioural medicine research. *Annals of Behavioral Medicine*, 20, 109-117.

Bryman, A. (2001). *Social Research Methods*, Chapters 3-12, 21-22, Oxford University Press.

Bulmer, M. (2003). *Francis Galton: Pioneer of Heredity and Biometry*, Johns Hopkins University Press.

Bunting, B.P., Adamson, G. and Mulhall, P. (2002). A Monte Carlo examination of MTMM model with planned incomplete data structures. *Structural Equation Modeling*, 9, 369-389.

Burckhardt, C.S. (1985). The impact of arthritis on quality of life. *Nursing Research*, 34, 11-16.

Burroughs, T.E., Desikan, R., Waterman, B.M, Gilin and McGill, J. (2004). Development and Validation of the Diabetes Quality of Life (QoL) Brief Clinical Inventory. *Diabetes Spectrum*, 17, 1, 41-49.

Bush, S., Mandel, F.S., and Giardina, P.J. (1998). Future orientation and life expectations of adolescents and young adults with thalassaemia major. *Ann N Y Aca Sci*, 850, 361-369.

Cadman, D., Boyle, M., Szatmari, P. and Offord, D. (1987). Chronic illness, disability and mental and social well-being: Findings of the Ontario child health study. *Pediatrics*, 79, 805-813.

Calleja, E.M., Shen, J.Y., Lesser, R.W., Grady, M., New, M.I. and Giardina, P.J. (1998). Survival and morbidity in transfusion-dependent thalassaemic patients on subcutaneous deferoxamine chelation: nearly two decades of experience. *Ann N.Y. Acad Sci*, 850, 472-473.

Canatan, D., Ratip, S., Kaptan, S. and Cosan, R. (2003). Psychosocial burden of beta-thalassaemia major in Antalya, south Turkey. *Soc Sci Med*, 56, 4, 815-819.

Cao, A., Rosatelli, C. and Galanello, R. (1991). Population based genetic screening. *Current Opinion in Genetics and Development*, 1, 48-53.

Cappelli, M., Megrath, P., Heick, C., Macdonald, N., Feldman, W. and Rowe, P. (1989). Chronic disease and its impact. *Journal of Adolescent Health Care*, 10, 283-288.

Cappellini, M.D., Cohen, A., Piga, A., Bejaoui, M., Perrotta, S., Agaoglu, L., et. al. (2006). A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassaemia. *Blood*, 107, 9, 3455-3462.

Caro, J., Huybrechts, K.F. and Green, T.C. (2002) Estimates of the effect on hepatic iron of oral deferiprone compared with subcutaneous desferrioxamine for treatment of iron overload in thalassaemia major: a systematic review. *BMC Blood Disord*, 2, 4.

Carver, C.S. (1997). You want to Measure Coping but Your Protocol's Too Long: Consider the Brief COPE. *International Journal of Behavioral Medicine*, 4, 1, 92.

Carver, D.J., Chapman, C.A., Thomas, V.S., Stadnyk, K.J. and Rockwood, K (1999). Validity and reliability of the Medical Outcomes Study Short Form-20 questionnaire as a measure of quality of life in elderly people living at home *Age Ageing*, 28: 169-174.

Carver, C.S., Scheier, M.F. and Weintraub, J.K. (1989). Assessing coping strategies: A theoretically based approach. *Journal of Personality and Social Psychology*, 56, 267-283.

Cash T.F. and Fleming, E.C. (2002). The impact of body image experiences: development of the body image quality of life inventory. *International Journal of Eating Disorders*, 31, 455-460.

Cash, T.F., Jakatdar, T.A. and Williams, E.F. (2003). The Body Image Quality of Life Inventory: Further validation with college men and women. *Body Image*, 1, 279, 279 – 287.

Cattell, R. B. (1966). The scree test for the number of factors. *Multivariate Behavioral Research*, 1, 629-637.

Ceci, A., Baiardi, P., Felisi, M., Cappellini, M.D., Carnelli, V., De Sanctis, V., et. al. (2003). The safety and effectiveness of deferiprone in a large scale, 3 year study in Italian patients. *British Journal of Haematology*, 118, 330-336.

Centres for Disease Control and Prevention (CDC) (2007) Available at: http://en.wikipedia.org/wiki/Centres_for_Disease_Control_and_Prevention. (Accessed 26th June 2007).

Chadwick, R., Ten Have, H., Husted, J., Levitt, M., McGleenan, T., Shickle, D., et. al. (1998). Genetic screening and ethics: European perspectives. *J Med Philos*, 23, 3, 255-73.

Chavis, W.M. and Norman, G.S. (1993). Sexuality and sickle cell disease. *J Natl Med Assoc*, 85 (2), 113-6.

Chren, M.M., Lasek, R.J., Sahay, A.P. and Sands, L.P. (2001). Measurement properties of skindex-16: A brief quality-of-life measure for patients with skin diseases. *Journal of Cutaneous Medicine and Surgery: Incorporating Medical and Surgical Dermatology*, 5, 2, 105-110.

Cieza, A. and Stucki, G. (2005). Content comparison of health-related quality of life (HRQOL) instruments based on the international classification of functioning, disability and health (ICF). *Qual Life Res*, 14, 1225-1237.

Clark, N.M. and Dodge, J.A. (1999). Exploring Self-Efficacy as a Predictor of Disease Management. *Health Educ Behav*, 26, 72-89.

Clarke, P.J., Marshall, V.W., Ryff, C.D. and Rosenthal, C.J. (2000). Well-being in Canadian seniors: findings from the Canadian study of health and aging. *Canadian Journal on Aging*, 19, 139-159.

Clausen, H., Brandt, N.J., Schwarz, M. and Skovby, F. (1996). Psychological impact of carrier screening for cystic fibrosis among pregnant women. *Eur J Hum Genet.* 4, 2, 120-3.

Coffman, C., Levine, S., Althof, S. and Stern, R. (1984). Sexual adaptation among young adults with cystic fibrosis. *Chest*, 86, 412-18.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.) Hillsdale, NJ: Erlbaum

Cohen, A.R., Galanello, R., Piga, A., DiPalma, A., Vullo, C. and Tricta, F. (2000). Safety profile of the oral iron chelator deferiprone: a multicentre study. *Br J Haematol*, 108, 305-312.

Colman, A. M. (2001). *Oxford Dictionary of Psychology*. Oxford University Press.

Comrey, A.L. (1988). Factor analytic methods of scale development in personality and clinical psychology. *Journal of Consulting and Clinical Psychology*, 56, 754-761.

Comrey, A.L. and Lee, H.B. (1992). *A first course in factor analysis* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Congleton, J., Hodson, M.E. and Duncan-Skingle, F. (1996). *Quality of life in adults with cystic fibrosis. Thorax*, 51, 936-940.

Cooley, T.B. and Lee, P. (1925). A series of cases of splenomegaly in children with anaemia and peculiar bone changes. *Transactions of the American Pediatric Society*, 37, 29.

Cooper K, Arber S, Fee L, Ginn J. (1999). *The Influence of Social Support and Social Capital on Health: A Review and Analysis of British Data.* London Health Education Authority.

Corrigan, P.W. (2004). Target specific stigma change: A strategy for impacting mental illness stigma. *Psychiatric Rehabilitation Journal*, 28, 2, 113

Cortina, J.M. (1993). What is a coefficient alpha? An examination of theory and application. *J Appl Psychol,* 78, 98-104.

Cote, I., Farris, K. and Feeny, D. (2003). Is adherence to drug treatment correlated with health related quality of life? *Qual Life Res*, 12, 621-633.

Cronbach, L.J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika,* 16, 297-334.

Cronbach, L.J. and Meehl, P.E. (1955). Construct validity in psychological tests. *Psychological Bulletin,* 52, 281-302.

Cummins, R.A. (1992). 'Comprehensive Quality of Life Scale' (Intellectual Disability, Melbourne: Psychology Research Centre', In: D. Felce and J. Perry, Quality of life: Its Definition and Measurement. *Research in Developmental Disabilities*, 16, 1, 51-74.

Cummins, R.A. (1997). 'Assessing Quality of Life' in R. Brown (ed.) *Quality of Life for People with Disabilities. Models, Research and Practice*, (2nd ed.), Cheltenham: Stanley Thornes (Publishers) Ltd.

Cummins, R.A. (2005). 'Moving from the Quality of Life Concept to a theory' In: R. Schalock (ed.). *Journal of Intellectual Disability Research – Special Issue on Quality of Life*, 49, 10, 699-706.

Cummins, O. and Anie, K. A. (2003). A comparison of the outcome of cognitive behaviour therapy and hydroxyurea in sickle cell disease. *Psychology, Health and Medicine*, 8, 2, 199-204.

Darlington, R. B. (1973), In Richard B. Darlington,Sharon Weinberg, and Herbert Walberg (1973). Canonical variate analysis and related techniques. *Review of Educational Research*, 453-454.

Dawes, J. (2008). Do Data Characteristics Change According to the number of scale points used? An experiment using 5-point, 7-point and 10-point scales. *International Journal of Market Research*, 50, 1, 61-77.

Deasy-Spinetta, P., Spinetta, J.J. and Osman, J.B. (1988). The relationship between learning deficits: a social adaptation in children with leukaemia. *Journal of Psychology and Oncology*, 6, 109-121.

DeBoer, M.F., Van den Borne, B., Pruyn, J.F.A., Ryckman, R.M., Volovics, L., Knegt, P.P. et. al. (1998). Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6 year longitudinal study. *Cancer*, 83, 2567-79.

DeJong, W., Kaptein, A.A., Van der Schans, C.P., Mannes, G.P., Van Aalderen, W.M., Grevink, R.G., and Koeter, G.H. (1997). Quality of life in patients with cystic fibrosis. *Pediat Pulmonol*, 23, 95-100.

Delhey, J., Böhnke, P., Habich, R. and Zapf, W. (2002). Quality of life in a European perspective: the EUROMODULE as a new instrument for comparative welfare research. *Social Indicators Research,* 58, 163-176.

Demo, D.H. (1985). The measurement of self-esteem: refining our methods. *Journal of Personality and Social Psychology*, 48, 1490-1502.

DeOreo, P.B. (1997). Hemodialysis patient-assessed functional health status predicts continued survival, hospitalisation and dialysis attendance compliance. *Am J Kidney Dis*, 30, 204-212.

Department of Health (DoH) (2009). Guidance on the routine collection of Patient Reported Outcome Measures (PROMs). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_092647. (Accessed 1st July 2009).

de Ridder, D. and Schreurs, K. (1999). Developing interventions for chronically ill patients: is coping a helpful concept? *Clin Psychol Rev*, 21, 205-40.

deVet, H.C.W., Ader, H.J., Terwee, C.B. and Pouwer, F. (2005). Are factor analytical techniques used appropriately in the validation of health status questionnaires? A systematic review on the quality of factor analysis of the SF-36. *Quality of Life Research*, 14, 1203-1218.

Devins, G.M., Mann, J., Mandin, H., Paul, P., Hons, K., Burgess, B., et. al. (1990). Psychosocial predictors in End Stage Renal Disease. *Journal of Nervous and Mental Diseases*, 178, 2, 133.

Deyo, R.A., Andersson, G., Bombardier, C., Cherkin, D. C., Keller, R.B., Lee, C.K. (1994). Outcome measures for studying patients with low back pain. *Spine*, 18 (Suppl), 2032S–6S.

Diener, E. and Lucas, R.E. (2000). 'Subjective emotional well being' In: M. Lewis and J.M. Haviland (eds.). *Handbook of emotions*, (2nd ed.), New York: Guilford.

Diener, E. and Suh, E. (1997). Measuring quality of life: economic, social and subjective indicators. *Social Indicators Research*, 40, 189-216.

Diener E., Suh, E.M., Lucas R. E. and Smith, H.L. (1999). Subjective well-being: Three decades of progress. *Psychological bulletin*, 125, 2, 276-302.

Dillman, D.A. (2000). *Mail and Internet Surveys: The Tailored Design Method* (2nd ed.). New York, Chichester, Weinheim, Brisbane, Singapore, Toronto, John Wiley and Sons, Inc.

DiMatteo, M.R. (2004). Variations in Patients' Adherence to Medical Recommendations: A Quantitative Review of 50 years of Research. , 42, 3, 200-209.

DiPalma, A., Vullo, C., Zani, B. and Facchini, A. (1998). Psychosocial Integration of Adolescents and Young Adults with Thalassaemia Major. *Ann N Y Acd Sci*, 850, 355-360.

Dodge, J.A. and Morrison, G. (1992). Diabetes mellitus in cystic fibrosis: a review. *J R Soc Med*, 85 (Suppl 19), 25–28.

Dodge, J.A., Morison, S., Lewis, P.A., Coles, E.C., Geddes, D., Russell, G., et. al. (1997). Incidence, population and survival of cystic fibrosis in the UK (1968-95). *Arch Dis Child*, 77, 493-6.

Dubos, R. (1976). The state of health and the quality of life. *The Western Journal of Medicine*, 125, 1-2.

Duncan, P.W., Jorgensen, H.S. and Wade, D.T. (2000). Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. *Stroke*, 31, 1429-1438.

Durkheim, E. (1928). *Suicide: a study in sociology*, G. Stimpson (ed.) (tr. JA Spaulding and G. Stimpson 1951). Free Press, New York. 1897, reprinted 1997.

Edgell, E.T., Coons, S. J., Carter, W.B., Kallich, J.D., Mapes, D., Damush, T.M., et. al. (1996). A Review of Health Related Quality of Life Measures Used in End-Stage Renal Disease. *Clinical Therapeutics*, 18, 5, 887 – 938.

Edlund, M. and Tancredi, L.R. (1985). Quality of life: an ideological critique. *Perspectives in Biology and Medicine*, 28, 591 – 607.

Edwards, C.L., Scales, M.T., Loughlin, C., Bennett, G.G.., Harrris-Peterson, S., DeCastro, L.M., et. al. (2005). A brief review of the pathophysiology, associated pain and psychosocial issues in sickle cell disease. *Int J Behav Med*, 12 (3), 171-9.

Edwards, R., Telfair, J., Cecil, H., and Lenoci, J. (2000). Self-efficacy as a predictor of adult adjustment to sickle cell disease. *Psychosom Med*, 63, 850-58.

Ehlers, K., Giardina, P.J., Lesser, M., Engle, M. and Hilgartner, M. (1991). Prolonged survival in patients with β-thalassaemia major treated with deferoxamine. *J Pediatrics*, 118, 540-545.

Eiser, C. (2000). 'Quality of life in cancer'. In: H.M. Koot and J.L.Wallander (eds.), *Quality of life in children and adolescents: Concepts. methods and findings*, 267-296. Harwood Academic Publishers.

Eleftheriou, A. (2000). Guidelines for the clinical management of Thalassaemia. Thalassaemia International Federation (TIF), Nicosia-Cyprus.

Embretson, S.E. and Reise, S. (2000). *Item Response Theory for Psychologists*, p376. Lawrence Erlbaum Associates, Mahwah.

Emerson, E.B. (1985). Evaluating the impact of deinstitutionalisation on the lives of mentally ill retarded people. *American Journal of Mental Deficiency*, 90, 277-288.

EuroQoL Group (1990). EuroQoL: a new facility for the measurement of health related quality of life. *Health Policy*, 16, 199 – 208.

Everitt, B.S. (2002). *The Cambridge dictionary of Statistics*, Second Edition. Cambridge University Press, Cambridge, UK.

Faden, R. and LePlege, A. (1992). Assessing quality of life: moral implications for clinical practice. *Med Care,* 30 (Suppl.), 166-175.

Farquhar, M. (1995). Elderly people's definitions of quality of life. Soc Sci Med, 41, 1439-1446.

Fayers, P.M. and Machin, D. (2000). Quality of Life: Assessment, Analysis and Interpretation. Chichester, England: John Wiley & Sons.

Feeny, D., Furlong, W., Boyle, M., Torrance, G.W. (1995). Multi-attribute health status classification systems. Health utilities index. *Pharmaceconomics,* 7, 490-502.

Felce, D. and Perry, J. (1995). Quality of life: Its Definition and Measurement. *Research in Developmental Disabilities,* 16, 1, 51-74.

Ferguson, E. and Cox, T. (1993). Exploratory factor analysis: a user's guide. *International Journal of Selection and Assessment*, 1, 84-94.

Ferrans, C.E. (1996). Development of a conceptual model of quality of life. *Sch Inq Nurs Pract*, 10, 3, 293-304.

Field, A. (2003). Exploratory factor analysis, In: Wright, D.B. (ed), *Discovering statistics in SPSS (p423-470).* London: Sage.

Fischer, C.S., Jackson, R, M., Steuve, C.A., Gerson, K., Jones, L.M. and Baldassare, M. (1977). *Networks and places.* Free Press, New York.

Fischer, J.S, Rocca, N.L., Miller, D.M., Ritvo, P.G., Andrews, H. and Paty, D. (1999). Recent developments in the assessment of quality of life in multiple sclerosis. *Mult Scler* 5, 251–9.

Fitzpatrick, R., Davey, C., Buxton, M.J. and Jones, D.R. (1998). Evaluating patient-based outcome measures for use in clinical trials. *Health Technology Assessment*, 2, 14 (i-iv), 1-74.

Fitzpatrick, R., Davey, C., Buxton, M. and Jones, D.R. (2001). Criteria for assessing patient based outcome measures for use in clinical trials. In: Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R (eds). *The advanced handbook of methods in evidence based healthcare*. London: Sage, 181-194.

Fleiss, J.L. (1986). *The design and analysis of clinical experiments*. New York: Wiley 1986.

Frater, A. and Costain, D. (1992). Any better? Outcome measures in medical audit. *BMJ* 304, 519–20.

Freeman, J.A., Hobart, J.C., Langdon, D.W. and Thompson, A.J. (2000). Clinical appropriateness: a key factor in outcome measure selection. The 36-item Short Form Health Survey in multiple sclerosis. *J Neurol Neurosurg Psychiatry*, 68, 150–6.

Friedland, J., Renwick, R., and McColl, M. (1996). Coping and social support as determinants if quality of life in HIV/AIDS. *Aids care*, 8, 15-31.

Frisbie, R. (1986). *The use of microcomputer programs to improve the reliability and validity of content analysis in evaluation.* Paper presented at the session, Qualitative research methods, at the Annual Meeting of the American Educational Research Association, San Francisco. 1986, April. (Accessed online on 10th August 2009).

Furlong, W. J., Feeny, D.H., Torrance, G.W., Barr, R.D. (2001). The Health Utilities Index (HUI®) system for assessing health-related quality of life in clinical studies. *Annals of Medicine*, 33, 5, pp 375-384.

Gabutti, V. and Borgna-Pignatti, C. (1994). Clinical manifestations and therapy of transfusional haemosiderosis. *Clinical Haematology*, 7 (4), 919-940.

Gabutti, V. and Piga, A. (1996). Results of long-term iron-chelating therapy. *Acta haematologica*, 95(1), 26-36.

Galton, F. (1879). Psychometric Experiments. *Brain II*, 149-162.

Garratt, A. (2009). Patient reported outcome measures in trials. *BMJ*, 338, a1190.

Garratt, A.M., Ruta, D.A, Abdalla, M.I. and Russell, I.T. (1994). SF 36 health survey questionnaire: II. Responsiveness to changes in health status in four common clinical conditions. *Quality and Safety in Health Care*, 3:186-192.

Garratt, A. and Ruta, D. (1999). 'The Patient Generated index' In: C.R.B. Joyce, H.M., McGee and C.A. O'Boyle (eds.), *Individual quality of life. Approaches to conceptualisation and assessment*, Harwood Academic Publishers, Amsterdam.

Garratt, A.M., Ruta, D.A., Abdalla, M. I., Buckingham, J.K. and Russell, I.T. (1993). The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ*, 306, 1440-1444.

Garratt, A., Schmidt, L., Mackintosh, A. and Fitzpatrick, R. (2002). Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ*, 324, 1417-9.

Gee, L., Abbott, J., Conway, S.P., Etherington, C. and Webb, A.K. (2000). Validation of the SF-36 for the assessment of quality of life in adolescents and adults with cystic fibrosis. *J Cyst Fibros*, 1, 137-145.

Gee, L., Abbott, J., Conway, S., Etherington, C. and Webb, A. (2000). Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax*, 55, 11, 946–954.

Geiss, S.K., Hobbs, S.A., Hammersley-Maereklein, G., Kramer, J.C. and Henley, M. (1992). Psychosocial factors related to perceived compliance with cystic fibrosis treatment. *J Clin Psychol*, 48 (1), 99-103.

Genetic Interest Group (GIG) (2007). Available at: (http://www.gig.org.uk/). (Accessed 20th February 2007).

Georganda, E.T. (1988). Thalassaemia and the adolescent: An investigation of chronic illness, individuals and systems. *Fam Systems Med*, 6 (2), 150-161.

Georganda, E.T. (1990). The impact of thalassaemia on body image, self-image, and self-esteem. *Ann N Y Acd Sci*, 612, 466-472.

George, L.K, Blazer, D.G., Hughes, D.C. and Fowler, N. (1989). Social support and the outcome of major depression. *British Journal of Psychiatry*, 154, 478-85.

Gill, T.M. (1995). Quality of life assessment. Values and pitfalls. *Journal of the Royal Society of Medicine*, 88, 680-682.

Gill, T.M. and Feinstein, A.R. (1994). A critical appraisal of the quality-of-life measurements. *National Library of Medicine*, 272 (8), 619-626.

Gilson, B. and Bergner, M. (1976). The Sickness Impact Profile: conceptual formulation and methodology for the development of a health status measure. *Int J Health Serv*, 6, 393-415.

Goffman, E. (1963). *Stigma. Notes on the management of spoiled identity*. Prentice-Hall, Englewood Cliffs, NJ.

Goldbeck, L. and Schmitz, T.G. (2001). Comparison of three generic questionnaires measuring quality of life in adolescents and adults with cystic fibrosis: the 36-Item short form health survey, the quality of life profile for chronic diseases, and the questions of life satisfaction. *Qual Life Res*, 10, 23-36.

Goldbeck, L., Zerrer, S. and Schmitz, T.G. (2007). Monitoring quality of life in outpatients with cystic fibrosis. *J Cyst Fibros*, 6, 3, 171-8.

Goldberg, D.P. and Hillier, V.F. (1979). A scaled version of the General Health Questionnaire. *Psychol Med*, 9, 139–45.

Goldberg, D.P. and Williams, P. (1988). *A user's guide to the General Health Questionnaire*. Windsor, UK. NFER Nelson.

Goldberg, D.P., Gater, R., Sartorius, N., Ustun, T.B., Piccinelli, M., Gureje, O. And Tutter, C. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychological Medicine*, 27, 191-197.

Gordon, C., Walpole, I., Zubrick, S.R. and Bower, C. (2003). Population Screening for Cystic Fibrosis: Knowledge and Emotional Consequences 18 months later. *American Journal of Medical Genetics*, 120A, 199-208.

Gothan, A., Brown, R. and Marsden, C. (1986). Depression in Parkinson's disease: a quantitative and qualitative analysis. *J Neurol Neurosurg Psychiatry*, 49, 381–9.

Grabowski, H.G. and Hansen, R.W. (1990). 'Economic scales and tests' In: B. Spilker, Editor, *Quality of Life Assessments in Clinical Trials*, New York, Raven Press p 61–69.

Grima, D.T., Torrance, G.W., G., Rice, F.G., Rosner, A.J. and LaFortune, L. (2000). Cost and Health Related Quality of Life Consequences of Multiple Sclerosis. *Multiple Sclerosis*, 6, 2, 91-98.

Grootscholten, C., Ligtenberg, G., Derksen, R.H.W.M., Schreurs, K.M.G., de Glas-Vos, J.W., Hagen, E.C., et. al. (2003). Health related quality of life in patients with systemic lupus erythematous: Development and validation of a lupus specific symptom checklist. Qual Life Res, 12, 6, 635-644.

Guadagnoli, E. And Velicer, W. (1988). Relation of sample size to the stability of component patterns. *Psychological Bulletin*, 103, 265-275.

Guertin, W.H. and Bailey, J.P. (1970). Introduction to modern factor analysis. Ann Arbor, MI: Edwards Brothers.

Guyatt, G.H., Freeny, D.H., Patrick, D,C. (1993). Measuring health-related quality of life. *Ann Intern Med*, 118, 622-9.

Guyatt, G.H., Kirschner, B., Jaeschke, R. (1992). Measuring health status: what are the necessary measurement properties? *J Clin Epidemiol*, 45, 1341–1345.

Guyatt, G.H., Osoba, D., Wu, A.W., Wyrwich, K.W., Norman, G.R. (2002). Methods for explaining the clinical significance of health status measures. *Clinical Therapeutics*, 24, (Suppl.), 5.

Haas, B. K. (1999). A Multidisciplinary Concept Analysis of Quality of Life. *Western Journal of Nursing Research*, 21, 6729.

Haas, B.K. (1999b). Well-being: Concepts and Measures. *Journal of Social Issues*, 58, 4, 641.

Hadorn, D.C and Uerbersax, J. (1995). Large scale health outcomes evaluation: how should quality of life be measured? Part 1 – Calibration of a brief questionnaire and a search for preference subgroups. *J Clin Epidemiol*, 48, 607–18.

Hagerty, M.R., Cummins, R., Ferriss, A.L., et al. (2001). Quality of life indexes for national policy: review and agenda for research. *Social Indicators Research*, 55, 1-96.

Hambleton, R. K., Swaminathan, H. and Rogers, H. J. (1991). *Fundamentals of Item Response Theory*. Newbury Park, CA: Sage Press.

Hart, H.E., Bilo, H.J.G., Redekop, W.K., Stolk, R.P., Assink, J.H. and Meyboom-de Jong, B. (2003). Quality of life with type I diabetes mellitus. *Qual Life Res*, 12, 1089-1097.

Hayes, J.A., Black, N.A., Jenkinson, C., Young, J.D., Rowan, K.M., Daly, K, et al. (2000). Outcome measures for adult critical care: a systematic review. *Health Technol Assess* 4, 1-111.

Hays, R.D., Sherbourne, C,D., Mazel, R.M. (1993). The RAND 36-Item Health Survey 1.0. *Health Economics,* 2, 3, 217-227.

Hays, R. D., and Hayashi, T. (1990). Beyond Internal Consistency Reliability: Rationale and User's Guide for Multitrait Scaling Analysis Program on the microcomputer. *Behav Res Meth Instruments Computers,* 22, 167-175.

Hays, R., Vickery, B., Hermann, B., Perrine, K., Cramer, J., Meador, K., et al. (1995). Agreement between proxy reports and self-reports of quality of life in epilepsy patients. *Qual Life Res*, 4, 159–65.

Hays, R.D., Kallich J.D., Mapes D.L., Coons, S.J. and Carter, W.B. (1994). Development of the Kidney Disease Quality of Life (KDQOL^{TM}) Instrument. *Quality of Life Research*, 3, 329-338.

Hays, R.D., Morales, L.S. and Reise, S.P. (2000). Item Response Theory and Health Outcomes Measurement in the 21st Century. *Med Care*, 38 (9 Suppl): II28–II42.

Heer, N., Choy, J. and Vichinsky, E.P. (1998). The Social Impact of Migration on Disease: Cooley's Anemia, Thalassemia, and New Asian Immigrants. *Ann N Y Acad Sci*, 850, 509-511.

Henry, B., Aussage, P., Grosskopf, C. and Goehrs, (2003). Development of the cystic fibrosis questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res,* 12, 63-76.

Herdman, M., Fox-Rushby, J. and Badia, X. (1998). A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res, 7, 323-335.

Hickey, A.M., Bury, G., O'Boyle, C.A., Bradley, F., O'Kelly, F. D. and Shannon, W. (1996). A new short individual quality of life measures (SEIQoL-DW_: application in a cohort of individual with HIV/AIDS. *BMJ,* 313, 29-33.

Hickey, A., O'Boyle, C.A., McGee, H.M. and Joyce, C.R.B. (1999). 'The Schedule for the Evaluation of Individual Quality of Life' In: C.R.B. Joyce, H.M., McGee and C.A. O'Boyle (eds.). *Individual quality of life. Approaches to conceptualisation and assessment,* Harwood Academic Publishers, Amsterdam.

Hickman, M., Modell, B., Greengross, P., Chapman, C., Layton, M., Falconer, S. et. al. (1999). Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *Br J Haematol*, 104, 860-867.

Hobart, J. C., Freeman, J. A. and Lamping, D.L. (1996). Physician and patient-oriented outcomes in progressive neurological disease: which to measure? *Current opinion in neurology*, 9, 6, 441-4.

Hobart, J.C., Lamping, D.L., Fitzpatrick, R., Riazi, A. and Thompson, A.J. (2001). The multiple sclerosis impact scale (MSIS-29). A new patient-based outcome measure. *Brain*, 124, 962-973.

Hobart, J.C., Riazi, A., Lamping, D.L., Fitzpatrick, R., and Thompson, A.J. (2004). Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. *Health Technology Assessment, 8 (9).* Health Technology Assessment HTA NHS R&D HTA Programme.

Hobart, J.C. and Thompson, A.J. (1996). 'Clinical trials of multiple sclerosis' In: A.T. Reder (ed.). *Interferon therapy of multiple sclerosis*, 398–407, New York: Marcel Dekker.

Hodson, M.E. and Geddes, D.M. (1995), In: M.E. Hodson and D.M. Geddes (eds.), *Cystic Fibrosis* (2nd ed.), London, Arnold.

Hoffbrand, A.V. and Wonke, B. (1997). Iron chelation therapy. *Journal of Internal Medicine*, 242 (Suppl. 740), 17-41.

