QUALITY OF LIFE AND ITS PREDICTOR MARKERS IN SICKLE CELL DISEASE IN IBADAN SOUTH WEST NIGERIA

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DECLARATION

I hereby declare that this thesis and the work presented therein are my own and have been produced by me as the result of my own original research.

No part of the thesis has previously been submitted for a degree or any other qualification at this University or any other institution.;

Where I have consulted the published work of others, this has been clearly attributed;

Where I have quoted from the work of others, the source is always given. Apart from such quotations, this thesis is entirely my work;

I have acknowledged all main sources of help.

Date: December 2018

DEDICATION

I humbly and joyfully dedicate this piece of work to IMMANUEL, the blessed and only Potentate, the King of kings and Lord of lords. "For unto us a child is born, unto us a son is given; the government shall be upon his shoulder; and his name shall be called Wonderful, Counsellor, The mighty God, The everlasting Father, The Prince of Peace….. And without controversy great is the mystery of godliness. God was manifest in the flesh, justified in the Spirit, seen of angels, preached unto the Gentiles, believed on in the world, received up into glory"

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Above all, unto the King eternal, immortal, invisible, the only wise God, be honour and glory for ever and ever.

ABSTRACT

Background

Sickle cell disease (SCD) is a genetic, potentially debilitating disease with global spread and public health concern commonly found in people of African origin. Nigeria has the highest burden of the disease in the world. The disease predisposes to high morbidity and mortality rate, increasing comorbid complications with advancing age and impaired quality of life. Understanding fine details of quality of life issues is important to guide the design of comprehensive care protocols. The Wilson and Cleary conceptual model of HRQL is a biophysiological model of health that lends itself as a tool to enhance our understanding of the relationships among the health concepts.

Aim

The aim of the study is to describe the health-related quality of life of people living with sickle cell disease and to characterise the predictors in adults with SCD.

Pertinent questions were answered in pursuit of the aim, they included:

1. What is the profile of HRQL in adults with SCD in the study area?
2. What are the factors that ssociate with the measures of HRQL?
3. How does the Wilson and Cleary model fit the HRQL data of the study population?
4. Are there relationships among the bio-physiological variables, symptoms, functional status, general health perceptions, individual characteristics and the overall quality of life as hypothesised by Wilson and Cleary?
5. What are the patterns and paths of the relationship of the HRQL determinants?
6. What is the relative importance of each determinant?
7. What is the utility score and its determinants in the population?

Methods

A cross-sectional design was used. Sociodemographic and patient-reported questionnaires were used to collect data from a population of 200 adults with SCD aged 18 years and older from two sickle cell clinics in Ibadan, Nigeria. The Wilson and Cleary conceptual model of health-related quality of life was empirically tested using structural equation modelling technique.

Results

Findings supported the Wilson and Cleary model indicating strong relationship between objective and subjective health. Adults with SCD have significantly impaired quality of life predicted by biological and physiological factors, symptoms status, functional status, general health perception and some characteristics of the individual. Symptoms status, indicated by bodily pain, depression, anxiety and somatic symptoms, was the most important contribution to reduced quality of life in the population.

Conclusion

The study underscores the need to include assessment of patients' quality of life as part of measures of medical outcomes beyond the presence or absence of diseases. The insight gained from the study can be used by clinicians to understand how changes in specific clinical characteristics affect a patients' overall health outcomes. A multidisciplinary approach is therefore required to manage the disease because interventions that focused only on biological and physiological variables without considering the patients' experiences of their symptoms will not be fully effective. Routine investigation of the patients' psychiatric status should be integrated in the disease management protocol to be targeted for immediate attention once traces are detected to improve the health-related quality of life of the patients.