Holahan, J.C. and Moos, R.H. (1981). Social support and psychological distress: a longitudinal analysis. *Journal of Abnormal Psychology*, 90, 365-370.

Holmes, W.C. and Shea, J.A. (1997). Performance of a new HIV/AIDS-targeted quality of life (HAT-QoL) instrument n asymptommatic seropositive individuals. *Qual Life Res*, 6, 561-71.

Holzemer, W.L., Corless, I.B., Nokes, K.M., Turner, J.G., Brown, M.A., Powell-Cope, G.M. et. al. (1999). Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care and Studies*, 13, 3, 185-197.

Honnor, V., Zubrick, S.R., Walpole, I., Bower, C. and Goldblatt, J. (2000). Population screening for cystic fibrosis in Western Australia: Community response. *Am J Med Genet*, 23, 291-302.

Horne, R., Weinman, W.J. and Hankins, M. (1999). The Beliefs about Medicines Questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health*, 14, 1-24.

Hörnquist, J.O. (1982). The concept of quality of life. *Scandinavian Journal of Social Medicine*, 10, 57-61.

Horsman, J., Furlong, W., Feeny, F. and Torrance, G. (2003). The Health Utilities Index (HUI): Concepts, Measurement Properties, and Applications. *Health and Quality of Life Outcomes*, 1, 1 54.

House, E. R. (1978). Assumptions underlying evaluation models. *Educational Researcher*. 7, 3, 4-12.

Huck, S.W. and Cormer, F. (1996). *Reading Statistics and Research.* New York: HarperCollins.

Hunt, S.M., McEwan, J. and McKenna, S.P. (1985). Measuring Health Status: a new tool for clinicians and epidemiologists. *Journal of the Royal College of General Practitioners*, 35, 273, 185-188.

Hyland, M.E. (1992). The items in quality of life scales: How item selection creates bias and how bias can be prevented. *PharmacoEconomics,* 1, 182–190.

Hyland, M.E. (2003). A brief guide to the selection of quality of life instrument. *Health Quality of Life Outcomes,* 1, 24.

Jacobson, A.M., de Groot, M. And Samson, J.A. (1994). The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care*, 17, 4, 267-74.

Janse, A.J., Gemke, R.J., Uiterwaal, C.S., Tweel, I. van der, Kimpen, J.L, and Sinnema, G. (2004). Quality of Life: Patients and Doctors Don't Always Agree: a Meta-Analysis. *Journal of Clinical Epidemiology*, 57, 7, 653 - 661.

Jenerette, C., Funk, M. and Murdaugh, C. (2006). Sickle cell disease: A stigmatising condition that may lead to depression. *Issues in Mental Health Nursing*, 26, 10, 1081-1101.

Jenkins, C.D. (1992). Assessment of outcomes in health intervention. *Soc Sci Med*, 35, 367-375.

Jenkins, C. D., and Stanton, B. A. (1984). 'Quality of life as assessed in the Recovery Study'. In N. K. Wenger, M. E. Mattson, C. D. Furberg, & J. Elinson (Eds.), *Assessment of quality of life in clinical trials of cardiovascular therapies*, p 266-280. New York: Le Jacq.

Jenkinson, C., Fitzpatrick, R., Swash, M. Levvy, G. (2001). *Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ): User Manual.* Oxford, Health Services Research Unit, University of Oxford.

Jette, D.U. and Downing, J. (1994). Health status of individuals entering a cardiac rehabilitation program as measured by the Medical Outcomes Study 36-Item Short-Form Survey (SF-36®). *Phys Ther*, 74, 6, 521-7.

Joachim, G. and Acorn, S. (2000). Stigma of visible and invisible chronic conditions. *Journal of Advanced Nursing*, 32, 1, 243-248.

Jones, P.W., Quirk, F.H. and Baveystock, C.M. (1991). The St George's Respiratory Questionnaire. *Respir Med,* Sep. 85, Suppl B, 25–37.

Joyce, C.R.B., O.Boyle, C.A. and McGee, H.M. (eds) (1999). Individual quality of life. Approaches to conceptualisation and assessment. Amsterdam, Harwood Academic Publishers.

Juniper, E.F., Guyatt, G.H., Ferrie, P.J. and Griffith, L.E. (1993). Measuring quality of life in asthma. American Review of Respiratory Disease, 147, 832-838.

Juniper, E.F., Guyatt, G.H. and Jaeschke, R. (1996). How to develop and validate a new health elated quality of life instrument. In B. Spilker (ed), Quality of life and pharmacoeconomics in clinical trials (2nd edition). Philadelphia, New York: Lippincott-Raven.

Juniper, E.F., Guyatt, G.H. Streiner, D.I. and King, D.R. (1997). Clinical impact versus factor analysis for quality of life questionnaire construction. *J Clin Epidemiol,* 50, 233-8.

Kaiser, H. F. (1960). The application of electronic computers to factor analysis. Educational and Psychological Measurement, 20, 141-151.

Kallich, J., McDermott, A., Xu, X., Fayers, P. and Cella, D. (2006). The relationship between patient knowledge of hemoglobin levels and health-related quality of life. Qual Life Res, 15, 57-68.

Kane, R. L. (Ed.). (2006). *Understanding health care outcomes research* (2nd ed.). Sudbury, Mass: Jones and Bartlett.

Kaplan, M.S., Berthelot, J.M., Feeny, D.H., McFarland, B.H. and Khan, S. (2007). The Predictive Validity of Two Measures of Health-Related Quality of Life: Mortality in a Longitudinal Population-Based Study. *Quality of Life Research,* 16, 9, 1539-1546.

Kaplan, R. M., Groessl, E.J., Sengupta, N., Sieber, W.J. and Ganiats, T.G. (2005). Comparison of Measured Utility Scores and Imputed Scores From the SF-36 in Patients With Rheumatoid Arthritis. *Med Care,* Vol. 43, 1, 79-87

Kaplan, R.M. and Saccuzzo D. P. (1993). *Psychological testing: principles, applications, and issues* (3rd ed.). Pacific Grove, CA, Brooks/Cole.

Kaplan, R.M. and Saccuzzo D. P. (2005). *Psychological testing: principles, applications, and issues* (6th edition). Belmont, CA; Wadsworth/Thomson. Chapters 1,2,4, 5, 8 and 19.

Kawachi, I. and Berkman, L.F. (2000). 'Social cohesion, social capital and health' In: L.F. Berkman and I. Kawachi (eds.). *Social Epidemiology*. Oxford University Press, Oxford.

Kellerman, J., Zeltzer, L., Ellenberg, L., Dash, J. and Rigler, D. (1980). Psychological effects of illness in adolescence: Anxiety, self-esteem and perception of control. *J Pediatr*, 97, 126-131.

Kettler, L.J., Sawyer, S.M., Winefield, H.R. and Greville, H.W. (2002). Determinants of adherence in adults with cystic fibrosis. *Thorax,* 57, 459-464.

Khattak, M.F. and Saleem, M. (1992). Prevalence of heterozygous beta-thalassaemia in northern areas of Pakistan. *J Pak Med Assoc*, 42, 32-34.

Kiecolt-Glaser, J.K., and Glaser, R. (1995). Psychoneuroimmunology and health consequences: data and shared mechanisms. *Psychosomatic Medicine*, 57, 269-74.

Kimmel, P.L., Weihns, K. and Peterson, R.A. (1993). Survival in Hemodialysis Patients: the Role of Depression. *Journal of the American Society of Nephrologists*, 4, 1, 12 – 27.

Klein, N., Sen, A., Rusby, J. Ratip, S., Modell, B. and Olivieri, N.F. (1998). The Psychosocial Burden of Cooley's Anemia in Affected Children and Their Parents. *Ann N Y Acd Sci,* 850, 512-513.

Kline, R.B. (1999). Book review of Psychometric theory (3rd ed.) by J.C. Nunnally and I.H. Bernstein (1994), New York: McGraw-Hill in the *Journal of Psychoeducational Assessment*, 17, 275-280.

Knowles, R.L., Griebsch, I., Bull, C., Brown, J., Wren, C. and Dezateux, C. (2007). Quality of life and congenital heart defects: comparing parent and professional values. *Arch Dis Child*, 92, 388-393.

Ko, Y. and Coons, S.J. (2006). Self-reported chronic conditions and EQ-5D index scores in the US adult population. *Curr Med Res Opin*, 22, 10, 2065-71.

Kontoghiorghes, G.J. and Evans, R.W. (1985) Site specificity of iron removal from transferrin by alpha-ketohydroxypyridine chelators. *FEBS Lett*, 189, 141-144.

Kontoghiorghes, G.J., Bartlett, A.N., Hoffbrand, A.V., Goddard, J.G., Sheppard, L., Barr, J., et. al. (1990). Long-term trial with the oral iron chelator 1, 2-dimethyl-3-hydroxypyrid-4-one (L1). I. Iron chelation and metabolic studies. *Br J Haematol*, 76, 295-300.

Kontoghiorghes, G.J., Sheppard, L., Hoffbrand, A.V., Charalambous, J., Tikerpae, J. and Pippard, M.J. (1987b) Iron chelation studies using desferrioxamine and the potential oral chelator, 1,2-dimethyl-3-hydroxypyrid-4-one, in normal and iron loaded rats. *J Clin Pathol*, 40, 404-408.

Krippendorff, K. (2004). *Content Analysis: An Introduction to Its Methodology.* 2nd edition, Thousand Oaks, CA: Sage.

Krousel-Wood, M.A. and Re, R.N. (1994). Health status assessment in a hypertension section of an internal medicine clinic. *Am J Med Sci*, 308, 4, 211-7.

Krousel-Wood, M.A., McCune, T.W., Abdoh, A. and Re, R,N. (1994). Predicting work status for patients in an occupational medicine setting who report back pain. *Arch Fam Med*, 3, 349-55.

Krupinski, J. (1980). Health and quality of life. *Soc Sci Med*, 14A, 203-11.

Kuijer, R.G. and DeRidder, D.T.D. (2003). Discrepancy in Illness-Related Goals and Quality of Life in Chronically Ill Patients: The Role of Sell-efficacy. *Psychology and Health*, 18, 3, 313-330.

Kurtin, P,S,, Davies, A.R., Meyer, K.B., DeGiacomo, J.M. and Kantz, M.E. (1992). Patient-based health status measures in outpatient dialysis: early experiences in developing an outcomes assessment program. *Med Care*, 30 (5Suppl):MS136-MS149.

Lacombe, P.A.,Vicente, J.A.G., Pages, J.C. and Morselli, P.L. (1996). Causes and problems of no response or poor response to drugs. *Drugs*, 261, 22, 3273-7.

Lane (1996). Available at: http://www.scotland.gov.uk/Publications/2006/01/13110743/11 (Accessed 16th April 2008).

Lauer, G. (1999). 'Concepts of quality of life in mental healthcare' In: S. Priebe, J.P.J. Oliver and W. Kaiser (eds.). *Quality of life and Mental Healthcare* (eds.), 19-34, Philadelphia, PA: Wrightson Biomedical.

Lawton, M.P. (1991). 'A multidimensional view of quality of life in frail elders' In: J.E. Birren, J. Lubben, J. Rowe and D. Deutchman (eds.). *The concept and measurement of quality of life in the frail elderly.* San Diego, Academic Press.

Lawton, M.P. (1996). 'Quality of life and affect in later life', In: C. Magai and S.H. McFadden et al. (eds.), *Handbook of emotion, human development, and aging.* San Diego, CA, Academic Press.

Lawton, M.P. (1999). Quality of life in chronic illness. *Gerontology*, 45, 181-183.

Lefcourt, H.M. (1982). *Locus of control: current trends in theory and research*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Lehman, A. F. (1996). 'Measures of quality of life among persons with severe and persistent mental disorders' In: G. Thornicroft and M. Tansella (eds.) *Mental Health Outcome Measures*, 75-92, Berlin: Springer.

Lehmann, H. and Huntsman, R.G. (1966). *Man's Haemoglobins*. North Holland Publishing Company.

Lemanek, K. L. (1990). Adherence issues in the medical management of asthma. *Journal of Pediatric Psychology,* 15, 437-458.

Likert, R. (1932). *A Technique for the Measurement of Attitudes. Archives* of Psychology, 140, 1-55.

Liu, B. (1976). Quality of life indicators in U.S. metropolitan areas: A statistical analysis. New York, Praeger Publishers.

Lohr, K.N., Aaronson, N.K, Alonso, J., Burnam, M.A., Patrick, D.L., Perrin, E.B., et al. (1996). Evaluating quality of life and health status instruments: development of scientific review criteria. *Clin Ther*, 18, 979–92.

Loomes, G. and McKenzie, L. (1989). The use of QALY's in healthcare decision making. *Soc Sci Med*, 28, 299-308.

Lord, F.M. and Novick, M.R. (1968). *Statistical theories of mental test scores*. Reading, MA: Addison-Wesley.

Lorig, K. and Gonzalez, V. (1992). The integration of theory with practice: a 12 year case study. *Health Education Q*, 19, 355-68.

Lowton, K. and Gabe, J. (2003). Life on a slippery slope: perceptions of health in adults with cystic fibrosis. *Sociology of Health and Fitness*, 25, 4, 289-319.

Lutgendrof, S., Antoni, M.H., Schneiderman, H., and Fletcher, M.A. (1994). Psychosocial counseling to improve quality of life in HIV-infection. *Patient Education and Counseling*, 24, 217-235.

Lydick, E. (2000). Approaches to the interpretation of quality-of-life scales. *Med Care,* 38 (9, suppl): II180-II183.

Lydick, E. and Epstein, R.S. (1993). Interpretation of quality of life changes. *Qual Life Res*, 2, 221–6.

Lydick, E and Yawn, B.P. (1998). 'Clinical interpretation of health related quality of life data' In: M.J. Staquet, R.D. Hays and P.M. Fayers (eds.) *Quality of life assessment in clinical trials: methods and practice*, 299–314, Oxford, Oxford University Press.

Madden, B.P. (2000). 'Lung transplantation' In: M.E. Hodson and D.M. Geddes (eds.), *Cystic Fibrosis* (2nd ed.), London, Arnold.

Maggio, A., D'Amico, G., Morabito, A., Capra, M., Ciaccio, C., Cianciulli, P., et. al. (2002). Deferiprone versus deferoxamine in patients with thalassaemia major: a randomized clinical trial. *Blood Cells Mol Dis*, 28, 196-208.

Marshall, S., Haywood, K. and Fitzpatrick, R. (2005). Impact of patient-reported outcome measures on routine practice: a structured review. *J of Eval in Clin Pract*, 12, 5, 559 - 568.

Marteau, T.M., Dundas, R. and Axworthy, D. (1997). Long term cognitive and emotional impact of genetic testing for carriers of cystic fibrosis: The effects of test results and gender. *Health Psychol*, 16, 51-62.

Maslow A. (1954). *Motivation and personality*. New York, Harper.

Massaglia, P. and Carpigano, M. (1985). *Psychology of the thalassaemia patient and his family. Thalassaemia today: The Mediterranean experience.* Proceedings of the second Mediterranean Meeting, Milano, 28-30.

MacCallum, R.C., Widaman, K.F., Zhang, S. and Hong, S. (1999). Sample size in fator analysis. *Psychological Methods*, 4, 84-89.

McCabe, M.P. and McKern, S. (2002). Quality of Life and Multiple Sclerosis: Comparison Between People with Multiple Sclerosis and People from the General Population. *Journal of Clinical Psychology in Medical Settings*, 9, 4, 287-295.

McClish, D.K., Penberthy, L.T., Bovbjerg, V.E., Roberts, J.D., Aisiku, I.P., Levenson, J.L., et. al. (2005). Health related quality of life in sickle cell patients: the PISCES project. *Health Qual Life Outcomes*, 29, 3, 50.

McDowell, I. and Jenkinson, C. (1996). Development standards for health measures. *Journal of Health Services Research and Policy*, 1, 238–46.

McDowell, I. and Newell, C. (1987). *Measuring health: a guide to rating scales and questionnaire.* Oxford, New York: Oxford University Press.

McDowell, I. and Newell, C. (1996). *Measuring health: a guide to rating scales and questionnaires* (2nd ed.), Oxford, Oxford University Press.

McHorney, C.A., Ware, J.E., Lu, J.F.R., Sherbourne, C.D. (1994). The MOS 36-Item Short-Form Health Survey (SF-36®): III. tests of data quality, scaling assumptions and reliability across diverse patient groups. *Med Care*, 32, 40-66.

McHorney, C,A,, Ware, J.E., Raczek, A.E. (1993). The MOS 36-Item Short-Form Health Survey (SF-36®): II. psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*, 31, 3, 247-63.

McHorney, C.A., Ware, J.E., Rogers, W., Raczek, A., Lu, J.F.R. (1992). The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts: results from the Medical Outcomes Study. *Med Care*, 30(Suppl 5):MS253-MS265.

McKevitt, C., Wolfe, C. and La Placa, V. (2002). *Comparing professional and patient perspectives on quality of life.* ESRC Growing Older Programme, Research Findings, volume 2.

McKeone, D. (1995). *Measuring Your Media Profile,* Gower Press.

Mechanic, D. (1978). Sex, illness, behaviour and the use of health services. *Soc Sci Med*, 128, 207-214.

Medical Outcomes Trust (MOT) (1991). *Medical Outcomes Trust: Improving Medical Outcomes from the Patient's Point of View*. Boston, MA: Medical Outcomes Trust.

Meeberg, G.A. (1993). Quality of life: a concept analysis. *Journal of Advanced Nursing*, 13, 32-38.

Meenan, R.F., Gertman, P.M., Mason, J.H. and Dunaif, R. (1982). The arthritis impact measurement scales. Further investigations of a health status measure. *Arthritis and rheumatism*, 25, 9, 1048-53.

Merril, S.S., Seeman, T.E., Kasl, S.V. and Berkman, L.F. (1997). Gender differences in the comparison of self-reported disability and performance measures. *J Gerontol Med Sci*, 52a, M19-26.

Meyer, K.B., Espindle, D.M., DeGiacomo, J.M., Jenuleson, C.S., Kurtin, P.S. and Davies, A.R. (1994). Monitoring dialysis patients' health status. *Am J Kidney Dis*, 24, 2, 267-79.

Mikelli, A. and Tsiantis, J. (2004). Brief report: Depressive symptoms and quality of life in adolescents with b-thalassaemia. *Journal of Adolescence*, 27, 213-216.

Millar, R. and Shevlin, M. (2007). The development and factor structure of a career locus of control scale for use with school pupils. *Journal of Career Development*, 33, 3, 224-249.

Millen, N. and Walker, C. (2001). Overcoming the stigma of chronic illness: Strategies for normalisation of a 'spoiled identity'. *Health Sociology Review*, 10, 2, 89-97.

Minnich, V. (1954) in Weatherall, D.J. and Clegg, J.B. (1972). *The Thalassaemia Syndromes* (2nd ed.), Blackwell Scientific Publications.

Modell, B. (1999). The history of community genetics: the contribution of the haemoglobin disorders. *Community Genetics*, 1, 3-11.

Modell, B. and Berdoukas, V. (1984). *The clinical approach to thalassaemia*. Grune and Stratton, New York, London.

Modell, B., Harris, R., Lane, B., Khan, M., Darlinson, M., Petrou, M. et. al. (2000). Informed choice in genetic screening for thalassaemia during pregnancy; audit from a national confidential inquiry. *BMJ*, 320, 337-341.

Modell, B., Khan, M., Darlinson, M. (2000). Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia register. *The Lancet*, 355, 2051-2052.

Modell, B., Khan, M., Darlinson, M., King, A., Layton, M., Old, J.M., Petrou, M. and Varnavides, I. (2001). A national register for surveillance of inherited disorders: beta thalassaemia in the United Kingdom. *Bulletin of the WHO*, 79, 11, 1006-1013.

Modell, B., Khan, M., Darlinson, M. (2003). Unpublished data.

Modell, B. Letsky, E., Flynn, D., Peto, R. and Weatherall, D.J. (1982). Survival and desferioxamine in thalassaemia major. *British Medical Journal (Clinical Research Ed.)*, 284, 1081-1084.

Moeschlin, S. and Schnider, U. (1964). Treatment of Primary and Secondary Hemochromatosis and Acute Iron Poisoning with a New Potent Iron Eliminating Agent (Desferrioxamine). *Ned Tijdschr Geneeskd*, 108, 1648-1653.

Moise, J.R., Drotar, D., Doershuk, C.F. and Stern, H. (1987). Correlates of psychosocial adjustment among young adults with cystic fibrosis. *J Dev Beh Pediatr*, 8, 141-8.

Morgan, M., McCreedy, R., Simpson, J. and Hay, R.J. (1997). Dermatology quality of life scales – a measure of the impact of skin diseases. *British Journal of Dermatology*, 136, 2, 202-206.

Muntaner, C. and Lynch, J. (2002). Social capital, class gender and race conflict, and population health: an essay review of Bowling Alones implications for social epidemiology. *International Journal of Epidemiology*, 31,261-267.

Myers, L.B. and Midence, K. (1998) (ed.). *Adherence to Treatment in Medical Conditions*, chapter 1, Harwood Academic Publishers.

Naughton, M.J. and Shumaker S.A. (2003). The case for domain of function in quality of life assessment. *Qual Life Res*, 12, 1, 73-80.

Nelson, E., Wasson, J., Kirk, J., Keller, A., Clark, D., Dietrich, et. al. (1987). Assessment of function in routine clinical practice: description of the COOP Chart method and preliminary findings. *J Chronic Dis*, 40 (Suppl.), 55S-69S.

Nerenz, D.R., Repasky, D.P., Whitehouse, F.W. and Kahkonen, D.M. (1992). Ongoing assessment of health status in patients with diabetes mellitus. *Med Care*, 30 (Suppl 5): MS112-MS124.

Neuendorf, K.A. (2002). *The Content Analysis Guidebook Online*. http://academic.csuohio.edu/kneuendorf/content/. Accessed 10th August 2009.

Nick, H., Wong, A., Acklin, P., Faller, B., Jin, Y., Lattmann, R. et al. (2002). ICL670, a pre-clinical profile. *Adv Exp Med Biol*, 509:185-203.

Norman, G.R., Stratford, P. and Regehr, G. (1997). Methodological problems in the retrospective computation of responsiveness to change: the lesson of Cronbach. *J Clin Epidemiol*, 50, 869-79.

Norusis, M.J. (1990b). *SPSS/PC+ Statistics (TM) 4.0: for the IBM PC/XT/AT and PS/2*. Chicago: SPSS, Inc.

Nunnally, J.C. (1967). *Psychometric theory*, New York: McGraw-Hill

Nunnally, J.C. (1996). Psychometric theory, In: C. Jenkinson, R. Layte, A. Coulter et. al. Evidence for the sensitivity of the SF-36 health status measure to inequalities in health: results from the Oxford healthy lifestyles survey. *J Epidemiol Community Health*, 50, 377-380.

Nunnally, J.C. and Bernstein, I.H. (1994). *Psychometric theory* (3rd ed.), New York: McGraw-Hill.

O'Boyle, C.A. (1997). *Measuring the quality of later life.* Philosophy Transactions of the Royal Society of London, 352, 1871-1879.

O'Carroll, R.E., Cossar, J.A., Couston, M.C. and Hayes,. P.C. (2000). Sensitivity to change following liver transplantation: A comparison of three instruments that measure quality of life. *J. Health Psychol*. 5, 1, 69-74.

Office of National Statistics (ONS), Omnibus Survey in Great Britain. Availabel at: http://www.statistics.gov.uk/STATBASE/Source.asp?vlnk=657&More=Y. (Accessed January 2008).

Old, J.M., Khan, S.N., Verma, I., Fucharoen, S., Kleanthous, M., Ioannou, P., et. al. (2001). A multi-center study in order to further define the molecular basis of beta thalassaemia in Thailand, Pakistan, Sri Lanka, Mauritius, Syria, and India and to develop a simple molecular diagnostic strategy by amplification refractory mutation systempolymerasechain reaction. *Hemoglobin*, 25, 397-407.

Ohaeri, J.U., Shokunbi, W.A., Akinlade, K.S. and Dare, L.O. (1995). The psychosocial problems of sickle cell disease sufferers and their methods of coping. *Soc Sci Med*, 40, 955 – 960.

Oliver, J. P.J., Huxley, P.J., Bridges, K. and Mohamad, H. (1996). *Quality of life and mental health services.* Routledge, London.

Olivieri, N.F. (1999). The beta-thalassaemias. *N Engl J Med*, 341, 99-109.

Olivieri, N.F. and Brittenham, G.M. (1997). Iron chelating therapy and the treatment of thalassaemia. *Blood*, 89, 3, 739-761.

Olivieri, N.F., Koren, G., Hermann, C., Bentur, Y., Chung, D., Klein, J., et. al. (1990). Comparison of oral iron chelator L1 and desferrioxamine in iron-loaded patients. *The Lancet*, 336, 1275-1279.

Olivieri, N.F., Nathan, D.G., MacMillan, J.H., Wayne, A.S., Liu, P.P., McGee, A., et. al. (1994). Survival in medically treated patients with homozygous beta thalassaemia. *New England Journal of Medicine,* 331, 9, 574-578.

Oppenheim, A.N. (1992). *Questionnaire Design, Interviewing and Attitude Measurement*, Continuum International Publishing (2nd ed.). Chapters 8, 14, 15,

Pakbaz, Z., Treadwell, M., Yamashita, R., Quirolo, K., Foote, D., Quill, L., et. al. (2005). Quality of life in patients with thalasssaemia intermedia compared to thalassaemia major. *Ann N Y Acd Sci*, 1054, 457-461.

Panepinto, J.A. (2008). Health related quality of life in sickle cell disease. *Pediatr Blood Cancer,* 10, 1-5.

Parkerson, G.R. Jr., Broadhead, W.E. and Tse, C-K.J. (1991). Validation of the Duke Social Support and Stress Scale Using the Duke Health Profile. *Family Medicine,* 23, 5, 357 - 360.

Patrick, D.L. and Deyo, R.A. (1989). Generic and disease-specific measures in assessing health status and quality of life (review). *Med care,* (3 Suppl), S217-32.

Patrick, D.L. and Erickson, P. (1993). *Health status and health policy*. Oxford, Oxford University Press.

Pearlman, R.A. and Uhlmann, R.F. (1988). Quality of life in chronic diseases: perceptions of elderly patients. *Journal of Gerontology,* 43, M25-M30.

Pearson, K. (1901). On Lines and Planes of Closest Fit to Systems of Points in Space" (PDF). Philosophical Magazine 2 (6): 559–572. Available at: http://stat.smmu.edu.cn/history/pearson1901.pdf. (Accessed 6th July 2009).

Pearson, H., Cohen, A., Giardina, P.J. and Kazazian, H. (1996). The changing profile of homozygous β-thalassaemia: Demography, ethnicity and age distribution of current North American patients and changes in two decades. *Pediatrics*, 97, 352-356.

Pennell, D.J., Berdoukas, V., Karagiorga, M., Ladis, V., Piga, A., Aessopos, A., et. al. (2006). Randomized controlled trial of deferiprone or deferoxamine in beta-thalassaemia major patients with asymptomatic myocardial siderosis. *Red Cells*, 107, 9, 3738.

Perrimond, H., Chagnon, C., Moulanier, I., Michel, G., Guidicelli, H. and Bernard, P.J. (1991). The value of nuclear magnetic resonance in the study of iron overload in thalassaemia patients. *Ann Pediatr* (Paris), 38, 175-184.

Peto, V., Jenkinson, C., Fitzpatrick, R., and Greenhall, R. (1995). The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res,* 4, 241-248.

Pfeffer, P.E., Pfeffer, J.M. and Hodson, M.E. (2003). The psychosocial and psychiatric side of cystic fibrosis in adolescents and adults. *J Cyst Fibros*, 2, 2, 61-8.

Pfennings, L.E.M.A., Van der Ploeg, H.M., Cohen, L., Bramsen, I., Polman, C.H. and Lankhorst, G.J. et. al. (1999). A health related quality of life questionnaire for multiple sclerosis patients. *Acta Neurol Scand*, 100, 148-55.

Piccinelli, M. and Simon, G. (1997). Gender and cross-cultural differences in somatic symptoms associated with emotional distress: an international study in primary care. *Psychol Med*, 27, 433-44.

Piga, A., Longo, F., Consolati, A., De Leo, A. and Carmellino, L. (1997). *Mortality and morbidity in thalassaemia with conventional treatment.* Bone Marrow Transplantation, 19 (Suppl.), 11-13 (proceedings of the Third International Conference on Bone Marrow Transplantation in Thalassaemia).

Pittman, A.K. (1964). Desferrioxamine and Acute Iron Poisoning. *C R Seances Soc Biol Fil*, 1587, 1135.

Politis, C. (1998). The psychosocial impact of chronic illness. *Ann N Y Acd Sci*, 850, 349-354.

Politis, C., DiPalma, A., Fisfis, M., Giasanti, A., Richardson, S.C., Vullo, C. et. al. (1990). Social integration of the older thalassaemic patient. *Archives of Disease in Childhood*, 65, 984-986.

Politis, C., Richardson, C. and Yfantopoulos, J.G. (1991). Public knowledge of thalassaemia in Greece and current concepts of the social status of the thalassaemic patients. *Soc Sci Med*, 32, 1, 59-64.

Politis, C., Vrettou, H., Fragatou, S., Hatzilaou, J., Richardson, C. and Salem, G. (1993). *Reactions to subcutaneous application of iron chelation therapy with desferioxamine. An urgent need for oral chelators.* Presented at the fourth International Conference on Oral Chelation in the treatment of Thalassaemia and Other Diseases. Limassol, Cyprus (March).

Politis, C., Vrettou, H., Fragatou, S., Hatzilaou, J., Flessa, C. and Richardson, C.S. (1996). *Survival and causes of death in thalassaemia major. The experience of the Hellenic Red Cross Thalassaemia Unit.* Presented at the Third International Symposium on Bone Marrow Transplantation in Thalassaemia. Pesaro (September).

Porter, J.B. and Davis, B.A. (2002). Monitoring chelation therapy to have optimal outcome in the treatment of Thalassaemia. *Best Practice and Research Clinical Haematology*, 15, 329 – 368.

Power, M., Bullinger, M., Harper, A. and the World Health Organisation Quality of Life Group (WHOQOL Group) (1999). The World Health Organisation WHOQOL-100: Tests of the Universality of Quality of Life in 15 Different Cultural Groups Worldwide. *Health Psychology*, 18, 5, 495-505.

Preacher, K.J., and MacCallum, R.C. (2003). Repairing Tom Swift's electric factor analysis machine. *Understanding Statistics*, 2, 13-43.

Proshanky and Fabian (1986). Available at: http://www.scotland.gov.uk/Publications/2006/01/13110743/11. (Accessed 16th April 2008).

Putnam, R.D. (2000). *Bowling alone. The collapse and revival of American Community*. New York: Simon and Schuster.

Quittner, A. L., Buu, A., Messer, M.A., Modi, A.C. and Watrous, M. (2005). Development and validation of the cystic fibrosis questionnaire in the United Stated. *Chest*, 128, 2347-2354.

Rajab, A. and Patton, M.A. (1997). Major factors determining the frequencies of haemoglobinopathies in Oman. *American Journal of Medical Genetics*, 71, 240-242.

Rasch, G. (1960). *Probabilistic models for some intelligence and attainment tests*. Chicago, IL: University of Chicago Press.

Ratip, S. (1996). *Clinical, genetic and psychosocial aspects of the β-thalassaemias.* MD thesis, University of London.

Ratip, S. and Modell , B. (1996). Psychological and sociological aspects of the thalassaemias. *Semin Hematol*, 33, 53-65.

Ratip, S, Skuse, D., Porter, J. Wonke, B. Yardumian, A. and Modell, B. (1995). Psychosocial and clinical burden of thalassaemia intermedia and its implications for prenatal diagnosis. *Archives of Disease in Childhood*, 72, 5, 408-412.

Rejeski and Mihalko (2001). Available at: http://www.scotland.gov.uk/Publications/2006/01/13110743/11. (Accessed 16th April 2008).

Rettig, K.D. and Leichtentritt, R.D. (1999). A general theory for perceptual indicators of family life quality. *Social Indicators Research*, 47, 307-342.

Rettig, R.A. and Sadler, J.H. (1997). Measuring and Improving the Health Status of End Stage Renal Disease Patients. *Health Care Financing Review*, 18, 4, 77-82.

Revicki, D.A., Rentz, A.M., Dubois, D., Kahrilas, P., Stanghellini, V., Talley, N.J., et. al. (2000). Gastroparesis Cardinal Symptom Index (GCSI): Development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res,* 13, 4, 833-844.

Riazi, A., Hobart, J.C., Lamping, D.L., Fitzpatrick, R., and Thompson, A.J. (2002). Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. *J Neurol Neurosurg Psychiatry,* 73, 701-704.

Riazi, A., Thompson, A.J., and Hobart, J.C. (2004). Self – efficacy predicts self – reported health status in multiple sclerosis. *Mult Scler*, 10, 1, 61 – 66.

Rigby, S.A., Domenech, D., Thornton, E.W., Tedman, S. and Young, C.A. (2003). Development and validation of a self-efficacy measure for people with multiple sclerosis: the Multiple Sclerosis Self-Efficacy Scale. *Mult Scler,* 9, 73-81.

Robinson, D., Anders, K., Cardozo, L. and Bidmead, J. (2007). Outcome measures in urogynaecology: the clinician's perspective. *Int Urogynecol J,* 18, 273-279.

Rofail, D., Viala, M., Trudeau, E. and Baladi, J.F. (2006). *Burden of iron* chelation therapy significantly impacts adherence to treatment in patients with iron overload. Presented at the European Haematological Association, Amsterdam (June).

Rogerson, R.J. (1995). *Environmental and health-related quality of life: conceptual and methodological similarities. Soc* Sci Med, 41, 1373-82.

Rommens, J.M., Iannuzzi, M.C., Kerem, B., et. al. (1989). Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science*, 245, 1059-65.

Rosenberg, M. (1965). *Society and The Adolescent Self-Image*. Princeton, N.J., Princeton University Press.

Ruggeri, M., Warner, R., Bisoffi, G. and Fontecedro, L. (2001). Subjective and objective dimensions of quality of life in psychiatric patients: a factor analytical approach. *British Journal of Psychiatry*, 178, 268-275.

Ruiz, M.T. and Verbrugge, L. (1997). A two way view of gender bias in medicine. *J Epidemiol Community Health*, 51, 106-109.

Rummel, R.J. (1970). *Applied Factor Analysis*. L. Evanston, IL, Northwestern, University Press.

Rund, D. and Rachmilewitz, E. (2005). B-thalassaemia. *N Engl J Med*, 353, 1135-1146.

Rutter, M., Tizard, J. and Whitmore, K. (1970). Appendix 6: A children's behaviour questionnaire for completion by parents. Education, health and behaviour, 412-421. London, Longmans.

Sanchez, M.H. (2006). What Consumers Want From Physician Websites: An Exploratory Analysis. *Services Marketing Quarterly*, 28, 2.

Sanders, C., Egger, M., Donovan, J. and Frankel, S. (1998). Reporting on quality of life in randomised trials: bibliographic study. BMJ, 317, 1191-1194.

Sankar, P., Cho, M.K., Wolpe, P.R. and Schairer, C. (2006). What is in a cause? Exploring the relationship between genetic cause and felt stigma. *Genet Med*, 8, 1, 33-42.

Schag, C.C., and Heinrich, R.L. (1986). The impact of cancer on daily living: A comparison with cardiac patients and healthy controls. *Rehabilitation Psychology*, 31, 157-167.

Schalock, R.L. (2000). The concept of quality of life: what we know and do not know. *Journal of Intellectual Disability Research*, 48, 3, 205.

Schumaker and Berzon (1995). Available at: http://www.scotland.gov.uk/Publications/2006/01/13110743/11. (Accessed 16th April 2008).

Schwartz, C.E., Coulthard-Morris, L., Zeng, Q., and Retzlaff, P. (1996). Measuring self-efficacy in people with multiple sclerosis: a validation study. *Arch Phys Med Rehabil*, 77, 394-98.

Schwarzer, R. (1992). Self-efficacy in the adoption and maintenance of health behaviour: Theoretical approaches and a new model. In R. Schwarzer (Ed.), Self-efficacy: Thought, control and action (pp. 217-243). Washington, D.C.: Hemisphere.

Scientific Advisory Committee (SAC) (2002). Scientific advisory committee of the medical outcomes trust assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res*, 11, 193-205.

Shepherd, S., Hovell, M., Harwood, I., Granger, L.E., Hofstetter, C.R., Molgaard, C. and Kaplan, R.M. (1990). A comparative study of the psychosocial assets of adults with cystic fibrosis and their health peers. *Chest*, 97, 1310-16.

Shrout, P.E. and Fleiss, J.L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*, 86, 420-8.

Selai, C.E., Trimble, M.R., Rossor, M.N., Harvey, R.J. (2001). Assessing quality of life in dementia: Preliminary psychometric testing of the Quality of Life Assessment Schedule (QOLAS). *Neuropsychological Rehabilitation*, 11, 3/4, 219-243.

Skantze, K., Wanke, M. and Bless, H. (1994). 'Subjective assessments and evaluations of change: some lessons from social cognition research' In: W. Stroebe and M. Hewstone, *European Review of Social Psychology,* 181-210, New York, John Wiley & Sons.

Skevington, S.M. (1999). Measuring quality of life in Britain: Introducing the WHOQOL-100. *J. Psychosomatic Res*., 47, 5, 449-459.

Skevington, S.M., Bradshaw, J. and Saxena, S. (1999). Selecting national items for the WHOQOL: conceptual and psychometric considerations. *Soc Sci Med,* 48, 473-487.

Skevington, S.M., Carse, M.S., Williams, A. C. (2001a). Validation of the WHOQOL-100: Pain management improves quality of life for chronic pain patients. *Clin. J. Pain*, 17, 3, 264-275.

Skevington, S.M., O'Connell, K.A., and WHOQOL group (2004). Can we identify the poorest quality of life? Assessing the importance of quality of life using the WHOQOL-100. *Qual Life Res,* 13, 23-34.

Skevington, S.M. and Wright, A. (200b1). Changes in the quality of life of patients receiving antidepressant medication in primary care: Validation of the WHOQOL-100. *Br. J. Psychiatry*, 178, 261-267.

Singer, E., Garfinkel, R., Cohen, S.M. and Srole, L. (1976). Mortality and mental health: evidence from the Midtown Manhattan Restudy. *Soc Sci Med,* 10 (11-12), 517-25.

Singh, S.J., Sodergren, S.C., Hyland, M.E., Williams, J., Morgan. M.D.L. (2001). A comparison of three disease-specific and two generic health-status measures to evaluate the outcome of pulmonary rehabilitation in COPD. *Respiratory Medicine*, 95, 71–77.

Skrabanek, P. and McCormick, J. (1990). 'Placebos', In: *Follies and Fallacies in Medicine*, 11-25. Prometheus, Buffalo.

Smith, G.D. (2002). Inflammatory bowel disease: developing a short disease-specific scale to measure health related quality of life (HRQoL). *International Journal of Nursing Studies*, 39, 6, 583-590.

Snowden, L.R. (2001). Barriers to effective mental health services for African Americans. *Mental Health Services Research*, 3 ,4, 181-187.

Solovieva, S., Santavirta, N., Santavirta, S. and Konttinen, Y.T. (2004). Assessing quality of life in individuals with hereditary blood coagulation disorders. *Qual Life Res*, 13, 987-1000.

Sowell, R.L., Seals, B.F., Moneyham, L. et. al. (1997). Quality of life in HIV-infected women in the south eastern United States. *Aids Care*, 9, 510-512.

Spearman, C.E. (1904). The proof and measurement of association between two things. *Am J Psychol*, 15, 72–101.

Spilker, B (1996) (ed.). *Quality of life and pharmacoeconomics in clinical trials* (2nd ed.) Philadelphia, PA, Lippincott-Raven.

Sprangers, M.A.G. and Aaronson, N.K. (1992). The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *J Clin Epidemiol*, 45, 743–60.

Sprangers, M.A.G., deRegt, E.B., Andres, F., Van Agt, H.M., Bijl, R.V., deBoer, J.B. et. al. (2000). Which chronic conditions are associated with better or poorer quality of life? *Journal of Clin Epidemiol*, 53, 895-907.

Sprangers, M.A.G. and Schwartz, C.E. (1999). Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*, 48, 1507-15.

Stewart, A.L., Greenfield, S., Hays, R.D., Wells, K., Rogers, W.H., Berry, S.D., et al. (1989). Functional status and well-being of patients with chronic conditions. Results from the medical outcomes study. *JAMA*, 262, 907–13.

Stewart, A.L., Hays, R.D., Ware, J.E. Jr. (1988). The MOS Short- Form General Health Survey: reliability and validity in a patient population. *Med Care*, 26, 724–35.

Stewart, A.L. and Ware, J.E. Jr (eds) (1992). *Measuring functioning and well-being: the Medical Outcomes Study approach.* Durham, NC: Duke University Press.

Strauss, G. and Wellisch, D. (1981). Psychosocial adaptation in older cystic fibrosis patients. *J Chron Dis,* 34, 141-6.

Streiner, D.L. and Norman, G.R. (1995). *Health measurement scales: a practical guide to their development and use,* (2nd ed.). Oxford, Oxford University Press.

Struttmann, T., Fabro, M., Romieu, G., de Roquefeuil, G., Touchon, J., Dandekar, T. and Ritchie, K. (1999). Quality-of-life assessment in the old using the WHOQOL 100: Differences between patients with senile dementia and patients with cancer. *Int. Psychogeriatrics*, 11, 3, 273-279.

Stufflebeam, D. L. And Webster, W. J. (1980). An analysis of alternative approaches to evaluation. *Educational Evaluation and Policy Analysis*. 2, 3, 5-19.

Stuifbergen, A.K., Seraphine, A. and Roberts, G. (2000). An Explanatory Model of Health Promotion and Quality of Life in Chronic Disabling Conditions. *Nursing Research*, 49, 3, 122-129.

Sung, J.C., Nichol, M.B., Venturini, F., Bailey, K.L., McCombs, J.S. and Cody, M. (1998). Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. *American Journal of Managed Care,* 4, 10, 1421-1430.

Supina, A.L., Feeny, D.H., Carroll, L.J. and Johnson, J.A. (2006). Misinterpretation with Norm-Based Scoring of Health Status in Adults with Type-1 Diabetes. Health and Quality of Life Outcomes (electronic journal), 4, 1, 15. Available at: http://www.hqlo.com/content/4/1/15. (Accessed 6th July 2009).

Sutcliffe, N., Clarke, A.E., Levington, C., Frost. C., Gordon, C. and Isenberg, D.A. (1999). Associates of health status in patients with systemic lupus erythematous. *J Rheumatol,* 26, 2353-2356.

Tabachnick, B.G. and Fidell, L.S. (2001). *Using Multivariate Statistics* (fourth ed.). Boston, London, Toronto, Sydney, Tokyo, Singapore, Allyn and Bacon.

Tartar, R.E., Erb, S., Biller, P.A., Switala, J. and Van Thiel, D.H. (1988). The quality of life following liver transplantation: a preliminary report. *Gastroenterology Clinics of North America*, 7, 2, 207-17.

Telfer, P., Coen, P.G., Christou, S., Hadjigavriel, M., Kolnaou, A., Pangalou, E., et. al. (2006). Survival of medically treated thalassaemia patients in Cyprus. Trends and risk factors over the period 1980-2004. *Disorders of Erythropoiesis*, 91, 1187-1192.

Telfer, P, Constantinidou, G., Andreou, P., Christou, S., Modell, B. and Angastiniotis, M. (2005). Quality of life in thalassaemia. *Ann N Y Acad Sci,* 1054, 273-282.

Telfer, P., Prescott, E., Holden, S., Walker, Hoffbrand, M. and Wonke, B. (2000). Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. *Br J Haematol,* 110, 971-7.

Terwee, C.B, Bot, S.D., de Boer, M.R. ,van der Windt, D.A., Knol, D.L., Dekker. J. et. al. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *J Clinical Epidemiology,* 60, 1, 34 - 42.

Testa, M.A. and Simonson, D.C. (1996). Assessment of quality of life outcomes. *Current Concepts*, 334 (13), 835-840.

Thalassaemia International Federation (TIF) (2000). Available at: http://www.thalassaemia.org.cy/ (Accessed 20th June 2007).

The Standards for Educational and Psychological Testing (1999). Available at: http://www.apa.org/science/standards.html#overview. (Accessed 3rd July 2009).

Thompson, B. (2004). *Exploratory and confirmatory factor analysis: Understanding concepts and applications.* Washington, DC: American Psychological Association.

Thompson, R.J., Gil, K.M., Abrams, M.R. and Phillips, G. (1992). Stress, coping, and psychological adjustment of adults with sickle cell disease. *Journal of Consulting and Clinical Psychology*, 60, 3, 433-440.

Thurstone, L.L. (1925). A method for scaling psychological and educational tests. *J Educ Psychol*, 16, 433-51.

Thurstone, L.L. (1928). Attitudes can be measured. *Am J Sociol*, 33, 529-554

Tillery, B.W. (2005). *Physical Science*, (6th ed.). New York: McGraw-Hill.

Trikkas, G., Politis, C., Voulgari, H. and Christodoulou, G.N. (1988). *Psychosocial findings in thalassemic patients.* Presented at the Seventeenth European Conference on Psychosomatic Research. Marburg, September.

Tsai, C., Bayliss, M.S., Ware, J.E. (1997). *SF-36® Health Survey Annotated Bibliography:* Second Edition (1988-1996). Boston, MA: Health Assessment Lab, New England Medical Center.

Tsiantis, J. (1990). Family reactions and relationships in thalassaemia. *Ann N Y Acd Sci*, 612, 451-461.

Turk, J. (1994). Impact of cystic fibrosis on family functioning. *Pediatrics*, 34, 67-71.

Turner-Bowker, D.M., Bartley, P.J., Ware, J.E., Jr. (2002). *SF-36® Health Survey & "SF" Bibliography:* Third Edition (1988-2000). Lincoln, RI: Quality Metric Incorporated.

UK Thalassaemia Society (UKTS) (2005). *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK.* UKTS.

Unruh, A.M. (1996). Gender variations in clinical pain experience. *Pain*, 65, 123.

Van Horn, P.S., Green, K.E. and Martinussen, M. (2009). Survey Response Rates and Survey Administration in Counselling and Clinical Psychology. *Educational and Psychological Measurement.* 69, 389-403.

Van Someren, M.V., Barnard, Y.F. and Sandberg, J.A.C. (1994). *The Think Aloud Approach: A practical guide to modelling cognitive processes.* Academic Press, London 1994

Vardaki, M.A., Philalithis, A.E. and Vlachonikolis, I. (2004). Factors associated with the attitudes and expectations of patients suffering from beta-thalassaemia: a cross-sectional study. *Scand J Caring Sci*, 18, 177-187.

Veenhoven, R. (2000). The four qualities of life. Ordering concepts and measures of the good life. *Journal of Happiness Studies*, 1, 1-39.

Vickers, A. J. (1999). Comparison of an ordinal and a continuous outcome measure of muscle soreness. *International Journal of Technology Assessment in Health Care*, 15, 4, 709-716.

Vickrey, BG., Hays, R.D., Engel, J. Jr., Spritzer, K., Rogers, W.H., Rausch R., et. al. (1995).Outcome assessment for epilepsy surgery: the impact of measuring health-related Quality of life. *Annals of Neurology.* 37, 2,158-66.

Vickrey, B.G., Hays, R.D., Graber, J., Rausch, R., Engel, J.and Brook, R.H. (1992). A health-related quality of life instrument for patients evaluated for epilepsy surgery. *Med Care*, 30, 4, 299-319.

Viramontes, J.L. and O'Brien, B. (1994). Relationship between symptoms and health-related quality of life in chronic lung disease. *J Gen Intern Med*, 9, 1, 46-8.

Visser, P.S., Krosnick, J.A., Marquette, J. and Curtin, M. (1996). "Mail Surveys for Election Forecasting? An Evaluation of the Colombia Dispatch Poll." *Public Opinion Quarterly*, 60, 181-227.

Wagner, A,K., Keller, S.D., Kosinski, M., Baker, G.A., Jacoby, A., Hsu, M.A., Chadwick, D.W. and Ware, J.E. (1995). Advances in methods for assessing the impact of epilepsy and antiepileptic drug therapy on patients' health-related quality of life. *Qual Life Res*, 4, 115-34.

Wallston, K.A., Wallston, B.S. and DeVellis, R. (1978). Development of the Multidimensional Health Locus of Control Scales. *Health Education Monographs*, 6, 160-170.

Ward, A., Caro, J.J., Green, T.C., Huybrechts, K., Arana, A., Wait, S., et. al. (2002). An international survey of patients with thalassaemia major and their views about sustaining life-long desferrioxamine use. *Clinical Pharmacology*, 2, 3, 1-9.

Ware, J.E. Jr. (1987). Standards for validating health measures: definition and content. *J of Chronic Diseases*, 40, 473-80.

Ware, J.E. Jr. (1993). Measuring patients' views: the optimum outcome measure. *BMJ*, 306, 1429–30.

Ware, J. E., Jr. (1995). The status of health assessment 1994. *Ann Rev Public Health*, 16, 327–54.

Ware, J.E., Kosinski, M., Bayliss, M.S., McHorney, C.A., Rogers, W.H., Raczek, A. (1995). Comparison of methods for the scoring and statistical analysis of SF-36® health profiles and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 33(Suppl.4):AS264-AS279.

Ware, J.E. Jr., Kosinski, M.A. and Keller, S.D. (1994). *SF-36 physical and mental health summary scales: a user's manual.* Boston (MA): Health Institute, England Medical Center.

Ware, J.E. Jr., Kosinski, M.A. and Keller, S.D. (1996). A 12-Item Short-Form Health Survey. Construction of scales and preliminary tests of reliability and validity. *Med Care*, 34, 3, 220-233.

Ware, J.E. and Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care,* 30, 473-483.

Ware, J.E. Jr., Snow, K.K., Kosinki, M. and Gandek, B. (1993). *SF-36 Health Survey manual and interpretation guide.* Boston (MA): New England Medical Center, The Health Institute, Nimrod Press.

Warner, R. (1999). The emics and etics of quality of life assessment. *Social Psychiatry and Psychiatric Epidemiology,* 34, 117 -121.

Weatherall, D.J. and Clegg, J.B. (1972). *The Thalassaemia Syndromes* (2nd ed.), Blackwell Scientific Publications.

Weatherall, D.J. and Clegg, J.B. (2001). Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ,* 79, 704-712.

Weber, R. P. (1990). *Basic Content Analysis.* 2nd ed., Newbury Park, CA: Sage.

Weinberger, M., Samsa, G.P., Hanlon, J.T., Schmader, K., Doyle, M.E., Cowper, P.A., Uttech, K.M., Cohen, H.J., Feussner, J.R. (1991). An evaluation of a brief health status measure in elderly veterans. *J Am Geriatr Soc*, 39, 7, 691-4.

Wenninger, K.,Weiss, C., Wahn, U. and Staab, D. (2003). Body image in cystic fibrosis-development of a brief diagnostic scale. *J Behav Med,* 26 (1), 81-94.

Whipple, G.H and Bradford, W.L. (1932). Racial or familial anemia of children: associated with fundamental disturbances of bone and pigment metabolism. *Am J Med Sci*. 44, 336-365.

Whipple, G.H. and Bradford, W.L. (1936). Mediterranean disease: thalassaemia (erythroblastic anemia of Cooley). *J Pediatr.* 9, 279 –311.

White, D., Stiller, K. and Haensel, N. (2007). Adherence of adult cystic fibrosis patients with airway clearance and exercise regimens. *Journal of Cystic Fibrosis,* 6, 163-170.

Wilson, I.B. and Cleary, P.D. (1995). Linking clinical variables with health related quality of life. *Journal of the American Medical Association*, 273, 59-65.

WHOQOL Group (1993). *Measuring quality of life: the development of the World Health Organisation Quality of Life Instrument (WHOQOL).* Geneva, World Health Organisation.

WHQOL Group (1995). The World Health Organization Quality of Life Assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*, 41, 1403-9.

WHOQOL Group (1998). The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychosomatic properties. *Soc Sci Med*, 46, 1569-85.

Wolcott, H.F. (1994). *Transforming qualitative data: Description, Analysis and Interpretation*. SAGE.

Wonke, B., Wright, C. and Hoffbrand, A.V. (1998). Combined therapy with deferiprone and Desferrioxamine. *British Journal of Haematology*, 103, 2, 361-364.

Woo, R., Giardina, P.J. and Hilgarther, M.W. (1984). A psychosocial needs assessment of patients with homozygous beta-thalassaemia. *Ann N Y Acad Sci*, 445, 316-23.

World Health Organization (WHO) (1947). *Constitution of the World Health Organisation*. WHO, Geneva.

World Health Organization (WHO) (1948). *Constitution of the World Health Organisation In: Basic Documents*. Geneva: World Health Organisation.

World Health Organization (WHO) (1971). *Statistical indicators for the planning and evaluation of public health programmes, T*ech Rep Series, 472. Geneva, WHO.

World Health Organization (WHO) (1980). *International Classification of Impairments, Disabilities and Handicaps.* ICIDH. Geneva, WHO.

World Health Organization (WHO) (1998). *International Classification of impairments, activities and participation. A manual of dimensions of disablement and functioning*. Geneva, WHO.

World Health Organization (WHO) (2001). *International Classification of functioning, disability and health.* WHO, Geneva.

WHOQOL Group (1995). The World Health Organization Quality of Life Assessment (WHOQOL): Position paper from the World Health Organization. *Soc. Sci. Med*. 41, 1403-1409.

WHOQOL Group (1998). The World Health Organization Quality of Life Assessment (WHOQOL): Development and general psychometric properties. *Soc. Sci. Med*. 46, 1569-1585.

Wyrwich K.W, Bullinger, M., Aaronson, N., Hays, R.D., Patrick, D.L., Symonds, T. and The Clinical Significance Consensus Meeting Group (2005). Estimating clinically significant differences in quality of life outcomes. *Quality of Life Research,* 14, 285-295.

Younossi, Z.M., Guyatt, G., Kiwi, M., Boparai, N. and King, D. (1999). Development of a disease-specific questionnaire to measure health related quality of life (HRQoL) in patients with chronic liver disease (CLD). *Gut*, 45, 295-300.

Zani, B., Di Palma, A.D. and Vullo, C. (1995). Psychosocial aspects of chronic illness in adolescents with thalassaemia major. *J. Adolesc*. 18, 387 - 402.

Ziller, R.C. (1974). Self-other orientation and quality of life. *Social Indicators Research*, 1, 301-27.

APPENDIX I

Ratip, S. (1996) Measure (16+)

APPENDIX 1: THE CLINICAL INSTRUMENT

CLINICAL HISTORY OF THALASSAEMIA PATIENTS

1. FAMILY TREE

2. PRESENT STATUS

Ht Wt m kg	Mean Hb g/dl	Haemoglobin F A A2 Other % % %	Ferritin mg/l	DF	Spleen cm

3. SHORT HISTORY

Age and circumstances of diagnosis

Haemoglobin: at presentation:pre-splenectomy:post-splenectomy

Transfusion history

Desferrioxamine history

CLINICAL BURDEN CHECKLIST

Gallstones	[ ]		
Bone pain	[ ]		
Joint pain	[ ]		
Pathological fractures	[ ]		
Facial deformity	[ ]		
Leg ulcers	[ ]		
Infections	[ ]		
Sexual dysfunction	[ ]		
Growth delay	[ ]		
Liver problems	[ ]		
Cardiac problems	[ ]		
Diabetes Mellitus		[ ]	
Hypothyroidism	[ ]		
Hypoparathyroidism	[ ]		
Deafness	[ ]		
Renal pain	[ ]		
Renal calculus	[ ]		
Gout	[ ]		
Folate deficiency	[ ]		

Other clinical information

KEY TO SCORING THE CLINICAL BURDEN FOR THE THALASSAEMIAS

1. Transfusion

0 = None
1 = Two or less per year.
2 = Three or four per year.
3 = More than four per year.

2. Desferrioxamine

0 = None
1 = One or less per week, or oral iron chelation.
2 = Two or three per week.
3 = More than three per week, or intravenous via portacath.

3. Leg Ulcers

0 = None
1 = One episode and less than one year in duration.
2 = Two episodes, or duration of between one to two years.
3 = More than two episodes, or duration of more than two years.

4. Gallstones

0 = None or asymptomatic.
1 = Occasionally symptomatic with pain.
2 = Frequent episodes of pain.
3 = Cholecystectomy.

5. Spleen

0 = No enlargement, or enlarged but no effect on blood indices.
1 = Enlarged but only mild effect on blood indices.
2 = Enlarged with significant effect on blood indices but not severe enough to warrant splenectomy.
3 = Splenectomy.

6. Facial Deformity

0 = None
1 = Mild: Visible on close inspection.
2 = Moderate: Obvious deformity but not disfiguring.
3 = Severe: Disfiguring deformity, or required cosmetic surgery.

7. Bone and Joint Pain

0 = None
1 = Occasional and mild; does not interfere with activities.
2 = Frequent and moderate; interferes with activities to a significant extent.
3 = Continuous and severe; interferes with activities to a major extent.

8. Pathological Fractures

0 = None
1 = One
2 = Two
3 = Three

9. Deafness

0 = None
1 = Unilateral and mild.
2 = Bilateral but mild, or unilateral but severe.
3 = Bilateral and severe.

10. Infections

0 = None
1 = Infrequent but still more prone than rest of the population.
2 = Frequent episodes; or occasional admission to hospital with infection.
3 = Frequent admissions to hospital with infection.

11. Growth

0 = Normal
1 = Height within one standard deviation below third centile.
2 = Height between one and three standard deviations below third centile.
3 = Height more than three standard deviations below third centile.

12. Sexual Dysfunction

0 = None
1 = Infertility of one year, or delay in puberty of one year.
2 = Infertility of between one to two years duration, or delayed puberty of more than one year, or mild impotence.
3 = Infertility of more than two years duration, or absence of puberty, or impotence, or early menopause.

13. Mobility

0 = Can walk as long as he/she wishes; no restriction in climbing stairs.
1 = Minor constraints such as weakness leading to intermittent rest; can walk more than one mile, can climb more than 20 stairs.
2 = Significantly affected; can only walk between half to one mile, or climb between 10 to 20 stairs.
3 = Can only walk less than half a mile, or climb less than 10 stairs.

14. Average Number of Hospital Admissions per Year

0 = None
1 = Once
2 = Twice
3 = More than twice

15. Liver

0 = Unaffected
1 = Evidence of infection with Hepatitis B (HBs Ag) or Hepatitis C.
2 = On alpha interferon or intensive intravenous Desferal chelation.
3 = Hepatoma or cirrhosis.