OUTPUTS FROM THESIS

The study has produced some publication as listed below:

1. Published papers

i. Ojelabi, A., Graham, Y., Haighton, K. & Ling, J. (2017). A systematic review of the application of the Wilson and Cleary health-related quality of life model in chronic diseases. *Health and Quality of Life Outcomes, 15*:241. https://doi.org/10.1186/s12955-017-0818-2.

ii. Ojelabi, A., Graham, Y. & Ling, J. (2017). Health-related quality of life predictors in children and adolescents with sickle cell disease: A systematic review. *International Journal of Tropical Disease & Health, 22*: 1-14.

2. Papers under review

i. Ojelabi, A.O., Hunter, D., Bamgboye, A. & Ling, J Psychometric properties of SF-36 in sickle cell disease in south west Nigeria. *BMC Medical Research Methodology*.

ii. Ojelabi A.O., Graham Y., Bamgboye A.E., Ling J. Preference-based measure of health-related quality of life and its determinants in sickle cell disease in Nigeria. *PlosOne.*

3. Conference Proceedings

i. Ojelabi A., Graham Y., Ling J. (2017). Anxiety, depression and somatic symptoms in patients with sickle cell disease in Ibadan, Nigeria**.** *International Society for Quality-of-Life Studies*, 15th Annual meeting 27 - 30 September 2017, Austria.

LIST OF ABBREVIATIONS

AMOS: Analysis of Moment Structures (A software programme used to fit SEM) marketed by SPSS

HbSC: the patient carries the ‘S’ gene heterozygously with the ‘C’ gene (the severe form of the disease).

HbSS: the patient carries the ‘S’ gene homozygously (the severe form of the disease)

HRQL: Health-related quality of life

QALY: Quality-adjusted life year

QOL: Quality of life

SCD: Sickle cell disease

SCT: the carrier status whereby only a single ‘S’ gene, responsible for the disease, is present in the person (Sickle cell trait).

SEM: Structural equation modelling

SPSS: Statistical Package for the Social Sciences

WCM: Wilson and Cleary model

WHO: World Health Organisation

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CHAPTER ONE

BACKGROUND AND LITERATURE REVIEW

1.0 Introduction

Worldwide, approximately 1,000 children are born daily with sickle cell disease (W H O, 2006; Aliyu *et al.*, 2008; Piel *et al.*, 2010; Frederic B Piel *et al.*, 2013) and between 70% and 80% of these are in Africa with a prevalence of 2% (W H O, 2006). Nigeria has the highest burden of the disease in the world with over four million people affected (Fleming *et al.*, 1979; Aliyu *et al.*, 2008; Nwogoh *et al.*, 2012). Sickle cell disease (SCD) is a chronic and potentially debilitating disease resulting from an inherited blood disorder associated with multisystem morbidity and high mortality (Juwah, Nlemadim and Kaine, 2003; Lucchesi *et al.*, 2016). The disease is responsible for 6.4% of under-five mortality in Africa (Modell and Darlison, 2008; Ware, 2013) and is associated with reduced life expectancy and increased risk of premature death (Quinn *et al.*, 2010). Studies have shown that SCD patients have poor health-related quality of life along with their families when compared with the general population (Tunde-Ayinmode, 2007; Brandow *et al.*, 2010; McClish *et al.*, 2016). Hence, the need to focus research efforts on disease management protocol or practices that will provide better quality of life for the patients (Ashley-Koch, A., Yang, Q. and Olney, 2000).

1.1 Statement of the Problem

For the last 30 years, the World Health Organisation (WHO) has collaborated with Thalassaemia International Federation, several sickle cell centres and organisations to prioritise hereditary haemoglobin disorders on the health agenda of member states (WHO, 2007). Both the United Nations (2008) and WHO (2006) have emphasised the need for research in countries most affected by SCD to improve the lives of the patients and educate medical professionals, care givers, and associated personnel (World Health Organisation,

2010). Furthermore, the WHO African Region has developed a regional strategy to promote awareness about the disease, engage in preventive activities that would reduce incidence, morbidity and mortality and improve quality of life (WHO Regional Committee for Africa, 2010; page 3).