16. Diabetes Mellitus

0 = None
1 = On diet for DM.
2 = On oral drug treatment and diet for DM.
3 = On insulin injections and diet for DM, or retinopathy or renal problems due to DM.

17. Cardiac

0 = Unaffected
1 = Paroxysmal cardiac symptoms such as palpitations, but not interfering with activities.
2 = Cardiac symptoms requiring drugs or interfering with activities such as having decreased mobility but not being house-bound.
3 = Heart failure resulting in intensive treatment with continuous intravenous Desferal and cardiac drugs, or severely interfering with activities such as being house-bound due to heart failure.

18. Thyroid and Parathyroid

0 = Unaffected
1 = On oral drug treatment for hypothyroidism or hypoparathyroidism.
2 = On oral drug treatment for hypothyroidism and hypoparathyroidism.
3 = Hospitalisation due to symptomatic hypocalcaemia, such as convulsions, due to hypoparathyroidism requiring intravenous calcium gluconate.

WEIGHTING TO BE APPLIED TO CLINICAL SCORES

The following multipliers must be applied to each patient's scores before further analysis

Clinical feature	Multiplier to be applied
Transfusion	3
Desferal	3
Spleen	1
Infections	1
Hospital admissions (other than for transfusions)	1
Growth	2
Facial deformity	2
Sexual dysfunction	3
Bone, joint pain	1.5
Fractures	1
Leg ulcers	2
Mobility	2
Deafness	1
Gallstones	1
Thyroid, parathyroid	1
Cardiac	4
Liver	1
Diabetes	1.5

APPENDIX 2: PSYCHOSOCIAL PROFILE QUESTIONNAIRES

Psychosocial parameters examined, and the questions relating to each

A. Questionnaire for adult patients

	Question
1. Education:	1 , 2
2. Sport:	3
3. Social life:	4 , 5
4. Anxiety:	6 , 7
5. Self-image:	8 , 9
6. Feelings of difference:	10
7. Family interactions:	11 , 12
8. Social integration:	13 , 14 , 15 , 16
9. Social isolation:	17 , 18 , 19
10.Stigmatisation:	20 , 21
11.Denial:	22 , 23
12.Well being:	24 , 25 , 26

B. Questionnaire for parents

1. Social life:	1 , 2
2. Anxiety:	3 , 4
3. Isolation:	5 , 6 , 7 , 8
4. Family relationships:	9 , 10
5. Denial:	11 , 12 , 13
6. Anger:	14
7. Confusion:	15 , 16
8. Disease Burden:	17 , 18 , 19
9. Employment:	20
10.Attitude to PND:	21 , 22 , 23 , 24 , 25 , 26 , 27

C. Questionnaire for parents to answer about their child (under 16 years of age)

1. Education:	1 , 2
2. Sport:	3
3. Difference from friends:	4 , 5
4. Social Interactions:	6
5. Family interactions:	7 , 8 , 9
6. Anxiety:	10 , 11
7. Isolation:	12 , 13
8. Stigmatisation:	14 , 15 , 16 , 17
9. Well being:	18 , 19 , 20

1. PSYCHOSOCIAL PROFILE QUESTIONNAIRE FOR ADULT THALASSAEMIA PATIENTS

1 a. Does or did thalassaemia affect your school? Position in tests/exams:

Low [ ]
Middle [ ]
Top [ ]

b. Would you have done better if you did not have thalassaemia?

No [ ] Yes [ ]
Why? .....

2. On average how much time off school have you lost ?

None [ ]
One day or less per month [ ]
One week or less per month [ ]
More than one week per month [ ]

3 a. Does thalassaemia affect your sport activities?

Not at all [ ]
A little [ ]
A lot [ ]

b. Would you have done better if you did not have thalassaemia?

Yes [ ] No [ ]
Why? .....

4. Does thalassaemia affect your social life?

Not at all [ ]
A little [ ]
A lot [ ]
Why? .....

5. Does thalassaemia affect your relationship with your friends?

Not at all [ ]
A little [ ]
A lot [ ]

6. Do you worry about thalassaemia?

Not at all [ ]
A little [ ]
Sometimes [ ]
A lot [ ]
All the time [ ]
Why? .....

7. What is your biggest worry or concern?

8. What are your hopes for the future?

Being healthy/normal [ ]
Having children [ ]
Having a partner [ ]
Doing well at school/work [ ]
Being cured [ ]
Having friends [ ]
Other .....

9. What does it mean to you to have thalassaemia?

Constantly worried [ ]
Cannot cope [ ]
Feeling helpless [ ]
Feeling weak [ ]
Does not bother me [ ]
Other .....

10. Do you think you are different from your friends/sibs?

No [ ]
Yes [ ] Explain .....

11. Do you think thalassaemia affects your relationship with sisters/brothers?
    No [ ]
    Yes [ ]
    Why? .....
12. Do you think thalassaemia affects your relationship with your parents?
    No [ ]
    Yes [ ]
    Why? .....
13. Are you married/do you have a partner?
    Yes [ ]
    No [ ] Because .....
14. Do you worry about whether you will be able to set up a family in the future?
    No [ ]
    Yes [ ] Why? .....
15. Do you have a job?
    Yes [ ]
    No [ ] Why? .....
16. Have you had any problems with employment?
    Yes [ ]
    No [ ]
    Why? .....
17. Who do you trust or turn to for help?
    Parents [ ]
    Brothers/sisters [ ]
    Relatives [ ]
    Friends [ ]
    Doctor [ ]
    Nurse [ ]
    Partner [ ]
    Religious Guide [ ]
    Thalassaemia Society [ ]
    Other .....
18. How often do you talk about your problems or worries?
    Not at all [ ]
    A little [ ]
    Sometimes [ ]
    A lot [ ]
19. Do you think you need more support?
    Yes [ ] No [ ]
    If yes from where and why?
20. Have you joined a Support Group: Thalassaemia Centre, UK Thalassaemia Society?
    Yes [ ] No [ ]
    Why? .....
21. Has anyone made any upsetting remarks concerning your illness?
    No [ ] Yes [ ]
    Explain.....
22. Do or did your friends/schoolmates know you have thalassaemia?
    Yes [ ] No [ ]
    Why? .....
23. Do or did your employer/teacher know you have thalassaemia?
    Yes [ ] No [ ]
    Why? .....
24. Do you feel healthy?
    Yes [ ]
    No [ ]
    Why? .....
25. How far can you walk with comfort?
26. How many stairs can you get up without getting tired?

1. KEY TO SCORING ADULT PATIENT QUESTIONNAIRE

1. Education

0 = Unaffected	No difference to outcome.
1 = Mild:	Affected but still achieved the expected position.
2 = Moderate:	Affected and ended up in a lower position than expected.
3 = Severe:	Major difference to expected outcome, or left school due to thalassaemia.

2. Time off school

0 = None
1 = One day or less per month.
2 = One week or less per month.
3 = More than one week per month.

3. Sport

0 = Unaffected	No difference to sport activities.
1 = Mild:	Slight tiredness but still played sports according to wishes.
2 = Moderate:	Affected; played sports at less than the desired level.
3 = Severe:	Affected in a major way; could not play sports due to thalassaemia.

4. Social Life

0 = Unaffected	No difference to social life; relationship with friends unaffected.
1 = Mild:	Able to socialise but limited to a small degree; relationship with friends virtually unaffected.
2 = Moderate:	Able to socialise but at a significantly reduced level; relationship with friends affected.
3 = Severe:	Virtually unable to socialise; relationship with friends affected to a major degree or no friends.

5. Anxiety

0 = None	
1 = Mild:	Worries about thalassaemia a little; does not feel it will have significant effect on quality of life
2 = Moderate:	Worries about thalassaemia sometimes; feels there will be significant effect on quality of life, i.e. inability to have a family,underachieve etc.
3 = Severe:	Worries about thalassaemia a lot or all the time, or fear of nearing death.

6. Self-Image

0 = Unaffected	Aspirations same as the normal population; no references to thalassaemia.
1 = Mild:	Aspirations same as the normal population, but refers to thalassaemia as an obstacle.
2 = Moderate:	Aspires to be like normal people; refers to thalassaemia as an obstacle.
3 = Severe:	Aspires to be like normal people, frequent references to thalassaemia as an obstacle, or feels defective or dependent.

7. Feelings of Difference

0 = None	
1 = Mild:	Slightly different; unable to do all the things friends/sibs do.
2 = Moderate:	Different, limited significantly by thalassaemia; unable to do many things friends/sibs do.
3 = Severe:	Very different, extremely limited by the disease; unable to do anything friends/sibs do.

8. Family Adjustment

0 = Unaffected	
1 = Mild:	Some overprotection by parents or jealousy by a sib.
2 = Moderate:	Uncomfortably overprotecting parents, or conflicts related to thalassaemia, or jealousy interfering with quality of life.
3 = Severe:	Rejection by parents or sibs, or conflicts due to thalassaemia leading to patient's departure from home.

9. Social Integration

0 =	Unaffected
1 = Mild:	Well integrated but intermittent problems with time off work/minor employment problems, or minor relationship problems due to thalassaemia.
2 = Moderate:	Problems with employment but able to work to a reduced extent; or significant problems with setting up a family due to thalassaemia.
3 = Severe:	Unemployed, or unable/unlikely to set up a family due to thalassaemia.

10. Social Isolation

0 = None	
1 = Mild:	Good support but feels he/she needs more support at times.
2 = Moderate:	Support from friends/relatives available but deficiency of support evident.
3 = Severe:	No one to turn to when in need of support.

11. Stigmatisation

0 = None	
1 = Mild:	Few references to stigmatisation in the past or at the present time, no effect on social life or employment.
2 = Moderate:	Relationships or employment or education affected to a significant degree by stigmatisation; or some avoidance of social activity leading to noticeable degree of isolation.
3 = Severe:	Relationships broken by stigmatisation, or isolated due to stigmatisation by friends/relatives, or unemployed due to stigmatisation, or education stopped as a result of stigmatisation.

12. Denial

0 = None:	Friends, relatives, employer knows he/she has thalassaemia; never hides, talks about thalassaemia spontaneously.
1 = Mild:	Tells friends/employer that he/she has thalassaemia; will tell anyone else but only if initiated.
2 = Moderate:	Close friends/employer know about patient's illness, otherwise tries not to mention it unless obliged to.
3 = Severe:	No one except closest friends/close relatives know patient has thalassaemia. Never tells anyone about illness.

APPENDIX II

Letter of invitation interview

University College London Hospitals NHS
NHS Foundation Trust

Version 1/Qualitative Interview Stage
28th August 2004

Dear < Insert Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

We are writing to you to invite you to take part in a research study. My research team and I are trying to develop a scale to measure the impact of beta-thalassaemia major (BTM). Further information about the study is enclosed.

Part of the study will involve being interviewed by a researcher and can take place whenever and wherever is convenient for you. You will be asked to talk about the impact of thalassaemia on your life.

Your agreeing to take part in this study is entirely voluntary and all information will be kept strictly confidential. If you decide not to take part in this study, any treatment you will continue to receive for your thalassaemia will not be affected.

Yours sincerely,

Dr. Anna Mandeville
Principal Research Investigator
Consultant Clinical Health Psychologist; Honorary Research Fellow, UCLH

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX III

Patient Information Sheet (PIS) interview

Version 1/Qualitative Interview Stage
28th August 2004

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

You are being invited to take part in a research study. Before you decide in participating, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others it you wish. Ask us if there is anything that is not clear or if you would like more information. Take the time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

We would like to invite you to take part in a research study which aims to develop a scale which will assess the impact of beta-thalassaemia major (BTM) upon patients. When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help us understand this in BTM we need a questionnaire specifically designed to ask those questions that are relevant to patients with BTM. Such a questionnaire has not been developed to date. In order to do this we firstly need some information from patients with BTM to find out about what things are important to them.

Why have I been chosen?

We are looking for volunteers who have BTM and are aged over 18 years. We are hoping to study around 15-20 patients in total. Your name has been chosen by the named nurse specialist/consultant at your participating hospital/centre.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, which you may keep. If you decide to take part you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We would like you to talk to a friendly interviewer who will want to discuss with you how TM has affected you and your life. The interview can take place whenever and wherever is convenient for you. The interview will probably take between 60 and 90 minutes. The researcher will ask about different accepts of your life and how they have been affected by BTM. If there is anything you are uncomfortable about discussing, you do not have to answer those questions.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Are there any possible benefits or risks involved in taking part?

As this research is only attempting to find out about your existing views, it is not thought that taking part should involve any significant risks to you. However, if you do find that the interview raises any concerns for you, please contact the principal investigator who will be able to discuss this with you.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism may be available to you.

Similarly, it is not thought that taking part in this study will have any direct impact on you but by talking part in this research you will be helping to design a questionnaire that will help to assess how effectively we are treating patients with TM. The questionnaire is also likely to be used to evaluate new treatments of TM as they are developed.

Will my taking part in this study be kept confidential?

With your permission, the interview will be tape recorded in order to allow transcription and analysis of the data. All information which is collected about you during the course of the research will be kept strictly confidential and you will not be personally identified on the tapes or the transcriptions of the interviews. Any information about you will have your name removed so that you cannot be recognised from it. Tapes will be kept in a locked filing cabinet which will only be accessible by the research team, and will be destroyed on completion of the study in three years time. Your GP will be sent an information sheet to let him/her know that you have taken part in this study if you so wish.

What will happen to the results of the research study?

The results of the study will be likely to be published but you will not be identified in any report or publication arising from this study.

Who is funding the research?

The Thalassaemia International Federation (TIF) in Cyprus, Nicosia, is currently liaising with pharmaceutical companies regarding financial support for this project.

Who has reviewed the study?

The study will be reviewed by the UK Thalassaemia Society (UKTS), University College Hospital (UCH) and Brunel University. It should be noted that this project is independent to those commissioned by the UKTS.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Who should I contact for further information?

If you have any questions about the study, please do not hesitate to contact the principal investigator, Dr. Anna Mandeville on 07989 306514 and/or lead researcher, Xenya Kantaris on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX IV

Consent form interview

University College London Hospitals NHS
NHS Foundation Trust

Version 1
3rd February 2005

Centre Number:
Patient Identification Number (ID):

INTERVIEW CONSENT FORM

Title of Project: A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

Name of Principal Investigator: Dr. Anna Mandeville
Name of lead research psychologist: Xenya Kantaris

Please initial box

1. I confirm that I have read and understand the information sheet dated ....., version ....., for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team where it is relevant to my taking part in research. I give permission for these individuals to have access to my medical record at my treatment centre/hospital to obtain blood test results and MRI results for the purpose of measuring my adherence to treatment in a scientific way. ☐

4. I agree to take part in the above study. ☐

5. I agree to my GP being informed of my participation in this study* ☐

6. I agree for my interview to be audiotaped. ☐

*This is optional. Please provide details below if you wish.

GP details:

Name of patient	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

1 copy for the patient; 1 copy for the researcher; 1 copy to be kept with hospital notes

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX V

G.P. information sheet interview

Version 1/Qualitative Interview Stage
28th August 2004

GP Information Sheet for < Insert Patient Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

This is an information sheet for all General Practitioners whose patients have recently taken part in a phase of the above study.

The aim of the study is to develop a scale of the impact of beta-thalassaemia major (BTM). When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help understand this in BTM we need a questionnaire specifically designed to ask the questions that are relevant to patients with BTM. We are in the process of designing such a questionnaire.

We have been looking for volunteers who have BTM and are aged over 18 years. We are hoping to interview around 15-20 patients in total.

For this study your patient has been interviewed by a researcher on how BTM has affected their life. The researcher has visited the patient in their home or in an outpatient clinic/ward to conduct the interview.

If you have any questions about the study, please do not hesitate to contact the research team's interviewer/researcher, Xenya Kantaris, on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

University College London Hospitals NHS
NHS Foundation Trust

Ethnic origin form

Title of project: A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

Ethnic origin of patient: please tick as appropriate

A) WHITE	1	☐ British
	2	☐ Irish
	3	☐ Other
B) MIXED	4	☐ White & Black Caribbean
	5	☐ White & Black African
	6	☐ White & Asian
	7	☐ Other
C) ASIAN OR ASIAN BRITISH	8	☐ Indian
	9	☐ Pakistani
	10	☐ Bangladeshi
	11	☐ Other
D) BLACK OR BLACK BRITISH	12	☐ Caribbean
	13	☐ African
	14	☐ Other
E) CHINESE OR OTHER ETHNIC GROUP	15	☐ Chinese
	16	☐ Other
F) REFUSED	17	☐

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX VII

ABOUT YOU form

Version 1, 11th September 2006

ABOUT YOU ☺

Name (optional):

Gender: (male/female) – please circle as appropriate

Date of Birth/Age:

Contact details (optional):

Type of thalassaemia – please circle as appropriate

Carrier
Trait of beta or alpha
Beta-intermedia
Beta-major

Hospital/consultant:

Date of diagnosis (if known):

G.P. details (optional)

What type of iron chelation therapy are you prescribed? (please tick as appropriate)

- □ Desferal only (pump)
- □ Combination (pump and oral chelator) - please specify _____
- □ Oral chelator only - please specify _____
- □ Other – please specify _____

Any other illness(es)/illness complications (please state)

Highest educational qualification – please circle as appropriate

No qualifications
G.C.S.E. 's or equivalent
University entry or equivalent
Degree
Higher degree
Other

Employment status – please circle as appropriate

Employed
Self-employed
Unemployed
Unemployed due to illness
Other e.g. student/housewife

Occupation (please state):

Marital status – please circle as appropriate

Single
Married
Living together as married
Separated
Divorced
Widowed

No. of children/dependents:

Ethnicity (please complete the appropriate separate sheet):

Any other information about yourself or your treatment that you would like to provide the research team

APPENDIX VIII

Impact statements extracted from the interviews (158)

Impact statements extracted from the interviews (n=158) **Appendix VIII**

1. Fatigue goes along with having thalassaemia (2, 503)
2. I always have lack of energy (4, 267)
3. I was more energetic (6, 244)
4. A lot of days that I actually took off sick simply because I could not make it because I just did not have the energy (2, 157-9)
5. You did not have the energy to keep up with it all (2, 86-7)
6. Feel drained (11, 345-6)
7. I feel really sick and tired (6, 245)
8. Always going to feel tired and lethargic (13, 929)
9. Can't be bothered to do nothing (6, 39)
10. I start feeling really, really tired (6, 41)
11. Very lethargic (11, 70-72)
12. I get really knackered.. (10, 224)
13. I feel a bit lethargic (12, 110)
14. It's not really a huge problem (16, 149)
15. I don't have as much stamina as I used to (9, 431-2)
16. You can't shift silly things like colds and sore throats (9, 1147-8)
17. Feeling run down (2, 60)
18. Feel run down (10, 166)
19. Bloatedness (13, 868)
20. Infusers cause sometimes the headaches and nauseaness (13, 648-9)
21. Get heachaches, shivery and feel sick (7, 582)
22. I tend to bruise quite a lot (9, 647)
23. You do get like bruising and stuff and scars (16,690)
24. I get swelling after I have my pump (9, 120)
25. I get dizzy often (9, 281)
26. Painful, hurtful (12, 1175)
27. A little painful but not unbearable (3, 357)
28. Very high temperature (12, 1725)
29. Very sudden onset of shakes (12, 1724)
30. It's painful having thalassaemia (11, 696)
31. I am full of aches and pains (6, 40)
32. I'm always in pain (4, 267)
33. Lose my appetite (9, 354)
34. Eating is not brilliant either (11, 70-72)
35. Recover, sleep or rest or take it easy more often (12,133)
36. I am unable to sleep (9, 1279)
37. I don't sleep very well (15, 56)
38. I got depressed (1, 856)
39. Very angry, very frustrated, very depressed having no sense of motivation, feeling life was pointless (12, 715-7)
40. Depression physically destroyed me (11, 1514)
41. I worry about my ferritin levels (15, 900-1)
42. I get a little worried when we have new staff (15, 926-7)
43. I worry about having thalassaemia (11, 445-6)
44. There's a lot of anger (11, 1358)
45. Big explosions, very huge amounts of anger, frustration (12, 687)

46. Sometimes you just lose your temper, really easy and get emotional (6, 1130-1)
47. I used to lose my temper with everyone and you know people at home and people at work (8, 212-3)
48. Any little thing triggers it off (6, 1165)
49. I would probably say that you are probably more of an emotional person (2, 606)
50. You feel a bit down or more stressed (7, 54)
51. I don't like feeling sorry for myself (13, 1386)
52. More irritable really (7, 204)
53. You're irritable all the time (13, 168)
54. Aggression, that is also true (8, 1704)
55. You get short-tempered as well (8, 195)
56. Sense of pointlessness (12, 972)
57. I'm very, very sensitive (12, 1305)
58. Always anxious (1, 819)
59. Having anxiety attacks (9, 1304-5).
60. I was suicidal on a few occasions (2, 540-1)
61. Taking advantage of me because I was little and I was ill (10, 1161)
62. I didn't want to expose myself to anyone and basically to seem vulnerable to other people (5, 464-5)
63. I'm unable to concentrate (11, 344)
64. Introspective, it makes them shy, it makes them lack initiative, it makes them very passive (12, 651-2)
65. Some have got shortened bodies (6, 308)
66. Keeps you youthful in your appearance in comparison to your peers (13, 1301)
67. I look young (10, 1917)
68. I look very young (12, 1019)
69. You always end up looking younger than your counterparts (8, 1290)
70. Complexion, there's a bit of pallor (12, 164)
71. Well I hate the fact that I am so small. It upsets me a lot that I am very short (11, 1291)
72. I suppose everyone was always a bit taller than me (8, 1289)
73. Arms are too short (6, 295)
74. My body image is probably my most conscious aspect that I have to deal with because I am different (1, 603-4)
75. I do what all my friends do, so I don't think it makes me different (16, 430)
76. I still think you can live your life normally I have. I don't see myself as any different to anyone else (16,1175-6)
77. It impacts I'm trying to be a normal human being. I'm comparing myself to a normal person (13, 982-3)
78. I think my life is normal (16, 1196)
79. The way you look, the way you are, you are just different (8, 1281)
80. Through puberty I was self-conscious of my body not being the same as their body (13, 1236-7)
81. My family never treat me different (7, 646)
82. Everything was difficult. I was comparing myself to others (12, 768)
83. I wasn't allowed on school trips (9, 1808)
84. You see your friends doing what you would like to be doing, then you can't do it or you are not as successful as them (1, 619-620)
85. When people don't know it's better because it doesn't make me different to them, but if they know then maybe they see me differently (16, 391-3)

86. I had no self-confidence (12, 789)
87. I am quite a confident person (3, 697)
88. Full confidence (12, 1202)
89. I feel confident and that helps me towards my treatment (1, 1493-4)
90. You always feel that there is something wrong with you (8, 1268)
91. A bit inferior (7, 649)
92. It makes me don't want to get out of bed because it's too exhausting. I don't want to wash or dress myself (11, 89-90)
93. An effort to get self yourself ready (15, 57)
94. Hard to motivate myself to get up and do the things that I am supposed to do (5, 82-3)
95. I can't do the shopping on my own (15, 165)
96. Don't go shopping on my own because of carrying bags (4, 297)
97. Travelling for long periods can be difficult (16,33)
98. Chores around the house are limited (11, 203-4)
99. I can't do most of my housework (6, 68)
100. I can't hoover (11, 140)
101. I can just about make the children's bed (11, 141)
102. There's a lot of things that I would like to do with my two year old that I can't do (6, 114-5)
103. I am not as active as I used to be, I have given up all the things I used to do just so that I can manage work and a home life (15, 100)
104. I think you really have to think about organising your life differently (9, 231-2)
105. Struggling to fit everything into my routine life (9, 841)
106. I just about have enough energy to look after the kids (6, 114
107. I get really short with the children (13, 208)
108. I do things that I have wanted to do in my life and go on holidays and get married which is always one girl's dream to do, have children, try and live a normal life and do everything else that everybody does (6, 25-28)
109. I always plan ahead (1, 871)
110. I think you should still plan everything just like someone who is healthy (15, 227-8)
111. Plan to get married and have children (5, 748).
112. I prefer to be alone (11, 604)
113. I don't think I need anyone to like support me that much (16, 1090)
114. I've got great friends (6, 1111)
115. I've got lots of good friends (6, 731)
116. They are my lifeline. They are the people I have faith in. I trust them (11, 1161)
117. People whether they are normal or thalassaemic are reluctant to have a relationship with a thalassaemic (1, 632-4)
118. I wasn't good enough (7, 1068)
119. Family absolutely hated me because of the thalassaemia and I had such stress (7, 903-4)
120. No-one has ever rejected me (3, 404)
121. I've got nothing to hide and I am not ashamed any more (13, 1665-6)
122. I know the fascism about an illness (11, 771)
123. We are penalised because we have this illness (11, 1311-2)
124. If people know about an illness in Greece they marginalise you or they will show pity on you (12, 561-562)

125. People pre-judge you all the time (13, 1359)
126. Employers might look at you as a liability for having thalassaemia (13, 1921)
127. I don't generally discuss it with my work colleagues (8, 723-4)
128. Socially picked on and bullied at school (1, 27)
129. If they knew I has thalassaemia they would treat me differently (13, 738)
130. Can be difficult getting full time employment because of this (3, 479-80)
131. I am not as active as I used to be, I have given up all the things I used to do just so that I can manage work and a home life (15, 100)
132. My leisure, social life did not kick off until late (1, 166-7)
133. It doesn't affect my social life (3, 405)
134. I don't do any leisure activities (4, 408)
135. I can't go to the gym or swimming (5, 190)
136. I just like jogging.. (8, 353-4)
137. Mobility is difficult (5, 107)
138. I can't do things as quickly as I used to; I'm quite stiff (9, 415)
139. I cannot do bending, lifting (2, 226)
140. Bending over is difficult (11, 123-4)
141. I can't do a lot of walking (6, 68)
142. I get the pain in my legs walking (4, 333)
143. I can't walk nowhere (10, 187)
144. I am not in a position to be able to lift heavy things, I don't have the strength (3, 78-9)
145. I really do not lift anything too heavy (2, 189-190)
146. Lifting things is bad (4, 296).
147. I can't lift heavy things (6, 68)
148. It's a bit of a struggle really sometimes (12, 111)
149. I wouldn't say that thalassaemia interferes with my life (3, 34)
150. It's been a huge struggle to get to where I am (5, 525)
151. At the moment it is having more impact than it did (10, 94)
152. It's a hinderance, it's a pain (13, 2018-9)
153. You have successes but they are limited (1, 621)
154. Thalassaemia continues to impact on my education (1, 422)
155. School was disrupted immensely (1, 24)
156. I spent so little time at school (9, 1006-7)
157. I missed a lot of school (1, 25)
158. My education has suffered a lot (5, 636)

APPENDIX IX

Items identified as irrelevant and/or redundant (97)

Redundant and/or Irrelevant items (n=97) **Appendix IX**

1. Fatigue goes along with having thalassaemia (2, 503)
2. I was more energetic (6, 244)
3. A lot of days that I actually took off sick simply because I could not make it because I just did not have the energy (2, 157-9)
4. Tired did not have the energy to keep up with it all (2, 86-7)
5. Feel drained (11, 345-6)
6. Can't be bothered to do nothing (6, 39)
7. I start feeling really, really tired (6, 41)
8. Very lethargic (11, 70-72)
9. I get really knackered.. (10, 224)
10. I feel a bit lethargic (12, 110)
11. It's not really a huge problem (16, 149)
12. Feeling run down (2, 60)
13. You do get like bruising and stuff and scars (16,690)
14. Painful, hurtful (12, 1175)
15. A little painful but not unbearable (3, 357)
16. Very high temperature (12, 1725)
17. Very sudden onset of shakes (12, 1724)
18. It's painful having thalassaemia (11, 696)
19. I'm always in pain (4, 267)
20. Eating is not brilliant either (11, 70-72)
21. I don't sleep very well (15, 56)
22. I got depressed (1, 856)
23. Depression physically destroyed me (11, 1514)
24. I worry about my ferritin levels (15, 900-1)
25. I get a little worried when we have new staff (15, 926-7)
26. I worry about having thalassaemia (11, 445-6).
27. There's a lot of anger (11, 1358)
28. I used to lose my temper with everyone and you know people at home and people at work (8, 212-3)
29. Any little thing triggers it (temper) off (6, 1165)
30. I would probably say that you are probably more of an emotional person (2, 606)
31. I don't like feeling sorry for myself (13, 1386)
32. More irritable really (7, 204)
33. Having anxiety attacks (9, 1304-5).
34. Keeps you youthful in your appearance in comparison to your peers (13, 1301)
35. I look young (10, 1917)
36. I look very young (12, 1019)
37. My body image is probably my most conscious aspect that I have to deal with because I am different (1, 603-4)
38. I do what all my friends do, so I don't think it makes me different (16, 430)
39. It impacts I'm trying to be a normal human being. I'm comparing myself to a normal person (13, 982-
40. I think my life is normal (16, 1196)
41. The way you look, the way you are, you are just different (8, 1281)
42. Through puberty I was self-conscious of my body not being the same as their body (13, 1236-7)

43. My family never treat me different (7, 646)
44. I wasn't allowed on school trips (9, 1808)
45. You see your friends doing what you would like to be doing, then you can't do it or you are not as successful as hem (1, 619-620)
46. When people don't know it's better because it doesn't make me different to them, but if they know then maybe they see me differently (16, 391-3)
47. I am quite a confident person (3, 697)
48. Full confidence (12, 1202)
49. I feel confident and that helps me towards my treatment (1, 1493-4)
50. You always feel that there is something wrong with you (8, 1268)
51. It makes me don't want to get out of bed because it's too exhausting. I don't want to wash or dress myself (11, 89-90)
52. Don't go shopping on my own because of carrying bags (4, 297)
53. I can't do most of my housework (6, 68)
54. I can't hoover (11, 140)
55. I can just about make the children's bed (11, 141)
56. There's a lot of things that I would like to do with my two year old that I can't do (6, 114-5)
57. I am not as active as I used to be, I have given up all the things I used to do just so that I can manage work and a home life (15, 100)
58. I think you really have to think about organising your life differently (9, 231-2)
59. I just about have enough energy to look after the kids (6, 114)
60. I do things that I have wanted to do in my life and go on holidays and get married which is always one girl's dream to do, have children, try and live a normal life and do everything else that everybody does (6, 25-28)
61. I think you should still plan everything just like someone who is healthy (15, 227-8)
62. Plan to get married and have children (5, 748).
63. I prefer to be alone (11, 604)
64. I don't think I need anyone to like support me that much (16, 1090)
65. I've got great friends (6, 1111)
66. I've got lots of good friends (6, 731)
67. They are my lifeline. They are the people I have faith in. I trust them (11, 1161)
68. People whether they are normal or thalassaemic are reluctant to have a relationship with a thalassaemic (1, 632-4)
69. I wasn't good enough (7, 1068)
70. Family absolutely hated me because of the thalassaemia and I had such stress (7, 903-4)
71. I've got nothing to hide and I am not ashamed any more (13, 1665-6)
72. I know the fascism about an illness (11, 771)
73. If people know about an illness in Greece they marginalise you or they will show pity on you (12, 561-562)
74. People pre-judge you all the time (13, 1359)
75. Employers might look at you as a liability for having thalassaemia (13, 1921)
76. I don't generally discuss it with my work colleagues (8, 723-4)
77. Socially picked on and bullied at school (1, 27)
78. If they knew I has thalassaemia they would treat me differently (13, 738)
79. Can be difficult getting full time employment because of this (3, 479-80)
80. My leisure, social life did not kick off until late (1, 166-7)
81. I can't go to the gym or swimming (5, 190)
82. I just like jogging.. (8, 353-4)

83. I can't do things as quickly as I used to; I'm quite stiff (9, 415)
84. I cannot do bending, lifting (2, 226)
85. I get the pain in my legs walking (4, 333)
86. I can't walk nowhere (10, 187)
87. I am not in a position to be able to lift heavy things, I don't have the strength (3, 78-9)
88. I really do not lift anything too heavy (2, 189-190)
89. Lifting things is bad (4, 296).
90. I wouldn't say that thalassaemia interferes with my life (3, 34)
91. It's been a huge struggle to get to where I am (5, 525)
92. At the moment it is having more impact than it did (10, 94)
93. Thalassaemia continues to impact on my education (1, 422)
94. School was disrupted immensely (1, 24)
95. I spent so little time at school (9, 1006-7)
96. I missed a lot of school (1, 25)
97. My education has suffered a lot (5, 636)

APPENDIX X

61-item questionnaire

61-item questionnaire

Scale category*	Facets incorporated within domains (themes emerged during the extraction process)	Items Derived from Content Analysis
General Physical Health (GPH) n = 15	- Overall quality of life (QoL) and general health - Energy, fatigue/tiredness - Pain and discomfort - Sleep	Lacked energy Felt tired Lacked stamina Been unable to shift a cold and/or sore throat Felt run down Felt bloated Had nausea Had headaches Been bruised Had some swelling Felt dizzy Been full of aches and pains Had a poor appetite Needed to rest more often Been unable to sleep
Psychological health and personal beliefs A Coping (C) n = 18	- Feelings/emotions - Thinking and Concentration - Planning ahead	Been depressed Been worried Been angry and frustrated Lost my temper on a number of occasions Been emotional Been a bit down or stressed Been irritable Been aggressive towards others Been generally short-tempered Had a sense of pointlessness Been very sensitive Been anxious Been suicidal on a few occasions Had trouble concentrating I have not planned ahead Been very shy Been vulnerable Been very passive
B Body Image, Appearance and Confidence (BIAC) n = 8	- Bodily image - Self-esteem and confidence	I have a shortened body I look younger than my age/peers I have a pale complexion I am short in height My arms are short I am different to others and am conscious of this I have no self-confidence

Scale category*	Facets incorporated within domains (themes emerged during the extraction process)	Items Derived from Content Analysis
		I feel a bit inferior to others
Social Relationships (SR) n = 7	- Relationships and support network - Leisure/social activities - Stigma	I have not been able to successfully form relationships with others I have been rejected in some way because I have thalassaemia I have been penalised in some way because I have thalassaemia My social life has been affected by my illness I have not done any leisure activities I have been really short with my family There are lots of things that I would have liked to have done with my family that I could not do.
Autonomy (A) n = 13	- Mobility - Achievements/normality - Education and work - Activities of daily living	I have had difficulty doing the shopping on my own Travelling has been difficult Doing chores around the house has been limited. I have been unable to manage my work and home/family life as usual Mobility is difficult I could not bend with ease I could not do alot of walking I have been unable to lift heavy things I have struggled to fit everything into my routine life Having thalassaemia has made most things difficult Lacked initiative It has been difficult to motivate myself It has been an effort for me to get myself ready in the morning.

*It should be noted that after the pre-testing phase the number of items within the Psychological health and personal beliefs category was increased. Within the C category the item, Been angry and frustrated was split, making that 19 items within that category and within the BIAC category the item, My arms are long was added making that 9 items within that category.

APPENDIX XI

Letter of invitation pre-testing

University College London Hospitals NHS
NHS Foundation Trust

Version 1/Pre-testing Stage
28th August 2004

Dear < Insert Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

We are writing to you to invite you to take part in a research study. My research team and I are trying to develop a scale to measure the impact of beta-thalassaemia major (BTM). Further information about the study is enclosed.

Part of the study will involve you filling out a questionnaire and giving us your opinion on it.

Your agreeing to take part in this study is entirely voluntary and all information will be kept strictly confidential. If you decide not to take part in this study, any treatment you will continue to receive for your thalassaemia will not be affected.

If you are interested in taking part in this research, please complete the enclosed documents and return them to us in the pre-paid envelope.

Yours sincerely,

Dr. Anna Mandeville
Principal Research Investigator
Consultant Clinical Health Psychologist; Honorary Research Fellow, UCLH

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XII

PIS pre-testing

Version 2/Pre-testing Stage
3rd February 2005

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

You are being invited to take part in a research study. Before you decide in participating, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others it you wish. Ask us if there is anything that is not clear or if you would like more information. Take the time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

We would like to invite you to take part in a research study which aims to develop a scale which will assess the impact of beta-thalassaemia major (BTM) upon patients. When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help us understand this in BTM we need a questionnaire specifically designed to ask those questions that are relevant to patients with BTM. Such a questionnaire has not been developed to date. In order to do this we firstly need some information from patients with TM to find out about what things are important to them.

Why have I been chosen?

We are looking for volunteers who have TM and are aged over 18 years. We are hoping to study around 10 patients in total. You have been chosen due to your attendance at your participating hospital/centre.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, which you may keep. If you decide to take part you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We would like you to fill in a newly-developed questionnaire, and once you have filled it in, to give us your opinion on it. A researcher will ask you several questions about the questionnaire for example, how easy was it to fill in? and whether there were any questions you did not understand. This will probably take about 15 minutes.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Are there any possible benefits or risks involved in taking part?

As this research is only attempting to find out about your existing views, it is not thought that taking part should involve any significant risks to you. However, if you do find that the interview raises any concerns for you, please contact the principal investigator who will be able to discuss this with you.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism may be available to you.

Similarly, it is not thought that taking part in this study will have any direct impact on you but by talking part in this research you will be helping to design a questionnaire that will help to assess how effectively we are treating patients with BTM. The questionnaire is also likely to be used to evaluate new treatments of BTM as they are developed.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential and you will not be personally identified from the questionnaire. Any information about you will have your name removed so that you cannot be recognised from it. Your GP will be sent a letter to let him/her know that you have taken part in this study if you so wish.

What will happen to the results of the research study?

The results of the study will be likely to be published but you will not be identified in any report or publication arising from this study.

Who is funding the research?

The Thalassaemia International Federation (TIF) in Cyprus, Nicosia, is currently liaising with pharmaceutical companies regarding financial support for this project.

Who has reviewed the study?

The study will be reviewed by the UK Thalassaemia Society (UKTS), University College Hospital (UCH) and Brunel University. It should be noted that this project is independent to those commissioned by the UKTS.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Who should I contact for further information?

If you have any questions about the study, please do not hesitate to contact the principal investigator, Dr. Anna Mandeville on 07989 306514 and/or lead researcher, Xenya Kantaris on 07811 158 461.

Thank you for taking the time to read this information.

APPENDIX XIII

Consent form pre-testing

University College London Hospitals NHS
NHS Foundation Trust

Version 2/3rd February 2005

Centre Number:
Patient Identification Number (ID):

PRE-TESTING CONSENT FORM

Title of Project: A study to develop and validate a health related quality of life (HRQoL) measure for beta-thalassaemia major (TM) adults

Name of Principal Researcher: Dr. Anna Mandeville
Name of lead research psychologist: Xenya Kantaris

Please initial box

1. I confirm that I have read and understand the information sheet dated ....., version ....., for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team where it is relevant to my taking part in research. I give permission for these individuals to have access to my medical records at my treatment centre/hospital to obtain blood test results and MRI results for the purpose of measuring my adherence to treatment in a scientific way (if necessary). ☐

4. I agree to take part in the above study. ☐

5. I agree to my GP being informed of my participation in this study* ☐

*This is optional. Please provide details below if you wish.

GP details:

Name of patient	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

1 copy for the patient; 1 copy for the researcher; 1 copy to be kept with hospital notes

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XIV

G.P. information sheet pre-testing

Version 1/Pre-testing Stage
28th August 2004

GP Information Sheet for < Insert Patient Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

This is an information sheet for all General Practitioners whose patients have recently taken part in a phase of the above study.

The aim of the study is to develop a scale of the impact of beta-thalassaemia major (BTM). When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help understand this in BTM we need a questionnaire specifically designed to ask the questions that are relevant to patients with BTM. We are in the process of designing such a questionnaire.

We have been looking for volunteers who have BTM and are aged over 18 years. We are hoping to study around 10 patients in total.

For this study your patient has completed a newly-developed questionnaire and has given their opinion on the questionnaire to a researcher.

If you have any questions about the study, please do not hesitate to contact the research team's researcher, Xenya Kantaris, on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XV

63-item questionnaire

ID# _____

Date: _____

THalassaemia Adult Life Index
(THALI-63)

Patient Report (ages 18+)

Instructions

The following questions ask for your views about the impact of thalassaemia and/or your treatment on your day-to-day life **during the past four weeks.**

For each of the statements below please **circle, O,** the number that best describes your situation.

Please answer all the questions below. If you are unsure about how to respond to a given question choose the one that seems the most appropriate; this is often your first response.

Thank you in advance for the completion of this questionnaire.

In the past four weeks, I have.....	Not at all	A little	Moderately	Quite a bit	Extremely
1. Lacked energy	1	2	3	4	5
2. Felt tired	1	2	3	4	5
3. Lacked stamina	1	2	3	4	5
4. Been unable to shift a cold and/or sore throat	1	2	3	4	5
5. Felt run down	1	2	3	4	5
6. Felt bloated	1	2	3	4	5
7. Had nausea	1	2	3	4	5
8. Had headaches	1	2	3	4	5
9. Been bruised	1	2	3	4	5
10. Had some swelling	1	2	3	4	5
11. Felt dizzy	1	2	3	4	5
12. Been full of aches and pains	1	2	3	4	5
13. Had a poor appetite	1	2	3	4	5
14. Needed to rest more often	1	2	3	4	5
15. Been unable to sleep	1	2	3	4	5
16. Been depressed	1	2	3	4	5
17. Been worried	1	2	3	4	5
18. Been angry	1	2	3	4	5
19. Been frustrated	1	2	3	4	5
20. Lost my temper on a number of	1	2	3	4	5

In the past four weeks, I have.....	Not at all	A little	Moderately	Quite a bit	Extremely
occasions					
21. Been emotional	1	2	3	4	5
22. Been a bit down or stressed	1	2	3	4	5
23. Been irritable	1	2	3	4	5
24. Been hostile towards others	1	2	3	4	5
25. Been generally short-tempered	1	2	3	4	5
26. Had a sense of pointlessness	1	2	3	4	5
27. Been very sensitive	1	2	3	4	5
28. Been anxious	1	2	3	4	5
29. Been suicidal on a few occasions	1	2	3	4	5
30. Been vulnerable	1	2	3	4	5
31. Had trouble concentrating	1	2	3	4	5
32. Been very shy	1	2	3	4	5
33. Lacked initiative	1	2	3	4	5
34. Been very passive	1	2	3	4	5

In the past four weeks, it has bothered me that.....	Not at all	A little	Moderately	Quite a bit	Extremely
35. I have a shortened body	1	2	3	4	5
36. I look younger	1	2	3	4	5

In the past four weeks, it has bothered me that.....	Not at all	A little	Moderately	Quite a bit	Extremely
than my age/peers					
37. I have a pale complexion	1	2	3	4	5
38. I am short in height	1	2	3	4	5
39. My arms are short	1	2	3	4	5
40. My arms are long	1	2	3	4	5
41. I am different to others and am conscious of this	1	2	3	4	5
42. I have no self-confidence	1	2	3	4	5
43. I feel a bit inferior to others	1	2	3	4	5

In the past four weeks.....	Not at all	A little	Moderately	Quite a bit	Extremely
44. It has been an effort for me to get myself ready in the morning	1	2	3	4	5
45. It has been difficult to motivate myself	1	2	3	4	5
46. I have had difficulty doing the shopping on my own	1	2	3	4	5
47. Travelling has been difficult	1	2	3	4	5
48. Doing chores around the house has	1	2	3	4	5

In the past four weeks.....	Not at all	A little	Moderately	Quite a bit	Extremely
been limited					
49. I have been restricted in doing things that I would have liked to have done with my family	1	2	3	4	5
50. I have been really short with my family	1	2	3	4	5
51. I have not planned ahead	1	2	3	4	5
52. I have not been able to successfully form relationships with others	1	2	3	4	5
53. I have been rejected in some way because I have thalassaemia	1	2	3	4	5
54. I have been penalised because of my illness	1	2	3	4	5
55. I have been unable to manage my work and home/family life as usual	1	2	3	4	5
56. My social life has been affected by my illness	1	2	3	4	5
57. I have not done any leisure activities	1	2	3	4	5
58. Mobility has been difficult	1	2	3	4	5
59. I could not bend with ease	1	2	3	4	5
60. I could not do a lot of walking	1	2	3	4	5

In the past four weeks.....	Not at all	A little	Moderately	Quite a bit	Extremely
61. I have been unable to lift heavy things	1	2	3	4	5
62. I have struggled to fit everything into my routine life	1	2	3	4	5
63. Having thalassaemia has made most things difficult	1	2	3	4	5

APPENDIX XVI

Ethics approval from the Northern and Yorkshire Research Ethics Committee

NHS

Northern and Yorkshire Multi-Centre Research Ethics Committee

Direct Dial: 0191 374 4151
Facsimile: 0191 374 4102

Northern & Yorkshire MREC
John Snow House
Durham University Science Park
Durham DH1 3YG

20th April 2005

School Research Committee
Brunel University
Uxbridge Campus
Middlesex UB8 3PH

Dear Sir/Madam

Full title of study: ***The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors***

REC reference number: ***04/MRE03/88***
Protocol number:

The Research Ethics Committee has reviewed the above application in accordance with the standard operating procedures for RECs.

The Committee has issued a favourable ethical opinion of the application.

The Chief Investigator has been notified of the Committee's opinion in our letter of 20 April 2005. The letter gives full details of the documents reviewed.

Statement of compliance

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88	**Please quote this number on all correspondence**

Yours sincerely,

Ms Sandy Brunton-Shiels
MREC Administrator

E-mail: sandy.brunton-shiels@durhamclspct.nhs.uk

NHS

Northern and Yorkshire Multi-Centre Research Ethics Committee

Direct Dial: 0191 374 4151
Facsimile: 0191 374 4102

Northern & Yorkshire MREC
John Snow House
Durham University Science Park
Durham DH1 3YG

20 April 2005

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Full title of study: ***The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors***

REC reference number: ***04/MRE03/88***
Protocol number:

Thank you for your letter of 24 March 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application amended		15/11/2004	16/03/2005

Investigator CV Dr Anna L Mandeville	N/A		18/11/2004
Investigator CV Xenya Kantaris	N/A		18/11/2004
Investigator CV Afsane Riaza	N/A		18/11/2004
Protocol	1	01/08/2004	18/11/2004
Covering Letter	N/A	14/11/2004	18/11/2004
Interview Schedules/Topic Guides	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Qualitative Interview Stage	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Postal Survey Stage (1)	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Pre-Testing Stage	1	28/08/2004	30/03/2005
GP/Consultant Information Sheets Qualitative Interview Stage	1	28/08/2004	18/11/2004
GP/Consultant Information Sheets Postal Survey Stage (1)	1	28/08/2004	18/11/2004
GP/Consultant Information Sheets Pre-testing Stage	1	28/08/2004	30/03/2005
GP/Consultant Information Sheets Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Participant Information Sheet Qualitative Interview Stage	1	28/04/2004	18/11/2004
Participant Information Sheet Postal Survey Stage (1)	1	28/08/2004	18/11/2004
Participant Information Sheet Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Participant Information Sheet Pre-testing Stage	2	03/02/2005	30/03/2005
Participant Information Sheet Qualitative Interview Stage	2	03/02/2004	16/03/2005
Participant Consent Form	2	03/02/2005	16/03/2005
Participant Consent	1	03/02/2005	16/03/2005

Form Interview Consent Form			
Participant Consent Form Pre-testing Stage	2	03/02/2005	30/03/2005
Response to Request for Further Information		24/03/2005	30/03/2005
Response to Request for Further Information		10/03/2005	16/03/2005
First Reminder		03/02/2005	16/03/2005
Second Reminder		03/02/2005	16/03/2005
Flowchart		16/03/2005	16/03/2005
Ethnic Origin Sheet	N/A		18/11/2004

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Dr Simon Thomas
Chair

E-mail: sandy.brunton-shiels@durhamclspct.nhs.uk

Enclosures *Standard approval conditions*

APPENDIX XVII

Ethics approval from Brunel University, Uxbridge

Ethics approval confirmation

From: David Bunce [David.Bunce@brunel.ac.uk]
Sent: 11 April 2007 17:31
To: Kantaris, Xenya (Medsch Hampstead/Paediatrics and Child Health)
Cc: Lynn Myers
Subject: Ethics approval confirmation

Re. 'The development of a disease specific measure of the impact of betathalassaemia major (BTM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors' (PhD research: Xenya Kantaris)

This is to confirm that the research ethics approval granted by the Northern and Yorkshire Multi-Centre Research Ethics Committee in relation to the above project (20 April 2005), complies with the research ethics approval procedures required by the School of Social Sciences, Brunel University.

David Bunce

_____
Chair, Research Ethics Committee
School of Social Sciences
Brunel University

--

APPENDIX XVIII

Brunel University sponsor letter

Brunel
UNIVERSITY
WEST LONDON

20th March 2007

Dear Sir/Madam,

Re: The development of a disease-specific measure of the impact of beta-thalassaemia major (BMT), and the examination of the relationship between health related quality of life (HRQoL) adherence and psychosocial factors.

I am writing on behalf of the School of Social Sciences and Brunel University, to confirm our acceptance of the role of Research Sponsor for the above project, being undertaken by Xenya Kantaris.

I confirm that in indicating our acceptance we have considered our responsibilities outlined in section 3.8 of the Research Governance Framework for Health and Social Care (Department of Health), and also checked these arrangements and Xenya Kantaris' research proposal with the University's insurers.

Any enquiries or concerns about Xenya Kantaris' research should be addressed in the first instance to Professor Lynn Myers, Lynn.Myers@brunel.ac.uk, who is her academic supervisor within the School of Social Sciences.

Please contact us if there is anything further that you require.

Yours sincerely,

Professor Michael Wright
Director of Research Programmes

ZURICH
MUNICIPAL

To Whom It May Concern

Our ref: Sue Gammage 11 April, 2007

Zurich Municipal Customer: Brunel University

Zurich Municipal
Southwood Crescent
Farnborough
Hampshire
GU14 ONJ

Telephone 0870 2418050

Direct Phone 01252 387877
Direct Fax 01252 375893
E-mail claire.purdy@zurich.com

This is to confirm that Brunel University have in force with this Company Professional Negligence Insurance until the policy expiry on 31 July 2007:

Policy Number:	NHE-01CA29-0013
Limit of Indemnity:	£ 5,000,000 any one claim
Excess :	£ 250 any one claim

Yours faithfully

C Purdy

Claire Purdy
Underwriting Services
Zurich Municipal
Farnborough

APPENDIX XX

Brunel University data protection letter

Brunel
UNIVERSITY
WEST LONDON

Brunel University, Uxbridge
UB8 3PH, UK
Telephone +44 (0)1895 274000
Web www.brunel.ac.uk

Re: Registration of Personal Data Records

Xenya Kantaris
x.kantaris@medsch.ucl.ac.uk

13 April 2007

Dear Xenya,

This is to inform you that I have received, and am satisfied with, the Registration of Personal Data Records form in relation to your PhD research.

Please ensure that the paper records are adequately protected, preferably in a locked filing cabinet, and securely destroyed when you decide they are no longer required.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Mary F. Liddell
Information Access Officer

APPENDIX XXI

Research and Development (R&D) approval from University College London Hospital (UCLH) and University College London (UCL)

University College London Hospitals NHS
NHS Foundation Trust

Joint UCLH/UCL Biomedical Research (R&D) Unit
Professor Ian Jacobs

Office Location:
1st Floor Maple House
149 Tottenham Court Road
London WC1

Postal Address:
Rosenheim Wing, Ground Floor
25 Grafton Way
London, WC1E 5DB

Email: philip.diamond@uclh.nhs.uk Tel: 020 7380 9833 Fax: 020 7380 9937 Web-site: www.uclh.nhs.uk

24 July 2007

Dr A Manderville
Pain Management
NHNN

Dear Dr Manderville,

Project ID: **07/0071 (*Please quote in all correspondence*)**
Title: **The development of a disease specific measure of the impact of beta-thalassaemia major and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors**

Thank you for registering the above study with the R&D Directorate. I am pleased to give the approval of UCL Hospitals NHS Foundation Trust for the study to proceed.

You will be aware that as principal investigator you have various responsibilities under the Department of Health's *Research Governance Framework for Health and Social Care*. Please note that you are required:

- to comply with the UCLH Information Security Policy (the R&D Directorate's data protection toolkit "Consent and Security" will help you meet the requirements of the Data Protection Act and is available at http://www.uclh.org/services/research/.
- to ensure that any co-investigator who is not an employee of UCLH has in place an up-to-date honorary contract.
- to keep copies of all consent forms with your project documentation. UCLH carries out audits of informed consent and if your project is selected for audit, you will need to provide access to the consent forms.

Please ensure that you have addressed any outstanding issues raised by the research ethics committee and have full ethical approval before you start your project. Also you must ensure that you comply with all the requirements of the ethics committee regarding progress reports, notification of protocol amendments and adverse events.

You are strongly recommended to use an investigator file to store all the documentation relating to this research project. This will help facilitate the research audit process which is now a research governance requirement. The attached list of headings is designed to help you assemble your investigator file.

Yours sincerely

pp P.O...

Professor Ian Jacobs
Director of R&D, UCL Hospitals NHS Foundation Trust

APPENDIX XXII

R&D approval from the Whittington Hospital

The Whittington Hospital NHS
NHS Trust

Research & Development
Dept of Medicine
Clerkenwell Building
Archway Campus
Whittington Hospital
Highgate Hill
London
N19 5LW

Tel: 020 7288 5269

Dr Anna L Mandeville
Consultant Clinical Health Psychologist
Camden&Islington Mental Health& Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
London
WC1N1BN

7th May 2006

Dear Dr Mandeville,

Title: The development of a disease specific measure of the impact of beta-thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL)

REC Ref: 04/MRE03/88

I am pleased to note that Northern and Yorkshire Multi-centre Research Ethics Committee reviewed this study and concluded that there is no ethical objection to this research being conducted at this site.

The R&D Department has also reviewed this study and is satisfied that it meets the necessary research governance standards. The R&D Department is pleased to give the approval of the Whittington Hospital NHS Trust for this research to proceed according to the study protocol. This approval is only valid concurrently with the appropriate ethical consideration for this study and is therefore subject to the conditions set out by Northern and Yorkshire Multi-Centre Research Ethics Committee and the conditions set out in this letter. Should you fail to adhere to these conditions, the Trust would consider your approval to undertake research to be invalid.

The study has been registered with the finance department who will contact you directly regarding any queries over the financial aspects of this study.

Please note that an honorary researcher contract is being arranged for Ms Kantaris, the researcher at this site and she should be in receipt of that before research work begins.

You will be aware that as chief/principal investigator you have various responsibilities under the Department of Health's *Research Governance Framework for Health and Social Care*. Please be reminded of your responsibilities as outlined in Appendix A to this letter.

All researchers undertaking research within the Trust are reminded of their duties and responsibilities under the Health and Safety at Work Act 1974, contained in

Appendix B and the Data Protection Act 1988 contained in Appendix C to this letter. Further information on the research governance framework for health and social care can be found on the DH web pages at:

Staff working within the Trust can also find the information on the Trust Intranet.

Conditions of approval:

- This approval is subject to your consent for information about your project to be included in NHS project registration/management databases and, where appropriate, the DoH National Research Register and the UCL Clinical Research Network register.
- Except in the case of commercially funded research projects, the following acknowledgement must appear in all publications arising from your work.

  "This work was undertaken by [investigators name] with the support of the Whittington Hospital NHS Trust, who received ["funding" or a "proportion of funding"]*from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the NHS Executive".

  * "a proportion of funding" where the research is also supported by an external funding body;
  * "funding" where no external funding has been obtained

- The R&D Office and appropriate LREC must be informed of any amendments to the protocol, including changes in study personnel.
- The R&D Office and appropriate LREC must be informed of any adverse events occurring at the Whittington study site or unexpected results that may affect the safety of the research. All adverse events must be reported following the Trust's Adverse Incident Reporting Policy.
- A Progress Report Form must be submitted to the R&D office and LREC one-year from the start of the study and thereafter on an annual basis. This form should also be used to notify the R&D Office and LREC when your research is completed and should be sent within 3 months of completion.
- The Trust will be carrying out audits of informed consent and checking compliance with other ethical and governance requirements. You are strongly advised to use an investigator file to store all the study documentation and to keep copies of all

consent forms in this file to help facilitate the research audit process. You will be notified in writing if your study is selected for audit.

Yours sincerely,

Senga Steel
Lead Research Nurse (R&D Manager)

Cc: Dr Farrukh Shah (Principal Investigator), Xenya Kantaris, Research Fellow

APPENDIX XXIII

R&D approval from Luton and Dunstable Hospital

HQS
accredited by the
Health Quality Service

The Luton and Dunstable Hospital

Associated Teaching Hospital of the University of London NHS Trust

NHS

Lewsey Road
LUTON
LU4 0DZ

Switchboard: 0845 127 0127

DEPARTMENT OF RESEARCH AND DEVELOPMENT
R&D Director: Dr. C. M. Travill

R&D Manager: Diana Hardy
Direct telephone: ++44 (0) 1582 718243
Fax: ++44 (0) 1582 718244
E-mail: diana.hardy@ldh.nhs.uk

R&D Assistant: Joanne Stanley
Direct telephone: ++44 (0) 1582 497253
Fax: ++44 (0) 1582 718244
E-mail: joanne.stanley@ldh.nhs.uk

Our ref: CMT/djh

3rd May, 2006

Dr. Daniel Thompson
Consultant Haematologist,
Luton & Dunstable Hospital NHS Trust

Dear Dr. Thompson,

Re: The development of a disease specific measure of the impact of beta-thalassaemia major ™ and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors

Thank you for submitting your research application in respect of the above. I am pleased to inform you that this project, which has been given Site-Specific Assessment approval by LREC to be carried out at the Luton & Dunstable Hospital, has been approved by the Research & Development Department.

I would like to take this opportunity of informing you that should any amendments be made to the project, e.g. protocol, consent form, patient information sheet, etc. it is your responsibility to inform not only LREC but also the Research & Development Department of these changes. I would also like to inform you that the Trust has appointed a Specialist Research Practitioner, whose primary responsibility is to monitor and report on research projects approved by the Trust (in compliance with the Research Governance Framework). The Specialist Research Practitioner may make contact with you to arrange a date to visit and monitor your research project.

I should be grateful to receive a follow up on the progress of the project in six months and attach a form for this purpose. Thereafter, please update me on progress at six monthly intervals.