In developed countries, studies have been carried out to explain factors that influence HRQL in SCD patients; some explanatory factors including the role of socio-demographics, disease severity, depression and the presence of complications have been discovered to explain HRQL in SCD patients (Palermo *et al.*, 2002; Barakat *et al.*, 2008; Palermo, Riley and Mitchell, 2008; Panepinto, 2008). However, such studies are mostly limited to children and are lacking in African countries including Nigeria. Moreover, there is a consensus on the global need for models to explain causal factors (Ferrans *et al.*, 2005). Researchers posited that a major focus for future research is the need to characterize determinants of HRQL and resolve methodological issues through empirical data (Wilson and Cleary, 1995; Muldoon *et al.*, 1998; Berlim and Fleck, 2003; Ferrans *et al.*, 2005). Studies on HRQL of people living with SCD have been few and the focus has been on selected determinants (Fisak *et al.*, 2011). Again, there is a lack of research that has examined multiple determinants of HRQL in SCD patients, in most cases, single determinants were studied which is perhaps, a reason for the limited scientific knowledge of correlates or predictors of HRQL that exist in literature (Palermo *et al.*, 2002).

Evolving research has shown that disease management is incomplete without the evaluation of the HRQL of the patient, hence the increasing agreement among clinicians and social scientists on the need to conduct 'quality of life assessments' considered as adjuvant to clinical and physiological assessments in many chronic conditions (Harrison *et al.*, 2005), when evaluating medical intervention outcomes (Bowling, 1995).

Furthermore, evaluating HRQL has become important in measuring the cost of healthcare because low HRQL has been reported to have inverse relationship with cost of healthcare

(Seid *et al.*, 2004), meaning that interventions and policies that improve HRQL could significantly reduce cost of healthcare. To improve HRQL then, factors that predict or determine HRQL need to be identified and path of relationship understood. Significant determinants may then be categorised in order of relative importance to set up priority variables to be targeted for intervention. Understanding causal factors or predictors of HRQL is a major goal of healthcare interventions (Berlim and Fleck, 2003) and is important to healthcare researchers and providers in designing interventions that will enable patients to have better quality of life.

In previous studies, individual predictors of HRQL in children and adolescents with SCD have been identified, some of which are pain (Barakat *et al.*, 2008; Schlenz *et al.*, 2012; Menezes *et al.*, 2013), socioeconomic status (Hijmans *et al.*, 2010), disease severity/complications (Palermo *et al.*, 2002; Panepinto, 2008; Amr, Amin and Al-Omair, 2011; Fisak *et al.*, 2011; Adeyemo *et al.*, 2015; Sehlo and Kamfar, 2015), comorbidities (Wrotniak *et al.*, 2014), depression (Sehlo and Kamfar, 2015), frequency of hospitalisation (Amr, Amin and Al-Omair, 2011; Dale *et al.*, 2011) and stigma (Adeyemo *et al.*, 2015). However, these and other predictors have only been studied individually but have not been modelled in any study to provide understanding of pattern and pathways of relationship, yet our understanding of factors affecting HRQL may be limited without modelling (Wilson and Cleary, 1995; Ferrans *et al.*, 2005; Sousa and Kwok, 2006).

This study therefore aims to examine the predictors of HRQL in adult with SCD and test the conceptual model of Wilson and Cleary in the study population. This will help to clarify relationships among the physiological/biological variables and the psychosocial variables and HRQL and the causal path of association between the predictors and the outcome variables. This would assist researchers and health care providers to learn about the conditions that have greater impact on patients' lives, evaluate the relative significance of different approaches to patients' care and consequently translate the clinical relevance of

HRQL (Wilson and Cleary, 1995; Sousa and Kwok, 2006) to contribute to the development of the study of quality of life of sickle patients in Nigeria.

1.2 Aim

The aim of the study is to describe the health-related quality of life of people living with sickle cell disease and to characterise the predictors in adults with SCD.