Yours sincerely,

Dr. Christopher M. Travill
Director of Research & Development

c.c. Mrs Xenya Kantaris, PhD Psychology Student, Brunel University, Department of Human Sciences, Uxbridge Campus, Middlesex UB8 3PH

Enc:

APPENDIX XXIV

Site specific assessment letter from the Northern and Yorkshire Research Ethics Committee

NHS

Northern and Yorkshire Research Ethics Committee

Room 215
TEDCO Business Centre
Viking Industrial Park
Jarrow
Tyne & Wear NE32 3DT

Telephone 0191 4283545/4283438 Fax 0191 4283303

Bill Hackett (Co-ordinator) e-mail: bill.hackett@suntpct.nhs.uk
Helen Wilson (Asst Co-ordinator) e-mail: helen.wilson@suntpct.nhs.uk

29 January 2007.

Ms Xenya Kantaris
7 Church Drive
London
NW9 8DN

Dear Ms Kantaris,

Full title of study: ***The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors***

REC reference number: ***04/MRE03/88***

I am writing to clarify the position in respect of Site Specific Assessment for the above study. As you are aware, the Northern and Yorkshire Research Ethics Committee is the Main REC for this study in the UK and in 2004 we gave a favourable opinion to the study in terms of ethical implications.

Under the Standard Operating Procedures for Research Ethics Committees in the UK, (paragraph 4.22, page 101), the appointment of local collaborators to this study does not require formal approval either by Local Research Ethics Committees or the Main REC although local collaborators should still seek research governance approval from the Research and Development Department for the care organisation where the collaborators are located and from where they will be assisting with the study.

The status of study 'collaborators' is quite different to that of 'Principal Investigators' and it is accepted that you have correctly differentiated and understood the differences between these two groups in appointing collaborators to assist in the study.

Our understanding is that your actions were correct in managing the process of appointing collaborators to various sites for this study.

Yours sincerely,

Bill Hackett ONC(Business studies);CMS;DMS;MBA
Committee Coordinator.

APPENDIX XXV

Site specific assessment approval letter

Northern & Yorkshire MREC
Sunderland Teaching Primary Care Trust (South Office)
Admin corridor
Ryhope Hospital
Ryhope
Sunderland
SR2 0LY

Telephone: 0191 5699515
Facsimile: 0191 5699545

24 April 2006

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Full title of study:	**The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors**
REC reference number:	**04/MRE03/88**

The REC gave a favourable ethical opinion to this study on 04 April 2005.

Further notification(s) have been received from local site assessor(s) following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s). I attach an updated version of the site approval form, listing all sites with a favourable ethical opinion to conduct the research.

Research governance approval

The Chief Investigator or sponsor should inform the local Principal Investigator at each site of the favourable opinion by sending a copy of this letter and the attached form. The research should not commence at any NHS site until research governance approval from the relevant NHS care organisation has been confirmed.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88	**Please quote this number on all correspondence**

Yours sincerely

Mr Bill Hackett
Committee Co-ordinator

Email: bill.hackett@suntpct.nhs.uk

Enclosure: *Site approval form*

Copy to: School Research Committee
Brunel University
Uxbridge Campus
Middlesex
UB8 3PH

Northern & Yorkshire MREC

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	04/MRE03/88	**Issue number:**	5	**Date of issue:**	24 April 2006
Chief Investigator:	Dr. Anna L. Mandeville				
Full title of study:	The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors				

This study was given a favourable ethical opinion by Northern & Yorkshire MREC on 04 April 2005. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes (1)*
Dr Farrukh Shah	Consultant Haematologist	Whittington Hospital NHS Trust	Moorfields & Whittington Local Research Ethics Committee	27/01/2006	
Dr Daniel S Thompson	Consultant Haematologist	Luton & Dunstable Hospital NHS Trust	Bedfordshire Local Research Ethics Committee	24/04/2006	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Administrator)
(delete as applicable)

..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

APPENDIX XXVI

Departmental honorary contract for UCLH/UCL

UNIVERSITY COLLEGE LONDON HOSPITALS NHS TRUST

TERMS OF PLACEMENT AS HONORARY APPOINTEE

Name:	**Xenya Kantaris**
Home Address:	**7 Church Drive** **The Hyde** **LONDON** **NW9 8DN**
Placement Title:	**Research/Observer**
Place of Work or Main Base:	**UCLH Red Cell Team in Haematology**
Starting Date of Honorary Appointment:	**[illegible]gust 20[illegible]**
Expire Date:	**1st August 2006**
Responsible to:	**Dr Anna Manderville and [illegible]ssor J B Porter**

FURTHER CONDITIONS

1. This honorary appointment will enable you to undertake your role as Research/Observer for UCL Hospitals NHS Foundation Trust.

2. Your honorary attachment to the Trust does not constitute employment and you will not be entitled to any form of payment on its cessation. For the avoidance of doubt, this appointment does not constitute an employment relationship.

3. **RESEARCH GOVERNANCE**

University College London Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. All research active appointees must familiarise themselves with the UCL Hospitals NHS Trust policies for research governance and be aware of the obligations this places on them. You must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. You are reminded that any breach in research governance policy will result in appropriate action. This may include discontinuation of your honorary appointment and cessation of your involvement with all research at UCL Hospitals NHS Trust.

4. **PROFESSIONAL REGISTRATION**

Dependent upon the nature of your role, you may be required to be registered with a relevant professional body eg GMC, NMC, CPSM.

A copy of confirmation of your professional registration should be attached and returned with this document.

A copy of your registration renewal document must also be provided to the Trust.

Failure to be registered with the appropriate professional body, and to maintain professional registration, may result in your honorary appointment being terminated.

5. PRE-APPOINTMENT HEALTH SCREENING

This honorary appointment is conditional upon confirmation of your medical fitness to undertake the full duties of the honorary appointment.

6. CRIMINAL RECORDS/CONVICTIONS

This honorary appointment is exempt from the Rehabilitation of Offenders Act 1974. It is therefore essential that you disclose conviction(s), that would otherwise be "spent" under the provisions of the Act, and that you have notified the Trust if you are are "bound over", have received a police caution, warning or reprimand or if you have been charged with a criminal offence that is not yet disposed of.

In cases where the role of the honorary appointment is defined as a "regulated position" under the terms of the Protection of Children Act 1999 (as amended by the Criminal Justice and Court Services Act 2000), checks will be carried out by the Criminal Records Bureau in accordance with the Protection of Children Act 1999. It is an offence for someone who is legally barred from working with children to knowingly apply for, offer to do, accept or do such work. Appointees will be notified if their appointment is designated as a "regulated position" and therefore subject to the above checks.

If you are convicted of a criminal offence whilst an appointee of the Trust, you must inform your manager of the nature of the conviction even if it does not relate to your work. Dependent upon the nature of the conviction and details of the sentence, the continuation of your honorary appointment may not be put at risk. However, the Trust reserves the right to terminate your appointment in relation to any such conviction or sentence.

7. CONFIDENTIALITY

During the course of your honorary appointment, you will have access to information of a confidential nature including (but not exclusively) patient and staff information. This information must be treated as strictly confidential at all times.

All appointees must familiarise themselves with the UCL Hospitals NHS Trust Information Governance Policy and be aware of the obligations it places on them. A breach of confidentiality will result in appropriate action, which may include discontinuation of your honorary appointment, being taken.

8. VALUING DIVERSITY

UCL Hospitals NHS Trust undertakes to provide equality of opportunity in its twin role as employer and provider of health services.

All appointees have a personal responsibility towards the public and their colleagues for the implementation of the Equal Opportunities Policy within their duties.

Appointees should familiarise themselves with the Equal Opportunities Policy and be aware of the obligation it places on them and the individual rights extended to them.

9. HEALTH, SAFETY, FIRE & SECURITY

9.1 Occupational Health

Occupational Health aims to make sure that appointees are fit for their work and are not becoming ill because of work. This means promoting the physical and mental health, safety and welfare of all working in the Trust, both by seeing individuals with problems and by advising management on measures to safeguard staff.

9.2 No Smoking Policy

The Trust has a policy of restricting smoking to designated areas as part of it's responsibility for the promotion of health. Smoking is not permitted in public areas and there may be a local agreement prohibiting or restricting it in the place where you work.

9.3 Safety at Work

It is the policy of the Trust to give the greatest importance to the health and safety of appointees, considering this is a management responsibility equal to that of any other managerial task.

Appointees are responsible for following all health, safety and hygiene regulations, as laid down locally from time to time and are required to play their full part in ensuring the safety of others.

In the event of an accident occurring to an appointee in the course of their work, the facts should be immediately reported to your supervisor who will decide on the arrangements for any necessary medical treatment. In the event of an accident, an accident report form must be completed by the injured party and any witnesses and be signed by the supervisor.

It should be noted that Trusts and individuals are not exempt from statutory enforcement procedures and will be subject to prosecution for failure to discharge their duties under the Health & Safety Act 1974. Should appointees not comply with health, safety and hygiene regulations, appropriate action will be taken.

9.4 Ionising Radiation (Medical Exposure) Regulations 2000

Under the above Regulations, the Trust is obliged to maintain a register of all persons entitled to act as Practitioners or Operators (ie to justify or to carry out a medical exposure) and to keep records of their training.

If your post includes the responsibilities of either Practitioner or Operator as defined by these regulations, you must provide the Trust with evidence of training. This should include evidence of completion of an approved training course plus details of practical experience.

Please note that if, during the course of your duties, you refer a person for a medical exposure you are obliged to provide sufficient relevant clinical information to the Practitioner who justifies the use of ionising radiation. You are expected to follow any guidelines for such referrals that the Trust provides.

9.5 Investigation of Untoward Incidents

All appointees are expected to assist management fully in the investigation of incidents by supplying written statements and, where appropriate, acting as a witness.

9.6 Fire Precautions

It is your responsibility to make sure that you are aware of the procedure to be followed on discovering a fire or hearing a fire alarm. Appointees should attend at least one period of fire training each year.

9.7 Personal Indemnity

The Trust has Public Liability Insurance which will cover you while you are on Trust premises, on Trust business or working for the benefit of the Trust against accidental injury.

Additionally, the Trust will provide coverage for negligent acts or omissions by you which occur whilst on Trust premises and whilst you are acting in your professional capacity in the course of your honorary appointment with NHS patients of the Trust. This coverage will not apply where your acts are recklessly negligent or criminal, occur outside the course and scope of your honorary position with the Trust or result from contact with non-Trust patients or employees. For this coverage to apply, you must notify the Trust of an incident or occurrence which has resulted in an injury or possible injury to a patient within 48 hours of the incident or occurrence or the date of knowledge or discovery of the incident or occurrence. This coverage does not extend to work which does not fall within the scope of the NHS indemnity for clinical negligence. It does not cover non-NHS and private practice work, for which the Trust would encourage you to ensure that you have adequate and appropriate defence cover to cover you for such work.

9.8 Security

The security of property belonging to the Trust, appointees and the public at large is a matter which must be the concern of every member of staff. In this respect, appointees are required to assist management in maintaining and improving security.

9.9 Identification Badges

If you are issued with an identity badge, it should be worn visibly all the time you are on duty or on site. If you are issued with an identity badge, it must be returned should you leave the Trust. If you lose the badge at any time, this must be reported to your manager.

9.10 Property and Claims for Compensation

You must comply with local regulations with regard to patients' cash/property. You are also asked to ensure that all property of the Trust in your charge is correctly used. Furthermore, it is your duty to report any loss or accidents which may give rise to a claim for compensation to your manager. In addition, you should also report any suspect fraud or theft.

9.11 Property Disclaimer

The Trust cannot accept responsibility for money/property lost or damaged on Health Service premises and strongly recommends appointees to consider taking out insurance policies to cover themselves against such a loss. Whilst lockers may be provided, these are intended for the convenience of appointees and no responsibility can be accepted for money, jewellery or similar valuables stolen from these lockers. Appointees providing their own tools or equipment belonging to them should take out their own insurance policies against theft or fire.

10. INTELLECTUAL PROPERTY (IP)

10.1 Intellectual Property (IP) may be generated during the course of your honorary appointment that may have value in the delivery of better patient care.

10.2 IP can be in the form of inventions, discoveries, surgical techniques or methods, developments, processes, schemes, formulae, specifications, or any other improvements which may give rise to certain rights such as patents, trade marks, service marks, design rights, copyright, know-how, trade or business names and other similar rights (all of the foregoing rights being referred to as "Intellectual Property Rights" or "IPR")

10.3 Potential IPR means any works, information or other elements from which IPR may derive.

10.4 You and the Trust confirm it is foreseeable that IPR may arise in the course of or in connection with your honorary appointment to the Trust.

10.5 Cases involving IPR and/or Potential IPR will be managed in accordance with the Trust's management procedures for intellectual property (IP). These procedures have been approved by the Trust Board and are available on request from the Research & Development Directorate and are consistent with the Management Framework for IP of the Department of Health.

10.6 IPR and/or Potential IPR created during the course of your honorary appointment will generally belong to the substantive employer or the Trust, unless agreed otherwise in writing.

10.7 Where you consider that IPR and/or Potential IPR has been created, you shall promptly notify the Research & Development Directorate providing full details.

11. TERMINATION OF HONORARY PLACEMENT

If your honorary appointment with the Trust arises as a result of your employment by another body (being either an NHS Trust or an academic establishment) should your employment terminate with that NHS Trust or academic establishment, your honorary appointment will terminate immediately. You are required to inform the Trust should such employment be terminated.

If you have any queries regarding the terms of your honorary placement, please contact your manager or Human Resources Manager.

Please sign both copies of the Terms of Placement as Honorary Appointee and return one signed copy to the relevant Human Resources Department (see below), keeping the remaining copy for yourself.

Signed: Jacqueline Gentles **Date:** 12.9.05

Print Name: Jacqueline Gentles

Job Title: Human Resources Officer
Human Resources Department

I ACKNOWLEDGE RECEIPT OF MY TERMS OF HONORARY PLACEMENT AND ACCEPT THE TERMS AND CONDITIONS SET OUT THEREIN.

Signed: ..... **Date:** 13.8.05

Print Name: XENYA KANTAKI

PLEASE RETURN ONE SIGNED COPY TO:-

THE HUMAN RESOURCES DEPARTMENT
UCL HOSPITALS NHS TRUST
2ND FLOOR, EAST WING
250 EUSTON ROAD
LONDON
NW1 2PQ

It is your responsibility to maintain appropriate knowledge of these guidelines and regulations and any others associated with research. Further information on Research Governance and the EU Directive can be obtained from the Trust's R&D department.

Progress Reporting

As a researcher at the Whittington Hospital you are required to provide the R&D department with an annual progress report and end of study report. You are also required to meet with the R&D Director, or a designated deputy, regularly throughout the course of the study to discuss how the research is progressing and identify difficulties associated with your research.

Data Protection

If you are required to obtain, process or use personal identifiable information either held on a computer, paper or audio-visual equipment you must do so in accordance with the Data Protection Act (1998). No exemptions or exceptions to compliance with the Act should be assumed without written consent from the Trust's Data Protection Officer.

You should be both familiar, and fully compliant, with any Trust policies and procedures that have been put in place to protect personal identifiable data of staff and patients. Further details on Data Protection are available from the IM&T department.

Confidentiality

All personal information regarding staff or patients received during the course of your employment with the Whittington Hospital NHS Trust, either directly or indirectly, must at all times be treated as confidential. Patient information must be handled in compliance with the Trust Caldicott policies and procedures. Further details are available from the IM&T Department.

Information should not be transmitted to any third party, except in the normal course of your duties, without the express written consent of the Whittington Hospital NHS Trust. Any breach of confidentiality will result in disciplinary action, and may be regarded as gross misconduct.

Medical staff only: this paragraph should be read in conjunction with paragraph 330 of the Hospital Medical and Dental Terms and Conditions of Service, which reads:

"A practitioner shall be free, without prior consent of the employing authority, to publish books, articles etc and to deliver any lecture or speak, whether on matters arising out of his or her hospital service or not."

Intellectual Property

All staff including those on honorary contracts must declare to the Whittington Hospital NHS Trust any i) financial interests or relationships ii) intellectual property development implications or iii) issues relating to financial probity, that could affect the Trust's decisions or policies. All staff must comply with any reporting requirements, systems and duties of action put in place by the Trust in this respect including the Trust's Standard Financial Instructions and Intellectual Property Policy

Health and Safety

You are required to adhere to any reasonable security procedures implemented by the Trust in the interests of the safety and the efficiency of the service, with regard to the Health and Safety at Work Act. You shall not intentionally or recklessly interfere with, or misuse, anything provided in the interests of health, safety or welfare. You must familiarise yourself with the routine to be followed in the event of a fire.

Personal Property
The Whittington Hospital accepts no responsibility for damage to, loss of, personal property, you are therefore, recommended to take out an insurance policy to cover your personal property.

Although applicable to employees, the principles of both the health and safety documents and the disciplinary rules may be applied directly to the terms of your attachment. The grievance procedure and disciplinary policy should also be interpreted as referring to your honorary attachment wherever there is reference to "employees" or "service" although your rights of appeal cannot extend beyond the Trust Board i.e. as far as possible the policies and procedures applicable to you shall mirror those of the Trusts employees. Copies of these documents are available from the Human Resources Department.

Please fill out the enclosed form for your pre-employment health check and return directly to Occupational Health. Upon commencement, you must visit Occupational Health to obtain health clearance. You can book an appointment on 0207 288 3351.

If you agree to accept the appointment on the terms specified above, please sign the form of acceptance at the foot of this letter and return it to me. A second copy of this letter is attached and should be retained by you for future reference.

May I take this opportunity to wish you a successful and satisfying period with this Hospital.

Meanwhile, please contact me if you have any queries on 020 7288 5128.

Yours sincerely

Vicki McManus
Human Resources Advisor
On behalf of The Whittington Hospital NHS Trust

I acknowledge I have received and retained a copy of this statement and understand and accept the contents therein.

Name: .....

Date: .....

APPENDIX XXVIII

Notification of amendment approval letter (1/3)

20 July 2007

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Study title: **The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors**

REC reference: **04/MRE03/88**
Amendment number: **Modified Amendment 1**
Amendment date: **02 July 2007**

Thank you for submitting the above amendment, which was received on 09 July 2007. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 12 June 2007 refers).

The modified amendment was considered at the meeting of the Sub-Committee of the REC held on 20 July 2007. A list of the members who were present at the meeting is attached.

Ethical opinion

The proposals are acceptable. I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Modified Amendment	Modified Amendment 1	02 July 2007

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88:	**Please quote this number on all correspondence**

Yours sincerely

Mr Bill Hackett
Committee Co-ordinator

E-mail: bill.hackett@suntpct.nhs.uk

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

Northern & Yorkshire REC

Attendance at Sub-Committee of the REC meeting on 12 June 2007

Dr P Carey, Consultant Haematologist
Dr J Gray, Statistician
Mr M Davidson, Lay member
(Mr W Hackett, Committee Coordinator)

Northern & Yorkshire REC

Attendance at Sub-Committee of the REC meeting on 20 July 2007

Dr F Douglas, Human Geneticist
Dr P Carey, Consultant Haematologist
Mr M Davidson, Lay member
(Mr W Hackett, Committee Coordinator)

12 June 2007

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Study title: **The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors**

REC reference: **04/MRE03/88**

Amendment number: **Notification of Substantial Amendment Form**
Amendment date: **23 April 2007**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 12 June 2007.

Ethical opinion

The members of the Committee present decided that they could not give a favourable ethical opinion of the amendment, for the following reasons:

The Committee would like clarification on what the patient has agreed to in terms of confidentiality and the sharing of information. Also, can you please advise whether the questionnaire is additional or a replacement. We regret to inform you that the amendment is therefore not approved. The study should continue in accordance with the documentation previously approved by the Committee.

Modifying the amendment

You may modify or adapt the amendment, taking into account the Committee's concerns. Modified amendments should be submitted on the standard Notice of Amendment form. The form should indicate that it is a modification of the above amendment.

A revised Notice of Amendment form must be submitted at least 14 days before you plan to implement the amendment. The Committee will then have 14 days from the date of

receiving the notice in which to notify you that the amendment is rejected, otherwise the amendment may be implemented.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	Notification of Substantial Amendment Form	23 April 2007
Questionnaire	About You questionnaire Version 1	11 September 2006

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88: **Please quote this number on all correspondence**

Yours sincerely

Mr Bill Hackett
Committee Co-ordinator

E-mail: bill.hackett@suntpct.nhs.uk

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

APPENDIX XXIX

Notification of amendment approval letter (2/3)

NHS

Northern and Yorkshire Multi-Centre Research Ethics Committee

Direct Dial: 0191 374 4151
Facsimile: 0191 374 4102

Northern & Yorkshire MREC
John Snow House
Durham University Science Park
Durham DH1 3YG

23 May 2007.

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Full title of study: ***The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors***

REC reference number: ***04/MRE03/88***

Protocol number:

Thank you for your letter of 24 March 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application amended		15/11/2004	16/03/2005

Investigator CV Dr Anna L Mandeville	N/A		18/11/2004
Investigator CV Xenya Kantaris	N/A		18/11/2004
Investigator CV Afsane Riaza	N/A		18/11/2004
Protocol	1	01/08/2004	18/11/2004
Covering Letter	N/A	14/11/2004	18/11/2004
Interview Schedules/Topic Guides	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Qualitative Interview Stage	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Postal Survey Stage (1)	1	28/08/2004	18/11/2004
Letters of Invitation to Participants Pre-Testing Stage	1	28/08/2004	30/03/2005
GP/Consultant Information Sheets Qualitative Interview Stage	1	28/08/2004	18/11/2004
GP/Consultant Information Sheets Postal Survey Stage (1)	1	28/08/2004	18/11/2004
GP/Consultant Information Sheets Pre-testing Stage	1	28/08/2004	30/03/2005
GP/Consultant Information Sheets Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Participant Information Sheet Qualitative Interview Stage	1	28/04/2004	18/11/2004
Participant Information Sheet Postal Survey Stage (1)	1	28/08/2004	18/11/2004
Participant Information Sheet Postal Survey Stage (2)	1	28/08/2004	18/11/2004
Participant Information Sheet Pre-testing Stage	2	03/02/2005	30/03/2005
Participant Information Sheet Qualitative Interview Stage	2	03/02/2005	16/03/2005
Participant Consent Form	2	03/02/2005	16/03/2005
Participant Consent	1	03/02/2005	16/03/2005

Form Interview Consent Form			
Participant Consent Form Pre-testing Stage	2	03/02/2005	30/03/2005
Response to Request for Further Information		24/03/2005	30/03/2005
Response to Request for Further Information		10/03/2005	16/03/2005
First Reminder		03/02/2005	16/03/2005
Second Reminder		03/02/2005	16/03/2005
Flowchart		16/03/2005	16/03/2005
Ethnic Origin Sheet	N/A		18/11/2004

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Dr Simon Thomas
Chair

E-mail: sandy.brunton-shiels@durhamclspct.nhs.uk

Enclosures *Standard approval conditions*

APPENDIX XXX

Letter of invitation postal survey 1

University College London Hospitals NHS
NHS Foundation Trust

Version 1/Postal Survey Stage (1)
28th AUGUST 2004

Dear patient,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

We are writing to you to invite you to take part in the first postal survey of the above named research study. My research team and I are trying to develop and validate a scale to measure the impact of beta-thalassaemia major (BTM). Further information about the study is enclosed.

Part of the study will involve you filling out the enclosed questionnaire and other documents about yourself.

Your agreeing to take part in this study is entirely voluntary and all information will be kept strictly confidential. If you decide not to take part in this study, any treatment you will continue to receive for your thalassaemia will not be affected.

If you are interested in taking part in this research, kindly complete and sign the documents enclosed and return them to us in the pre-paid envelope. If you would like to discuss any of the above do not hesitate to telephone me on 07811 158 461.

Best wishes,

Yours sincerely,

Dr. Anna Mandeville
Principal Research Investigator
Consultant Clinical Health Psychologist; Honorary Research Fellow, UCLH

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXI

PIS postal survey 1

Version 1/Postal Survey Stage (1)
28th August 2004

Note: If you have decided not to participate in this research and/or you are not a beta-thalassaemia major (BTM) patient kindly return the research documents blank.

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

You are being invited to take part in the above named research study. Before you decide in participating, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Do ask the research team if there is anything that is not clear or if you would like more information. Take the time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

We would like to invite you to take part in a research study which aims to develop and validate a scale which will assess the impact of beta-thalassaemia major (BTM) upon patients. When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help us understand this in BTM we need a questionnaire specifically designed to ask those questions that are relevant to patients with BTM. We have just developed such a questionnaire. The questionnaire enclosed was developed directly from interviews with people with BTM. The questions are based on what people told us about the effect of BTM on their lives. We would like you to complete this questionnaire so that we can test the usefulness of it by comparing it to other questionnaires, so that we can develop a shorter version of it.

Why have I been chosen?

We are looking for volunteers who have BTM and are aged over 18 years. Your name has been chosen from the membership database at the UK Thalassaemia Society (UKTS).

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, which you may keep. If you decide to take part you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We are looking for volunteers who would be prepared to complete the enclosed questionnaire and documentation and return them to us, in the pre-paid envelop provided. There are a few questions and so it may take around 10 minutes to complete. The questions are about your

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

personal views and beliefs about a range of issues. For most of the questions you would just need to tick a box to indicate your answer; there is very little involved. However, it would be okay for someone else to help you to complete the forms, if this would be easier for you. Also, it is okay to take breaks between the different sections of the questionnaire, if it is too tiring or you are too busy to complete it in one go.

If you do not wish to participate in this study, you need to take no further action. If the questionnaire is not returned, we will presume that you are unable to participate. Do not worry, as we realise that it would not be possible for everyone to take part.

Are there any possible benefits or risks involved in taking part?

As this research is only attempting to find out about your existing views, it is not thought that taking part should involve any significant risks to you. However, if you do find that the interview raises any concerns for you, please contact the principal investigator who will be able to discuss this with you.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism may be available to you.

Similarly, it is not thought that taking part in this study will have any direct impact on you but by talking part in this research you will be helping to design a questionnaire that will help to assess how effectively we are treating patients with TM. The questionnaire is also likely to be used to evaluate new treatments of TM as they are developed.

Will my taking part in this study be kept confidential?

Only the research team and your GP will know that you have taken part in this study. Your GP will be sent a letter to let him/her know that you have taken part in this study, if you so wish. All your responses will be used anonymously to help us to develop the questionnaire.

What will happen to the results of the research study?

The results of the study will be likely to be published but you will not be identified in any report or publication arising from this study.

Who is funding the research?

The Thalassaemia International Federation (TIF) in Cyprus, Nicosia, is currently liaising with pharmaceutical companies regarding financial support for this project.

Who has reviewed the study?

The study will be reviewed by the UK Thalassaemia Society (UKTS), University College Hospital (UCH) and Brunel University. Whilst the UKTS support this research it should be noted that this project is independent to those commissioned by the UKTS.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Who do I contact for further information?

If you have any questions about the study, please do not hesitate to contact the principal investigator, Dr. Anna Mandeville on 07989 306514 and/or lead researcher, Xenya Kantaris on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXII

Consent form postal survey 1 and 2

Version 2
3rd February 2005

Centre Number:
Patient Identification Number (ID):

CONSENT FORM

Title of Project: A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

Name of Principal Investigator: Dr. Anna Mandeville
Name of lead research psychologist: Xenya Kantaris

Please initial box

1. I confirm that I have read and understand the information sheet dated ....., version ....., for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

4. I agree to my GP being informed of my participation in this study*. ☐

*This is optional. Please provide details below if you wish.

GP details:

Name of patient	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

1 copy to be sent to the patient; 1 copy for the researcher; 1 copy to be kept with hospital notes

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXIII

G.P. information sheet postal survey 1

Version 1/Postal Survey Stage (1)
28th August 2004

GP Information Sheet for < Insert Patient Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

This is an information sheet for all General Practitioners whose patients have recently taken part in a phase of the above study.

The aim of the study is to develop a scale of the impact of beta-thalassaemia major (BTM). When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help understand this in BTM we need a questionnaire specifically designed to ask the questions that are relevant to patients with BTM. We have just developed such a questionnaire.

Your patient has recently completed this questionnaire so that we can test the usefulness of it by comparing it to other questionnaires, so that we can develop a shorter version of it.

We have been recruiting patients who have BTM and are aged over 18 years from the UK Thalassaemia Society's membership database.

If you have any questions about the study, please do not hesitate to contact the research team's researcher, Xenya Kantaris, on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXIV

Item Discriminant Validity (item reduction stage)

Item Discriminant Validity (item reduction stage) **Appendix XXXIV**

Scale Item	General	Coping	Body	Social	Autonomy
G1 (Q1)	0.780**	0.41**	0.15	0.16	-0.07
G2 (Q2)	0.87**	0.57**	0.24*	0.24*	0.01
G3 (Q3)	0.77**	0.40**	0.25*	0.15	0.11
G4 (Q5)	0.88**	0.44**	0.23*	0.27*	0.15
G5 (Q11)	0.72**	0.41**	0.35**	0.23*	0.07
G6 (Q12)	0.74**	0.25**	0.26*	0.28**	0.10
G7 (Q14)	0.81**	0.53**	0.32**	0.24*	0.14
C1 (Q17)	0.49**	0.84**	0.46**	0.30**	0.17
C2 (Q18)	0.50**	0.86**	0.30**	0.18	0.13
C3 (Q19)	0.49**	0.91**	0.44**	0.25*	0.20
C4 (Q21)	0.48**	0.86**	0.38**	0.30**	0.22
C5 (Q22)	0.33**	0.84**	0.230**	0.07	0.03
C6 (Q23)	0.43**	0.83**	0.29**	-0.01	-0.08
C7 (Q27)	0.41**	0.84**	0.44**	0.04	-0.01
B1 (Q35)	0.14	0.11	0.74**	0.14	-.004
B2 (Q36)	0.25*	0.29**	0.70**	-0.09	-0.19
B3 (Q37)	0.31**	0.34**	0.68**	0.08	-0.10
B4 (Q38)	0.15	0.28*	0.73**	0.20	0.00
B5 (Q41)	0.03	0.14	0.77**	0.58**	0.57**
B6 (Q42)	0.44**	0.52**	0.63**	0.57**	0.52**
B7 (Q43)	0.36**	0.42**	0.66**	0.58**	0.50**
S1 (Q49)	0.29**	0.28**	0.42**	0.70**	0.68**
S2 (Q50)	0.21	0.06	0.13	0.62**	0.27*
S3 (Q52)	0.09	0.26*	0.50**	0.60**	0.42**
S4 (Q53)	0.29**	0.19	0.35**	0.80**	0.47**
S5(Q54)	0.25*	0.24*	0.37**	0.71**	0.34**
S6(Q56)	0.48**	0.38**	0.36**	0.83**	0.52**
S7(Q57)	0.45**	0.31**	0.27*	0.678**	0.72**
A1(Q48)	0.16	0.19	0.13	0.24*	0.82**
A2(Q58)	0.38**	0.20	0.28*	0.56**	0.90**
A3(Q59)	0.45**	0.33**	0.26*	0.58**	0.90**
A4(Q60)	0.47**	0.40**	0.33**	0.53**	0.90**
A5(Q61)	0.40**	0.41**	0.37**	0.50**	0.90**
A6(Q62)	0.05	0.30**	0.29**	0.12	0.80**
A7(Q63)	0.05	0.30**	0.31**	0.09	0.84**

G =GPH, C= C, B=BIAC, S=SR, A= A. * Correlation is significant at the 0.05 level (two tailed). ** Correlation is significant at the 0.01 level (two tailed).

APPENDIX XXXV

Reliability: alphas if item deleted (item reduction stage)

Reliability: alphas if item deleted (item reduction stage) **Appendix XXXV**

Scale (Alpha)	General (0.90)	Coping (0.94)	Body (0.83)	Social (0.83)	Autonomy (0.94)
Scale Item	**Alpha if item deleted**	**Alpha if item deleted**	**Alpha if item deleted**	**Alpha if item deleted**	**Alpha if item deleted**
G1 (Q1)	$\alpha = 0.89$				
G2 (Q2)	$\alpha = 0.88$				
G3 (Q3)	$\alpha = 0.89$				
G4 (Q5)	$\alpha = 0.88$				
G5 (Q11)	$\alpha = 0.90$				
G6 (Q12)	$\alpha = 0.90$				
G7 (Q14)	$\alpha = 0.89$				
C1 (Q17)		$\alpha = 0.93$			
C2 (Q18)		$\alpha = 0.93$			
C3 (Q19)		$\alpha = 0.92$			
C4 (Q21)		$\alpha = 0.93$			
C5 (Q22)		$\alpha = 0.93$			
C6 (Q23)		$\alpha = 0.93$			
C7 (Q27)		$\alpha = 0.93$			
B1 (Q35)			$\alpha = 0.80$		
B2 (Q36)			$\alpha = 0.81$		
B3 (Q37)			$\alpha = 0.81$		
B4 (Q38)			$\alpha = 0.80$		
B5 (Q41)			$\alpha = 0.79$		
B6 (Q42)			$\alpha = 0.82$		
B7 (Q43)			$\alpha = 0.81$		
S1 (Q49)				$\alpha = 0.81$	
S2 (Q50)				$\alpha = 0.82$	
S3 (Q52)				$\alpha = 0.83$	
S4 (Q53)				$\alpha = 0.79$	
S5(Q54)				$\alpha = 0.81$	
S6(Q56)				$\alpha = 0.78$	
S7(Q57)				$\alpha = 0.83$	
A1(Q48)					$\alpha = 0.94$
A2(Q58)					$\alpha = 0.93$
A3(Q59)					$\alpha = 0.93$
A4(Q60)					$\alpha = 0.93$
A5(Q61)					$\alpha = 0.93$
A6(Q62)					$\alpha = 0.94$
A7(Q63)					$\alpha = 0.94$

G =GPH, C= C, B=BIAC, S=SR, A= A.

United Kingdom Thalassaemia Society

(Registered Charity No. 275107)

19 THE BROADWAY, SOUTHGATE CIRCUS, LONDON N14 6PH.
Tel: 020 8882 0011 Fax: 020 8882 8618

E-mail: office@ukts.org Website: www.ukts.org

Honorary President: *Professor Sir David Weatherall*

Ms Xenya Kantaris
7 Church Drive
London
NW9 8DN

25th November 2004

Dear Ms Kantaris

The Management Committee of the UK Thalassaemia Society (UKTS) has reviewed your research proposal and supports this research effort to help our patient members and their families.

We understand that you wish to send questionnaires to our adult patient members as part of your research. It is not our policy to provide funding for research students; however we would be pleased to help in other ways, e.g. by labelling questionnaire packs and sending them out; even though it is not our usual practice to post documentation of this kind to our members.

In addition, please note that your research will be completely independent of any research which we here at UKTS may commission; and therefore any documents posted to our members should clearly state this.

Please feel free to contact us again at any time. We wish you good luck with your research.

Yours sincerely

M Michael

Michael Michael
President, UK Thalassaemia Society

APPENDIX XXXVII

Communalities (Addendum in Chapter 6)

Communalities (Addendum in Chapter 6) **Appendix XXXVII**

	Initial	Extraction
Q1	1.000	.806
Q2	1.000	.832
Q3	1.000	.817
Q4	1.000	.746
Q5	1.000	.815
Q6	1.000	.730
Q7	1.000	.730
Q8	1.000	.765
Q9	1.000	.745
Q10	1.000	.890
Q11	1.000	.759
Q12	1.000	.885
Q13	1.000	.787
Q14	1.000	.741
Q15	1.000	.701
Q16	1.000	.849
Q17	1.000	.882
Q18	1.000	.934
Q19	1.000	.898
Q20	1.000	.922
Q21	1.000	.853
Q22	1.000	.859
Q23	1.000	.853
Q24	1.000	.845
Q25	1.000	.824
Q26	1.000	.922
Q27	1.000	.822
Q28	1.000	.884
Q29	1.000	.700
Q30	1.000	.869
Q31	1.000	.813
Q32	1.000	.834
Q33	1.000	.848
Q34	1.000	.888
Q35	1.000	.898
Q36	1.000	.737
Q37	1.000	.738
Q38	1.000	.841
Q39	1.000	.809
Q40	1.000	.826
Q41	1.000	.758
Q42	1.000	.775
Q43	1.000	.909
Q44	1.000	.840
Q45	1.000	.804
Q46	1.000	.873
Q47	1.000	.846

Q48	1.000	.784
Q49	1.000	.827
Q50	1.000	.838
Q51	1.000	.772
Q52	1.000	.828
Q53	1.000	.885
Q54	1.000	.870
Q55	1.000	.856
Q56	1.000	.845
Q57	1.000	.712
Q58	1.000	.908
Q59	1.000	.878
Q60	1.000	.772
Q61	1.000	.833
Q62	1.000	.831
Q63	1.000	.823

Extraction Method: Principal Component Analysis

APPENDIX XXXVIII

Principal Component Analysis (PCA) extraction statistics for the first 15 factors from the 63-item Thalassaemia Adult Life Index (THALI) (Addendum in Chapter 6)

Principal Component Analysis (PCA) extraction statistics for the first 15 factors from the 63-item Thalassaemia Adult Life Index (THALI)

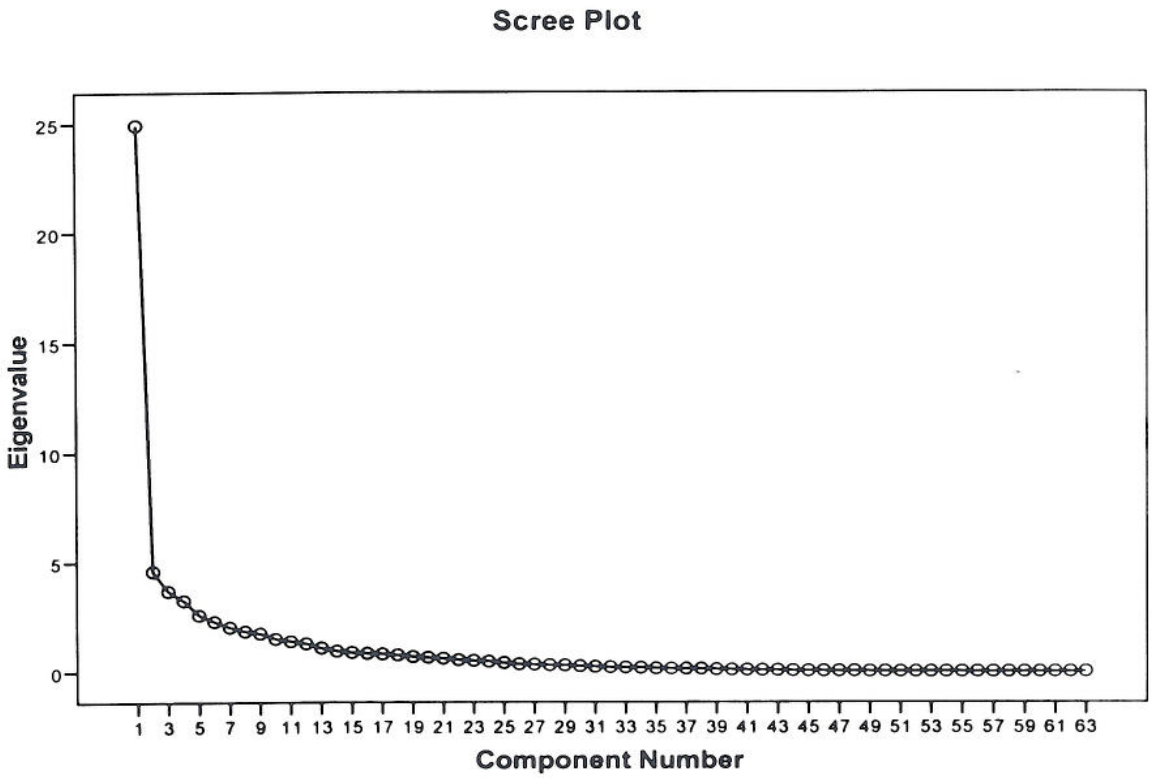
(Addendum in Chapter 6) **Appendix XXXVIII**

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	24.915	39.547	39.547
2	4.568	7.251	46.798
3	3.668	5.822	52.620
4	3.228	5.124	57.744
5	2.566	4.073	61.817
6	2.272	3.606	65.423
7	2.016	3.200	68.623
8	1.827	2.900	71.522
9	1.726	2.740	74.262
10	1.479	2.348	76.610
11	1.370	2.175	78.785
12	1.267	2.011	80.796
13	1.066	1.692	82.487
14	.920	1.460	83.948
15	.852	1.352	85.299

Extraction Method: Principal Component Analysis

APPENDIX XXXIX

Scree plot (Addendum in Chapter 6)


Scree Plot
Eigenvalue
25
20
15
10
5
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63
Component Number

APPENDIX XXXX

Pattern Matrix (Addendum in Chapter 6)

Pattern Matrix **(Addendum in Chapter 6)** **Appendix XXXX**

Item	Component 1	Component 2	Component 3	Component 4
Q18	.848			
Q24	.799			
Q25	.792			
Q20	.781			
Q30	.712			
Q23	.697			
Q19	.669			
Q21	.610			
Q27	.466			
Q22	.411			
Q52		.797		
Q1		-.497		
Q43		.440		
Q41		.393		
Q46			-.899	
Q58			-.854	
Q61			-.743	
Q47			-.712	
Q60			-.647	
Q48	.321		-.615	
Q63			-.526	
Q57			-.502	
Q59			-.499	
Q49			-.418	
Q55			-.376	
Q35				.915
Q38				.883
Q36				.565
Q29	.367			.480
Q45		.324		
Q16				
Q31			-.308	
Q14				
Q54				
Q53				
Q56				
Q62				
Q10				
Q9				
Q44				
Q50		.308		
Q34				
Q33				
Q32				

Q42		.336		
Q11				
Q8				
Q2		-.367		
Q6				
Q3			-.350	
Q5		-.306		
Q4				
Q7	.335			
Q40				
Q17	.333			
Q37				
Q51				
Q26	.335			
Q12				
Q28			-.363	
Q39				.327
Q15				
Q13	.306			

Extraction Method: Principal Component Analysis. Rotation Method: Oblimin with Kaiser Normalization.

APPENDIX XXXXI

Reliability: alphas if item deleted (Addendum in Chapter 6)

Reliability: alphas if item deleted (Addendum in Chapter 6) Appendix XXXXI

Scale (alpha)	Feelings and Emotions (0.96)	Problems with Physical Health and Difference (0.73)	Problems with Daily Activities and Routine (0.93)	Body Image (0.81)
Scale Item	**Alpha if item deleted**	**Alpha if item deleted**	**Alpha if item deleted**	**Alpha if item deleted**
FE Q17	α=0.95			
	α=0.95			
FE Q18	α=0.95			
	α=0.95			
FE Q19	α=0.95			
FE Q20	α=0.95			
FE Q21	α=0.95			
	α=0.95			
FE Q22	α=0.95			
FE Q23	α=0.95			
FE Q24	α=0.95			
FE Q25	α=0.96			
FE Q26	α=0.95			
FE Q27		α=0.66		
FE Q29		α=0.62		
		α=0.61		
FE Q30		**α=0.76**		
PPH Q1		α=0.73		
PPH Q2			α=0.93	
PPH Q5			α=0.93	
PPH Q41			α=0.93	
PPH Q43			α=0.93	
PDAR Q46			α=0.93	
PDAR Q47			α=0.93	
PDAR Q48			α=0.92	
PDAR Q49			α=0.92	
PDAR Q55			α=0.92	
PDAR Q57			α=0.92	
PDAR Q58				α=0.68
PDAR Q59				α=0.76
PDAR Q60				α=0.69
PDAR Q61				**α=0.86**
BI Q35				
BI Q36				
BI Q38				
BI Q39				

FE = Feelings and Emotions sub-scale (13 items)
PPH = Problems with Physical Health and Difference sub-scale (5 items)
PDAR = Problems with Daily Activities and Routine sub-scale (10 items)
BI = Body Image sub-scale (4 items)

Alphas higher than the total alpha if an item deleted are in **bold.**

APPENDIX XXXXII

Letter of invitation postal survey 2

University College London Hospitals NHS
NHS Foundation Trust

Version 1/Postal Survey 2
28th August 2004

Dear patient,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

We hope this letter finds you well.

We are writing to you to invite you to take part in the second postal survey of the above named research study. My research team and I are trying to develop and validate a scale to measure the impact of beta-thalassaemia major (BTM). Further information about the study is enclosed.

We have developed a scale to measure the impact of beta-thalassaemia major in the adult patient population in the UK. We now wish to see how this scale compares with other measures.

Part of the study will involve you completing questionnaires as well as some information sheets about yourself. **The completion of these documents should take no longer than 20 minutes.**

Your agreeing to take part in this study is entirely voluntary and all information will be kept strictly confidential. If you decide not to take part in this study, any treatment you will continue to receive for your thalassaemia will not be affected.

If you are interested in taking part in this research, please complete the documents enclosed and return them to us in the pre-paid envelope.

Thank you once again.

Best wishes,

Dr. Anna Mandeville
Principal Research Investigator
Consultant Clinical Health Psychologist; Honorary Research Fellow, UCLH

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXXIII

PIS postal survey 2

Version 1/Postal Survey 2
28th August 2004

Note: If you have decided not to participate in this research and/or you are not a beta-thalassaemia major (BTM) patient kindly return the research documents blank.

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

You are being invited to take part in this research study. Before you decide in participating, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others it you wish. Ask us if there is anything that is not clear or if you would like more information. Take the time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

We would like to invite you to take part in the final part of a study which will evaluate a developed quality of life (QoL) measure for adult beta-thalassaemia major (BTM) patients. As you know chronic illness has a tremendous impact on the QoL of individuals. It is therefore important to measure the effects of illness and their treatment on the QoL of sufferers. We would like you to complete the enclosed questionnaires.

Why have I been chosen?

We are looking for volunteers who have BTM and are aged over 18 years.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We are looking for volunteers who would be prepared to complete the enclosed questionnaires and documents and return them to us, in the pre-paid envelope provided. It may take around 20 minutes to complete. The questions are about your personal views and beliefs about a range of issues. For most of the questions you would just need to tick a box to indicate your answer; there is very little involved. However, it would be okay for someone else to help you to complete the questionnaires, if this would be easier for you. Also, it is okay to take breaks between the questionnaires if it is too tiring or you are too busy to complete them in one go.

If you do not wish to participate in this study, you need to take no further action. If the questionnaires are not returned, we will presume that you are unable to participate. Do not worry, as we realise that it would not be possible for everyone to take part.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Are there any possible benefits or risks involved in taking part?

As this research is only attempting to find out about your existing views, it is not thought that taking part should involve any significant risks to you. However, if you do find that they raise any concerns for you, please contact the lead research psychologist who will be able to discuss these with you.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service (NHS) complaints mechanism may be available to you.

Similarly, it is not thought that taking part in this study will have any direct impact on you but by talking part in this research you will be helping to design a questionnaire that will help to assess how effectively we are treating patients with TM. The questionnaire is also likely to be used to evaluate new treatments of TM as they are developed

Will my taking part in this study be kept confidential?

Only the research team and your GP will know that you have taken part in this study. Your GP will be sent a letter to let him/her know that you have taken part in this study, if you so wish, All your responses will be used anonymously.

What will happen to the results of the research study?

The results of the study will be likely to be published but you will not be identified in any report or publication arising from this study.

Who is funding the research?

The Thalassaemia International Fëderation (TIF) in Cyprus, Nicosia, is currently liaising with pharmaceutical companies regarding financial support for this project.

Who has reviewed the study?

The study will be reviewed by the UK Thalassaemia Society (UKTS), University College London Hospital (UCLH) and Brunel University. It should be noted that this project is independent to those commissioned by the UKTS.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

Who do I contact for further information?

If you have any questions about the study, please do not hesitate to contact the principal investigator, Dr. Anna Mandeville on 07989 306514 and/or lead researcher, Xenya Kantaris on 07811 158 461.

Thank you for taking the time to read this information.

APPENDIX XXXXIV

Power calculation summary

Power Calculation – validation stage (3/3)

Exact - Correlations: Difference from constant (one sample case)

Options:	Exact distribution	
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= One
	Effect size r	= **0.5**
	α err prob	= **0.05**
	Power (1-β err prob)	= **0.90**
	Population correlation ρ	= 0
Output:	Lower critical ρ	= 0.300898
	Upper critical ρ	= 0.300898
	Total sample size	= **31**
	Actual power	= 0.906201

APPENDIX XXXXV

The THalassaemia Adult Life Index (THALI-35)

ID No.
Date:

The THalassaemia Adult Life Index (THALI-35)
Version 1.0
Patient Self-Report (ages 18+)

Instructions

The following statements ask for your views about the impact of thalassaemia and/or your treatment on your day-to-day life during the past four (4) weeks.

For each of the statements below circle the number that best describes your situation.

Please answer all the questions below. If you are unsure about how to respond to any given question, choose the one that seems the most appropriate; this if often your first response.

Thank you in advance for the completion of this questionnaire.

In the past four weeks, I have.....	Not at all	A little	Moderately	Quite a bit	Extremely
1. Lacked energy.	1	2	3	4	5
2. Been worried.	1	2	3	4	5
3. Been restricted in doing things that I would have liked to have done with my family.	1	2	3	4	5
4. Been limited in doing chores around the house.	1	2	3	4	5
5. Felt tired.	1	2	3	4	5
6. Been angry.	1	2	3	4	5
7. Been really short with my family.	1	2	3	4	5
8. Had difficulty with my mobility.	1	2	3	4	5
9. Lacked stamina.	1	2	3	4	5
10. Been frustrated.	1	2	3	4	5
11. Not been able to successfully form relationships with others.	1	2	3	4	5
12. Not been able to bend with ease.	1	2	3	4	5
13. Felt run down.	1	2	3	4	5
14. Been emotional.	1	2	3	4	5
15. Been rejected in some way because I have thalassaemia.	1	2	3	4	5
16. Not been able to do a lot of walking.	1	2	3	4	5

In the past four weeks, I have.....	Not at all	A little	Moderately	Quite a bit	Extremely
17. Felt dizzy.	1	2	3	4	5
18. Been a bit run down or stressed.	1	2	3	4	5
19. Been penalised because of my illness.	1	2	3	4	5
20. Been unable to lift heavy things.	1	2	3	4	5
21. Been full of aches and pains.	1	2	3	4	5
22. Been irritable.	1	2	3	4	5
23. Felt that my social life has been affected by my illness.	1	2	3	4	5
24. Struggled to fit everything into my routine life.	1	2	3	4	5
25. Needed to rest more often.	1	2	3	4	5
26. Been very anxious.	1	2	3	4	5
27. Not done any leisure activities.	1	2	3	4	5
28. Felt that having thalassaemia has made most things difficult.	1	2	3	4	5

In the past four weeks, it has bothered me that	Not at all	A little	Moderately	Quite a bit	Extremely
29. I have a shortened body.	1	2	3	4	5
30. I look younger than my age/peers.	1	2	3	4	5
31. I have a pale complexion.	1	2	3	4	5
32. I am short in height.	1	2	3	4	5
33. I am different to others, and am conscious of this.	1	2	3	4	5
34. I have no self-confidence.	1	2	3	4	5
35. I feel a bit inferior to others.	1	2	3	4	5

APPENDIX XXXXVI

The Medical Outcomes Study 36 item Short Health Survey (SF-36)

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

APPENDIX XXXXVII

The BRIEF COPE

Brief COPE

These items deal with ways you've been coping with the stress in your life as an adult with thalassaemia major. There are many ways to try to deal with problems. These items ask what you've been doing to cope with your illness as an adult. Obviously, different people deal with things in different ways but I'm interested in how you've tried to deal with it. Each item says something about a particular way of coping. I want to know, to what extent you've been doing what the item says - how much, or how frequently? Don't answer on the basis of whether it seems to be working or not—just whether or not you're doing it. Use these response choices. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can. Please write your response after each item. Thank you.

1 = I haven't been doing this at all
2 = I've been doing this a little bit
3 = I've been doing this a medium amount
4 = I've been doing this a lot

1. I've been turning to work or other activities to take my mind off things.
2. I've been concentrating my efforts on doing something about the situation I'm in.
3. I've been saying to myself "this isn't real.".
4. I've been using alcohol or other drugs to make myself feel better.
5. I've been getting emotional support from others.
6. I've been giving up trying to deal with it.
7. I've been taking action to try to make the situation better.
8. I've been refusing to believe that it has happened.
9. I've been saying things to let my unpleasant feelings escape.
10. I've been getting help and advice from other people.
11. I've been using alcohol or other drugs to help me get through it.
12. I've been trying to see it in a different light, to make it seem more positive.
13. I've been criticizing myself.
14. I've been trying to come up with a strategy about what to do.
15. I've been getting comfort and understanding from someone.
16. I've been giving up the attempt to cope.
17. I've been looking for something good in what is happening.
18. I've been making jokes about it.
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.
20. I've been accepting the reality of the fact that it has happened.
21. I've been expressing my negative feelings.
22. I've been trying to find comfort in my religion or spiritual beliefs.
23. I've been trying to get advice or help from other people about what to do.
24. I've been learning to live with it.
25. I've been thinking hard about what steps to take.
26. I've been blaming myself for things that happened.
27. I've been praying or meditating.
28. I've been making fun of the situation.

APPENDIX XXXXVIII

The Rosenberg Self-Esteem scale (RSE)

Rosenberg Self-Esteem Scale

Instructions: Below is a list of statements dealing with your general feelings about yourself. If you strongly agree, circle SA. If you agree with the statement, circle A. If you disagree, circle D. If you strongly disagree, circle SD.

1.	On the whole, I am satisfied with myself.	SA	A	D	SD
2.	At times, I think I am no good at all.	SA	A	D	SD
3.	I feel that I have a number of good qualities.	SA	A	D	SD
4.	I am able to do things as well as most other people.	SA	A	D	SD
5.	I feel I do not have much to be proud of.	SA	A	D	SD
6.	I certainly feel useless at times.	SA	A	D	SD
7.	I feel that I'm a person of worth, at least on an equal plane with others.	SA	A	D	SD
8.	I wish I could have more respect for myself.	SA	A	D	SD
9.	All in all, I am inclined to feel that I am a failure.	SA	A	D	SD
10.	I take a positive attitude toward myself.	SA	A	D	SD

Thank you.

APPENDIX XXXXIX

The Sickle Cell Self-Efficacy Scale (SCSES)

Self-efficacy

The following questions ask about how sure you are in dealing day-to-day with thalassaemia major. There are no right or wrong answers, we just want to know what you think. So for each question tell us how sure you are by putting a check in the box that best tells us how you feel. Please answer every question.

	Not at all sure	Not sure	Neither	Sure	Very sure
1) How sure are you that you can keep doing most of the things you do day-to-day?					
2) How sure are you that you can control how often or when you get tired?					
3) How sure are you that you can do something to help yourself feel better if you are feeling sad or blue?					
4) As compared with other people with thalassaemia major, how sure are you that you can manage your life from day-to-day?					
5) How sure are you that you can manage your thalassaemia major symptoms so that you can do the things you enjoy doing?					
6) How sure are you that you can deal with the frustration of having thalassaemia major?					

APPENDIX XXXXX

The Body Image Quality of Life Inventory (BIQLI)

The BIQLI Questionnaire

Instructions: Different people have different feelings about their physical appearance. These feelings are called "body image." Some people are generally satisfied with their looks, while others are dissatisfied. At the same time, people differ in terms of how their body-image experiences affect other aspects of their lives. Body image may have positive effects, negative effects, or no effect at all. Listed below are various ways that your own body image may or may not influence your life. For each item, circle how and how much your feelings about your appearance affect that aspect of your life. Before answering each item, think carefully about the answer that most accurately reflects how your body image usually affects you.

-3	-2	-1	0	+1	+2	+3
Very Negative Effect	Moderate Negative Effect	Slight Negative Effect	No Effect	Slight Positive Effect	Moderate Positive Effect	Very Positive Effect

1.	My basic feelings about myself—feelings of personal adequacy and self-worth.	-3	-2	-1	0	+1	+2	+3
2.	My feelings about my adequacy as a man or woman—feelings of masculinity or femininity.	-3	-2	-1	0	+1	+2	+3
3.	My interactions with people of my own sex.	-3	-2	-1	0	+1	+2	+3
4.	My interactions with people of the other sex.	-3	-2	-1	0	+1	+2	+3
5.	My experiences when I meet new people.	-3	-2	-1	0	+1	+2	+3
6.	My experiences at work or at school.	-3	-2	-1	0	+1	+2	+3
7.	My relationships with friends.	-3	-2	-1	0	+1	+2	+3
8.	My relationships with family members.	-3	-2	-1	0	+1	+2	+3
9.	My day-to-day emotions.	-3	-2	-1	0	+1	+2	+3
10.	My satisfaction with my life in general.	-3	-2	-1	0	+1	+2	+3

-3	-2	-1	0	+1	+2	+3
Very Negative Effect	Moderate Negative Effect	Slight Negative Effect	No Effect	Slight Positive Effect	Moderate Positive Effect	Very Positive Effect

11.	My feelings of acceptability as a sexual partner.	-3	-2	-1	0	+1	+2	+3
12.	My enjoyment of my sex life.	-3	-2	-1	0	+1	+2	+3
13.	My ability to control what and how much I eat.	-3	-2	-1	0	+1	+2	+3
14.	My ability to control my weight.	-3	-2	-1	0	+1	+2	+3
15.	My activities for physical exercise.	-3	-2	-1	0	+1	+2	+3
16.	My willingness to do things that might call attention to my appearance.	-3	-2	-1	0	+1	+2	+3
17.	My daily "grooming" activities (i.e., getting dressed and physically ready for the day).	-3	-2	-1	0	+1	+2	+3
18.	How confident I feel in my everyday life.	-3	-2	-1	0	+1	+2	+3
19.	How happy I feel in my everyday life.	-3	-2	-1	0	+1	+2	+3

APPENDIX XXXXXI

G.P. information sheet interview

Version 1/Postal Survey 2
28th August 2004

GP Information Sheet for < Insert Patient Name>,

A study to develop a disease specific measure of the impact of beta-thalassaemia major (BTM)

This is an information sheet for all General Practitioners whose patients have recently taken part in a phase of the above study.

The aim of the study is to develop a scale of the impact of beta-thalassaemia major (BTM). When studying a disease it is important to understand not only the clinical symptoms but also what impact the disease has on the everyday life of the patients affected. To help understand this in BTM we need a questionnaire specifically designed to ask the questions that are relevant to patients with BTM. We have just developed such a questionnaire.

The aim of this study is to compare this measure with other measures to see how it compares scientifically.

Your patient has recently completed a set of standardised questionnaires. We have been recruiting patients who have TM and are aged over 18 years from a clinical sample in the UK.

If you have any questions about the study, please do not hesitate to contact the research team's researcher, Xenya Kantaris, on 07811 158 461.

Thank you for taking the time to read this information.

Principal Research Investigator: Dr. Anna Mandeville; Xenya Kantaris (0845 155 5000 ext. 3396); Professor Lynn Myers (01895 274000); Professor John Porter (020 7679 6224/0207 380 9638)

APPENDIX XXXXXII

Item discriminant validity (validation stage)

Item Discriminant Validity (validation stage) **Appendix XXXXXII**

Scale Item	General (r)	Coping (r)	Body (r)	Social (r)	Autonomy (r)
G1 (Thali1)	0.86**	0.58**	0.28	0.60**	0.78**
G2 (Thali5)	0.91**	0.55**	0.24	0.55**	0.83**
G3 (Thali9)	0.87**	0.52**	0.18	0.59**	0.81**
G4 (Thali13)	0.85**	0.61**	0.23	0.64**	0.80**
G5 (Thali17)	0.66**	0.63**	0.34*	0.63**	0.55**
G6 (Thali21)	0.81**	0.50**	0.34*	0.67**	0.82**
G7 (Thali25)	0.88**	0.43*	0.22	0.56**	0.83**
C1 (Thali2)	0.38	0.67	0.36	0.51	0.40
C2 (Thali6)	0.51	0.87	0.55	0.74	0.46
C3 (Thali10)	0.56	0.91	0.45	0.71	0.51
C4(Thali14)	0.42	0.88	0.47	0.58	0.36
C5 (Thali18)	0.77	0.83	0.33	0.63	0.68
C6(Thali22)	0.62	0.89	0.44	0.73	0.59
C7(Thali26)	0.60	0.86	0.47	0.75	0.58
B1(Thali29)	0.26	0.40*	0.87**	0.63**	0.24
B2(Thali30)	0.05	0.22	0.44**	0.22	0.18
B3(Thali31)	0.26	0.33	0.76**	0.44**	0.32
B4(Thali32)	0.25	0.41*	0.87**	0.59**	0.25
B5(Thali33)	0.14	0.32	0.82**	0.59**	0.20
B6(Thali34)	0.40*	0.54**	0.73**	0.65**	0.41*
B7(Thali35)	0.31	0.56**	0.82**	0.69**	0.30
S1(Thali3)	0.80**	0.67**	0.36*	0.83**	0.81**
S2(Thali7)	0.61**	0.80**	0.51**	0.83**	0.58**
S3(Thali11)	0.478**	0.81**	0.56**	0.77**	0.50**
S4(Thali15)	0.27	0.43*	0.62**	0.64**	0.34*
S5(Thali19)	0.37*	0.45**	0.77**	0.78**	0.41*
S6(Thali23)	0.65**	0.65**	0.64**	0.91**	0.73**
S7(Thali27)	0.68**	0.54**	0.48**	0.77**	0.69**
A1(Thali4)	0.89**	0.58**	0.30	0.64**	0.89**
A2(Thali8)	0.87**	0.45**	0.15	0.59**	0.88**
A3(Thali12)	0.78**	0.39*	0.12	0.54**	0.86**
A4(Thali16)	0.79**	0.44**	0.22	0.55**	0.88**
A5(Thali20)	0.77**	0.50**	0.45**	0.64**	0.83**
A6(Thali24)	0.72**	0.61**	0.33	0.71**	0.74**
A7(Thali28)	0.56**	0.55**	0.50**	0.77**	0.70**

G =GPH, C= C, B=BIAC, S=SR, A= A. * Correlation is significant at the 0.05 level (two tailed). ** Correlation is significant at the 0.01 level (two tailed).

APPENDIX XXXXXIIIa

Reliability: internal consistency and alphas if item deleted (validation stage)

Reliability: internal consistency and alphas if item deleted (validation stage)

Appendix XXXXXIIIa

Scale (Alpha)	General ($\alpha = 0.93$)	Coping ($\alpha = 0.93$)	Body ($\alpha = 0.87$)	Social ($\alpha = 0.90$)	Autonomy ($\alpha = 0.92$)
Scale Item	Alpha if item deleted	Alpha if item deleted	Alpha if item deleted	Alpha if item deleted	Alpha if item deleted
G1 (Thali1)	$\alpha = 0.91$				
G2 (Thali5)	$\alpha = 0.91$				
G3 (Thali9)	$\alpha = 0.91$				
	$\alpha = 0.91$				
G4 (Thali13)					
G5 (Thali17)	$\alpha = 0.93$				
G6 (Thali21)	$\alpha = 0.92$				
G7 (Thali25)	$\alpha = 0.91$				
C1 (Thali2)		**α =0 .94**			
C2 (Thali6)		$\alpha = 0.92$			
C3 (Thali10)		$\alpha = 0.91$			
C4(Thali14)		$\alpha = 0.92$			
C5 (Thali18)		$\alpha = 0.92$			
C6(Thali22)		$\alpha = 0.91$			
C7(Thali26)		$\alpha = 0.92$			
B1(Thali29)			$\alpha = 0.84$		
B2(Thali30)			**$\alpha = 0.91$**		
B3(Thali31)			$\alpha = 0.86$		
B4(Thali32)			$\alpha = 0.83$		
B5(Thali33)			$\alpha = 0.84$		
B6(Thali34)			$\alpha = 0.86$		
B7(Thali35)			$\alpha = 0.84$		
S1(Thali3)				$\alpha = 0.88$	
S2(Thali7)				$\alpha = 0.88$	
S3(Thali11)				$\alpha = 0.89$	
S4(Thali15)				$\alpha = 0.90$	
S5(Thali19)				$\alpha = 0.88$	
S6(Thali23)				$\alpha = 0.86$	
S7(Thali27)				$\alpha = 0.89$	
A1(Thali4)					$\alpha = 0.90$
A2(Thali8)					$\alpha = 0.90$
A3(Thali12)					α =0 .91
A4(Thali16)					$\alpha = 0.90$
A5(Thali20)					$\alpha = 0.91$
A6(Thali24)					$\alpha = 0.92$
A7(Thali28)					$\alpha = 0.92$

G =GPH, C= C, B=BIAC, S=SR, A= A. Alphas higher than the total alpha if an item is deleted are in **bold.**

APPENDIX XXXXXIIIb

Reliability: internal consistency and alphas if item deleted (validation stage) (alternative scales)

Reliability: internal consistency and alphas if item deleted (validation stage) (alternative scales)

Appendix XXXXXIIIb

Psychometric Properties	BRIEF COPE	SF-36	RSE	SCSES	BIQLI
Cronbach's Alpha	$\alpha = 0.91$	$\alpha = 0.96$	$\alpha = 0.88$	$\alpha = 0.87$	$\alpha = 0.97$
Alpha if higher when 1 item deleted	N.A.	N.A.	N.A.	N.A.	N.A.

APPENDIX XXXXXIV

Correlations between the BIAC and the BRIEF COPE

Correlations between the BIAC and the BRIEF COPE

Appendix XXXXXIV

BRIEF COPE	GPH	C	BIAC	SR	A
SD	.09	.16	.42(*)	.20	.08
AC	.07	.15	.42(*)	.20	.07
D	.09	.15	.42(*)	.20	.08
SM	.09	.1	.42(*)	.20	.08
ES	.09	.15	.43(*)	.21	.08
IS	-	.07	.35(*)	.13	.01
BD	.09	.15	.42(*)	.20	.08
V	-	.07	.34(*)	.12	.01
PR	-	.16	.42(*)	.21	.08
P	.01	.07	.35(*)	.12	.01
H	.09	.03	.30	.05	.10
ACC	-	.07	.34(*)	.12	.01
R	-	.07	.34(*)	.12	.01
SB	.02	.07	.34(*)	.12	.01

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed); N = 35.

Key for BRIEFCOPE sub-scales

self-distraction (SD)
active coping (AC)
denial (D)
substance misuse (SM)
use of emotional support (ES)
humour (H)
use of instrumental support (IS)
acceptance (A)
religion (R)
venting (V)
positive reframing (PR)
planning (P)
self-blame (SB)
behavioural disengagement (BD)

APPENDIX XXXXXV

Correlations between the GPH, A, and the SF-36

Correlations between the GPH, A, and the SF-36

Appendix XXXXXV

	GPH	C	BIAC	SR	A
PF	**.79(**)**	**.39(*)**	.20	**.46(**)**	**.82(**)**
RLPH	**.63(**)**	.27	.12	.33	**.61(**)**
RLEP	**.38(*)**	.33	.03	.25	**.43(*)**
EF	**.58(**)**	.25	.07	.13	**.51(**)**
EWB	**.64(**)**	**.66(**)**	**.33(*)**	**.57(**)**	**.58(**)**
SF	**.75(**)**	**.54(**)**	.23	**.55(**)**	**.66(**)**
PAIN	**.81(**)**	**.44(**)**	.19	**.49(**)**	**.81(**)**
GH	**.70(**)**	.33	.06	**.34(*)**	**.62(**)**

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed); N = 35.

Key for SF-36 sub-scales

physical functioning (PF)
energy/fatigue (E/F)/vitality
emotional well-being (EWB)/mental health
bodily pain (PAIN)
role limitations due to physical health (RLPH)
role limitations due to emotional health problems(RLEP)
social functioning (SF)
general health perceptions (GHP)

h

APPENDIX XXXXXVI

Correlations between the THALI sub-scales and the RSE, the SCES and BIQLI summed scores

Correlations between the THALI sub-scales and the RSE, the SCES and BIQLI summed scores

Appendix XXXXXVI

	GPH	C	BIAC	SR	A
SUMRSE	.22	.04	.31	.04	.22
SUMSCES	.29	.07	.30	.01	.31
SUMBIQLI	.15	.04	**.39(*)**	.13	.17

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed); N = 35.

APPENDIX XXXXXVII

R&D approval from Manchester Royal Infirmary

Central Manchester and Manchester Children's University Hospitals NHS Trust

Research & Development
1st Floor Post Graduate Centre
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
Tel: 0161-276-4902
Fax: 0161-276-5766
Alison.robinson@cmmc.nhs.uk

16 July 2007

Ref: 10524-Ltr 2-Ryan

Dr Kate Ryan
Consultant Haematologist
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

Dear Dr Ryan

Research Study: "Development of a disease specific measure of the impact of better thalassaemia major (TM) and the examination of the relationship between Health Related Quality of life (HRQoL), adherence and psychosocial factors"
PIN: 10524 (Please use this reference number in any future correspondence)

Thank you for submitting a Pan Manchester Research Notification for the above study. I am pleased to be able to confirm that the R&D Office now has all the required information concerning this research and that the Trust's Director of Research and Development has given approval for the project be undertaken.

We acknowledge that the *Brunel University* has accepted the role of Research Sponsor for this study (ref. Research Governance Framework[1] as issued by the Department of Health).

Details of the project have been recorded on the Trust R&D Management Information System and the project has been given a unique identification number (PIN), as shown above. (A copy of the signed Notification Form is enclosed for your records).

Please note, it is a requirement of the approval given by the Trust that the research project is being conducted in line with the guidance given within the Research Governance Framework[1]. Further guidance is available on the R&D web pages (see above), or request a CD from the R&D office.

Please draw your attention to the need to comply with both the Health and Safety at Work Act and the Data Protection Act. If you require further information or advice in any of these latter areas please contact the Trust's Health & Safety Advisor, Mr Ken Wood, on 276 4262 or the Trust's Data Protection Officer, Ms Cara Lally on 276 4878.

In line with this framework I would be grateful if you would inform me of the actual start date of this particular project and any changes that might be made to it during its course. Your help and support would be gratefully received.

I would like to take this opportunity to wish you well with your research

[1] ' Research Governance Framework for Health and Social Care' Version 2 DoH 2005
http://www.doh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.htm

Ref: 10524-Ltr 2-Ryan

Yours sincerely,

Alison Robinson
Research Operations Manager

Enc (signed PMNF)

Cc

Ms Xenya Kantaris
7 Church Drive
London
NW9 8DN

APPENDIX XXXXXVIII

R&D approval from The Royal Hallamshire Hospital

Ref: STH14633/SR

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

17 July 07

Dr J Wright
Consultant Haematologist
Haematology Department
H Floor
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Dr Wright

Authorisation of project

STH ref: STH 14633
Study title: The development of a disease specific measure of the impact of beta-thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors

Chief Investigator: Dr A Mandeville (University College London)
Local Collaborator: Dr Josh Wright (Sheffield Teaching Hospitals NHS Foundation Trust)

Sponsor: Brunel University
Funder: Not applicable

The Research Department has received the required documentation for the study as listed below:

1.	**Sponsorship IMP studies (non-commercial)**	Not applicable
	Sponsorship responsibilities between institutions	Not applicable
	Responsibilities of investigators	Not applicable
	Monitoring Arrangements	Not applicable
2.	**STH registration document: completed and signed**	NHS REC Application Form, Version 4.1, Part A&B, Submitted 15 Nov 04 NHS REC Application Form, Version 4.1, Part C, Dr J Wright, 04 Sep 06 STH Finance Form, Dr J Wright, 21 Jun 07
3.	**Evidence of favourable scientific review**	Brunel University, School of Social Sciences
4.	**Protocol – final version**	Version 1, 01 Aug 04

5.	**Participant Information sheet – final version**	Pre-testing Stage, Version 2, 03 Feb 05
6.	**Consent form – final version**	Version 2, 03 Feb 05
7.	**Signed letters of indemnity**	NHS Indemnity
8.	**ARSAC / IRMER certificate**	Not applicable
9.	**Evidence of hosting approval from STH directorate**	STH Finance Form Dr D Bax 20 Jun 07
10.	**Evidence of approval from STH Data Protection Officer**	STH Finance Form Mr P Wilson 11 Jul 07
11.	**Letter of approval from REC**	Northern and Yorkshire REC 04/MRE03/88 20 Apr 05 23 May 07
12.	**Proof of locality approval**	Not applicable
13.	**Clinical Trial Authorisation from MHRA**	Not applicable
14.	**Honorary Contract**	Ms X Kantaris 22 Feb 07
15.	**Associated documents**	
	Letter of Invitation to Participants Pre-testing Stage	Version 1, 28 Feb 04
	Letter of Invitation to Participants Qualitative Interview Stage	Version 1, 28 Feb 04
	Letter of Invitation to Participants Postal Survey Stage (1)	Version 1, 28 Feb 04
	Letter of Invitation to Participants Postal Survey Stage (2)	Version 1, 28 Feb 04
	GP/Consultant Information Sheets Pre-testing Stage	Version 1, 28 Feb 04
	GP/Consultant Information Sheets Qualitative Interview Stage	Version 1, 28 Feb 04
	GP/Consultant Information Sheets Postal Survey Stage (1)	Version 1, 28 Feb 04
	GP/Consultant Information Sheets Postal Survey Stage (2)	Version 1, 28 Feb 04
	Participant Information Sheet Qualitative Interview Stage	Version 1, 28 Feb 04
	Participant Information Sheet Postal Survey Stage (1)	Version 1, 28 Feb 04
	Participant Information Sheet Postal Survey Stage (2)	Version 1, 28 Feb 04
	Participant Information Sheet Qualitative Interview Stage	Version 2, 03 Feb 05
	Participant Consent Form Interview Consent Form	Version 1, 03 Feb 05
	Participant Consent Form Pre-testing Stage	Version 2, 03 Feb 05
	Ethnic Origin Sheet	-

Ref: STH14633/SR

16. Signed financial agreement/contract	STH Finance Form Dr D Bax 20 Jun 07 Ms L Fraser 17 Jul 07

The project has been reviewed by the Research Department and authorised by the Director of R&D on behalf of STH NHS Foundation Trust to begin.

Yours sincerely

Professor S Heller
Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
Telephone +44 (0) 114 2713740
Fax +44 (0) 114 2711790

cc. Ms X Kantaris, University College London

Head of School of Social Sciences
Professor Dany Nobus

Brunel UNIVERSITY WEST LONDON

Brunel University, Uxbridge,
Middlesex, UB8 3PH, UK
Telephone +44 (0)1895 274000
Fax +44 (0)1895 269724
Web www.brunel.ac.uk

Dr Sarah Rudkin,
Research Facilitator,
Research Department,
305 Western Bank, Sheffield, S10 2TJ

Dear Dr Rudkin

Re Ms Xenya Kantaris project

I have reviewed her research proposal. It is a good quality: well deigned piece of research.

Yours sincerely

L. B. Myers

Professor Lynn Myers
Professor of Health Psychology

APPENDIX XXXXXIX

R&D approval from Leicester Royal Infirmary

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH AND DEVELOPMENT

Director: Professor D Rowbotham
Assistant Director: John Hampton
Co-ordinator: Lisa Wann
Direct Dial: 0116 258 8239
Fax No: 0116 258 4226
EMail: lisa.wann@uhl-tr.nhs.uk

Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Tel: 0116 249 0490
Fax: 0116 258 4666
Minicom: 0116 258 8188

07 November 2007

Dr Claire Chapman
Consultant Haematologist
Sandringham Building
Leicester Royal Infirmary
Leicester
LE1 5WW

Dear Dr Chapman

ID: 10346 **The development of a disease specific measure of the impact of beta-thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors.**

SSA Ref: Exempt **REC Ref: 04/MRE03/88**

Sponsor Brunel University

Please note that Trust Indemnity ceases 31/03/2008

As you are aware all research undertaken within the NHS requires both a favourable ethical opinion from an independent ethics committee, and R&D Approval from each NHS Trust it is taking place within. We have received confirmation that your study has gained a favourable opinion from the local Ethics Committee. All papers submitted have also been reviewed by University Hospitals of Leicester NHS Trust R&D Office and I am pleased to confirm NHS R&D Approval from the Trust, on the following conditions:

- All papers submitted to this office are followed to the letter; should any amendments or changes be required these must be submitted to this office.
- Only researchers detailed on the second page of this letter are to be involved in the study. If this changes, the changes must be submitted to this office as a non-substantial amendment.
- Your study is now covered by NHS Indemnity, as required, and excluding aspects covered by external indemnity, e.g. ABPI, University. This indemnity is in place to the above date – the end date you supplied. Should you wish your study to extend past this date you must notify the R&D Office, as not doing so would mean you are no longer covered to conduct your research. One method for this is through Annual Reports, see over page.
- Ongoing Pharmacovigilance and safety reporting is essential in all research studies. Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) must be reported appropriately and timely. Please ensure you are aware of our SOP on Safety Reporting which is available on the UHL R&D web pages: http://www.uhl-tr.nhs.uk/our-services/research--development
- Your application detailed resources to be used in this study, you must ensure the budget detailed is followed as the Trust will not cover any additional costs associated to this research.
- If honorary research contracts have been issued it is your responsibility to ensure this/these are kept up to date.

Approved Documents:
Protocol Version 1 01.08.04
Validation Tool Version 1 03.06.07
Letter of invitation – Postal survey stage 2 Version 1 28.08.04
Letter of invitation – Qualitative interview stage Version 1 28.08.04
Letter of invitation - Postal survey stage 1 Version 1 28.08.04
Letter of invitation – Pre testing stage Version 1 28.08.04
GP/Consultant information sheet Qualitative interview stage Version 1 28.08.04
GP/Consultant information sheets postal survey Version 1 28.08.04
GP/Consultant information sheet pre testing stage Version1 28.08.04
GP/Consultant information sheet postal survey stage 2 Version 1 28.08.04
PIS Qualitative interview stage Version 1 28.04.04
PIS postal survey stage 1 Version 1 28.08.04
PIS postal survey stage 2 Version 1 28.08.04
PIS pre testing stage Version 2 03.02.05
PIS Qualitative interview stage Version 2 03.02.05
PCF Version 2 03.02.05
PCF interview consent form Version 1 03.02.05
PCF pre testing stage Version 2 03.02.05

Reporting Requirements
Within University Hospitals of Leicester we are keen to encourage well structured, good quality research; to ensure this high standard is achieved and maintained we are keen to make you aware of national and local reporting requirements:

- Annual & Final Reports on the progress are required each year, or final on completion. These reports are needed by both the R&D Office and local Ethics Committee. Templates for these reports are available on the R&D & NRES website, and we look forward to the receipt of these on the anniversary of your ethics approval, and on the completion of your study.
- Additionally Annual Safety Reports are required for CT-IMP (Clinical Trials of Investigational Medicinal Products) studies and should be submitted to the MHRA annually 60 days prior to the anniversary of MHRA

Below is a list of the Researchers Approved to work on this Application within UHL
Dr Claire Chapman Consenting Doctor

Yours sincerely

John Hampton
Assistant Director for Research and Development

APPENDIX XXXXXX

R&D approval from Birmingham City Hospital

Sandwell & West Birmingham Hospitals NHS Trust

RESEARCH AND DEVELOPMENT

B T Cooper, MD, FRCP — Director R&D
L Jones — R&D Manager (Acting)
B Baines — R&D Administrator

(0121) 507 4946
(0121) 507 4091
Fax(0121) 507 4945
r&d@swbh.nhs.uk

Arden House
City Hospital
Dudley Road
Birmingham
B18 7QH

BTC/bb/RLW1801

2 July 2007

Dr A. L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N 1BN

Dear Dr Mandeville

Re: **The development of a disease specific measure of the impact of beta-thalassaemia major and the examination of the relationship between health related quality of life adherence and psychosocial factors**

Thank you for submitting your request to conduct this research in the Trust.

I am pleased to inform you that the request is approved for the project you describe, and that your research can proceed subject to the following conditions:

1. That you keep an up to date and accurate record of your research in a study file, and that you make this file and other records available for audit by the Research and Development Office when requested.

2. That you inform the R&D office of any significant protocol amendments.

3. That you notify the R&D office of any adverse events arising from this research in accordance with Trust Procedure for safety reporting in research.

4. That where the research continues for more that 1 year, you provide the R&D office with an annual report of your research progress, when approval will be reviewed.

Should you have any queries regarding this matter, please contact the R&D Manager.

Yours sincerely,

B. T. Cooper, MD, FRCP
Director R&D

Copy Dr C Wright, Consultant Haematologist – Haematology Department/City Hospital

APPENDIX XXXXXXI

Departmental honorary contract for Manchester Royal Infirmary

Honorary Research Contract

between

Central Manchester and Manchester Children's University Hospital NHS Trust

and

Mrs Xenya Kantaris

Fixed term contract for *3 months* from effective date (see below)

Signatures

Researcher  Date 25/7/07

Trust Director of Research & Development
Professor Henry Kitchener

Date
Effective Date

6 Aug 07.

Central Manchester and Manchester Children's University Hospitals
NHS Trust

Research and Development
G26 Giving for Living Centre
Royal Manchester Children's Hospital
Pendlebury
Manchester
M27 4HA

☎🖷: 0161 922 2933
e✉: gemma.whiteley@cmmc.nhs.uk

Our Ref: HRCSF/0707/1256/XKANTARIS

Mrs X Kantaris
7 Church Drive
London
NW9 8DN

Thursday 19th July 2007

Dear Mrs Kantaris

RE: HONORARY RESEARCH CONTRACT FOR RESEARCHER (FIXED TERM, 'NON VULNERABLE' PROJECT)

I am pleased to enclose your honorary research contract with the Trust; this is a fixed term honorary contract for 3 months and allows you to be involved with the project entitled "The development of a disease specific measure of the impat of beta-thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors" project identification number 10524.

This research project has not been identified as being subject to Enhanced Criminal Records Bureau Disclosure and as such you should not undertake any work which involves unsupervised contact with children or vulnerable adults; if such contact becomes a requirement then you will need to be subject to the Enhanced CRB Disclosure process before any such work is carried out; in such circumstances please contact the R&D office (address above) immediately.

Therefore your contract is issued on the basis that you will not have unsupervised contact with children or vulnerable adults and the research contract only allows you to be involved with this particular piece of research.

I enclose two copies of the contract, please sign both copies and return to myself and I will arrange for them to be signed on behalf of the Trust.

Please note that the contract only becomes effective when fully signed (both by researcher and on behalf of the Trust) and returned to the R&D department. You will be notified by letter enclosing your fully signed copy when this has been done.

If you have any queries regarding the honorary research contract, please do not hesitate to contact me.

Yours sincerely

Gemma Whiteley
Research Support Associate

CC. Dr Kate Ryan, Consultant Haematologist - letter only

APPENDIX XXXXXXI

Departmental honorary contract for The Royal Hallamshire Hospital

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Please ask for: Lindsay Jackson
Telephone: (0114) 271 3286
Fax: (0114) 271 3850

Human Resources Department
4 Claremont Place
Sheffield
S10 2TB

22 February 2007

Mrs. Xenya Kantaris
7 Church Drive
The Hyde
London
NW9 8DN

Dear Mrs. Kantaris,

HONORARY CONTRACT

I am instructed by the Sheffield Teaching Hospitals NHS Foundation Trust to offer you an appointment as Honorary Investigator within the Directorate of Specialised Medicine - Haematology, Royal Hallamshire Hospital commencing from the date of this contract until 31 December 2007.

This Honorary Contract is not a contract of employment and confers no employment rights or entitlements except the rights of access to patients, notes and hospital premises within the remit of the Sheffield Teaching Hospitals NHS Foundation Trust. It is subject to you maintaining the strictest confidentiality of information with which you may come into contact during the course of your appointment, maintaining acceptable standards of conduct and that you make yourself familiar with the relevant policies and procedures of the Trust and specifically in relation to Health and Safety and Fire. Failure to abide by these provisions will result in this authorisation being withdrawn.

Sheffield Teaching Hospitals NHS Foundation Trust manages all research in accordance with the requirements of the Research Governance Framework. As a contract holder of Sheffield Teaching Hospitals NHS Foundation Trust you must comply will all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance.

This honorary contract is subject to a confidential annual review to assess all aspects of your work and progress.

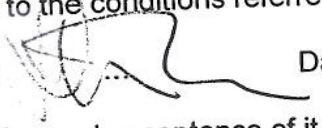
The Sheffield Teaching Hospitals NHS Foundation Trust accept no responsibility for the damage to or loss of personal property, with the exception of small valuables handed to their officials for safe custody. You are, therefore, recommended to take out an insurance policy to cover your personal property.

If you agree to accept the appointment offered in the foregoing letter on the terms specified therein, please sign the form of acceptance at the foot of this page and return it to the Human Resources Department, 4 Claremont Place, as soon as possible. The second signed copy of this letter is to be retained for your future reference.

Yours sincerely

Lindsay Jackson
Team Leader/HR Advisor
On Behalf of Sheffield Teaching Hospitals NHS Foundation Trust

I hereby accept the offer of the appointment as mentioned in the foregoing letter, subject to the conditions referred to therein.

Signed  Date 26/2/07

This offer, and acceptance of it, shall together constitute a contract between the parties.

cc. Marica Brozicevich/Angela Driscoll

APPENDIX XXXXXXI

Departmental honorary contract for Birmingham City Hospital

Sandwell & West Birmingham Hospitals NHS Trust

RESEARCH AND DEVELOPMENT

B T Cooper, MD, FRCP — Director R&D
L Jones — R&D Manager (Acting)
B Baines — R&D Administrator

(0121) 507 4946
(0121) 507 4091
Fax(0121) 507 4945
r&d@swbh.nhs.uk

Arden House
City Hospital
Dudley Road
Birmingham
B18 7QH

BTC/bb/RLW1801

5 July 2007

Dr A. L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N 1BN

Dear Dr Mandeville

Re: **The development of a disease specific measure of the impact of beta-thalassaemia major and the examination of the relationship between health related quality of life adherence and psychosocial factors**

I can confirm that the Trust is happy to accept the terms of the existing NHS Honorary Contract from The Whittington Hospital NHS Trust for Mrs Xenya Kantaris to undertake the above study data analysis.

There is no entitlement for researcher's to the payment for following; salary, annual leave, statutory/public holidays, statutory or occupational sick leave from this Trust.

Failure to comply with any Trust Policy requirements may result in the termination of this contract.

Please contact the Research and Development Office if you have any further queries regarding the above.

Yours sincerely

Louise Jones
R&D Manager (Acting)

Sandwell & West Birmingham Hospitals NHS Trust

RESEARCH AND DEVELOPMENT

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Our Ref bb/RLW1801

11 APR 2008

7 April 2008

Dr A. L. Mandeville
Consultant Clinical Health Psychologist
Camden & Islington Mental Health & Social Care NHS Trust
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N 1BN

Dear Dr Mandeville

Re: Research Governance Monitoring of Completed Projects

Project Title: **The development of a disease specific measure of the impact of beta-thalassaemia major and the examination of the relationship between health related quality of life adherence and psychosocial factors**

Project Reference: **RLW1801**

According to our records, you are the Principal Investigator for the above study, which ended December 2007.

As part of your responsibility to comply with the Department of Health's Research Governance Framework I would ask you complete the enclosed "Completed Project Monitoring Form".

Please return to the R&D Department, within 14 day's so that we may update the R&D Records accordingly.

If you have any queries regarding this monitoring form please contact the R&D office on 0121 507 4091. Many thanks for your assistance with this matter.

Yours sincerely

Balvinder Baines
R&D Administrator

Enc

APPENDIX XXXXXXI

Notification of amendment approval letter (3/3)

13 September 2007

Dr. Anna L. Mandeville
Consultant Clinical Health Psychologist
Hunter Street Health Centre
8 Hunter Street
LONDON
WC1N1BN

Dear Dr. Mandeville

Study title: **The development of a disease specific measure of the impact of beta -thalassaemia major (TM) and the examination of the relationship between health related quality of life (HRQoL), adherence and psychosocial factors**

REC reference: **04/MRE03/88**
Amendment number: **Amendment 2**
Amendment date: **16 August 2007**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 13 September 2007.

Ethical opinion

The members of the Committee present gave a **favourable ethical opinion** of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire	Version 1	03 June 2007
Notice of Substantial Amendment (non-CTIMPs)	Amendment 2	16 August 2007

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE03/88:	**Please quote this number on all correspondence**

Yours sincerely

Mr Bill Hackett
Committee Co-ordinator

E-mail: bill.hackett@suntpct.nhs.uk

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

Northern & Yorkshire REC

Attendance at Sub-Committee of the REC meeting on 13 September 2007

Dr F Douglas, Human Geneticist
Dr P Carey, Consultant Haematologist
Mr M Davidson, Lay Member