1.3 Objectives

The specific objectives of this thesis are to:

- describe the HRQL profile of adults with SCD attending haematological clinics at Adeoyo and UCH Ibadan, Nigeria;
- characterize predictors of HRQL in adults with SCD attending haematological clinics at Adeoyo and UCH Ibadan, Nigeria;
- test the Wilson-Cleary model on the HRQL in a data of adults with SCD attending haematological clinics at Adeoyo and UCH Ibadan, Nigeria
- create a hierarchy of importance of the determinants as targets for potential intervention; and
- determine the utility score and the associated factors in the sample.

1.4 Research Questions

1. What is the profile of HRQL in adults with SCD in the study area?
2. What are the factors that ssociate with the measures of HRQL?
3. How does the Wilson and Cleary model fit the HRQL data of the study population?
4. Are there relationships among the bio-physiological variables, symptoms, functional status, general health perceptions, individual characteristics and the overall quality of life as hypothesised by Wilson and Cleary?
5. What are the patterns and paths of the relationship of the HRQL determinants?
6. What is the relative importance of each determinant?

7. What is the utility score and its determinants in the population?

1.5 Significance of the Study

One of the current challenges of research in quality of life is devising appropriate models to clarify the elements of HRQL and the causal relationships among them (Ferrans *et al.*, 2005). Identifying predictors of HRQL in adults with SCD will help to guide therapeutic interventions so that life will be worth living for the patients.

Leading health organisations (CDC, 2000; Healthy people, 2011; WHO. 2007) have identified HRQL as a goal for all people across all life stages (Bakas *et al.*, 2012) and quality of life issues has become major concerns of policymakers, researchers and health care practitioners (Till *et al.*, 1994). The findings may also help in counselling and advocacy and health education to improve the HRQL of SCD patients.

The responsiveness of changes in predictors will help to track changes in HRQL for clinical research improvement in healthcare. Prediction of changes over time in HRQL due to specific interventions will be possible. In literature, attention has been focused on HRQL either as a measure of the impact of chronic illness on functioning or as a measure of treatment outcome, only few studies have examined the factors that determine HRQL in SCD populations (Fisak *et al.*, 2011). In Nigeria, studies in HRQL are rare, only one study has been found which investigated the perception of stigmatization and HRQL of adolescents with SCD (Adeyemo *et al.*, 2015). No study has attempted to model and characterize several variables that have been hypothesized in previous studies as individual predictors of HRQL in SCD.

The Wilson and Cleary model allows a simultaneous testing of several variables and a link between the biological and psychosocial variables does not appear to have been tested in SCD population anywhere. This study is thus the first to test WCM in a sickle cell population and in Nigeria.

Measuring HRQL is important for evaluating different aspects of disease management. An empirically tested theoretical model will assist researchers and practitioners to better understand latent relationships between HRQL and the determinants. This may influence or guide researchers in the development of appropriate means to optimize both the physiological outcomes and HRQL of people with SCD. Furthermore, understanding the patient's HRQL can offer a unifying theme for diverse health and social service, and economic programmes which aim to improve population well-being as well as bridge boundaries between disciplines and between social, mental, and medical services. This will supplement public health's traditional measures of morbidity and mortality and help determine the burden of the disease or assist in counselling the patients. In addition, proper analysis and documentation of the behaviour of the outcome variable HRQL, can help identify subgroups with relatively poor perceived health and help to guide interventions to improve their situations. These can inform targeted health policies and promote the practice of needs-based allocation of resources, as well as guide healthcare strategic plans development legislation as recommended by the World Health Organisation ((W H O, 2006).

1.6 Contributions to knowledge

This thesis makes an original contribution to knowledge in the following areas:

1. Quality of life has become a major concern of policymakers, researchers and healthcare practitioners (Till *et al.*, 1994) but a major current challenge is devising appropriate models to clarify the elements of HRQL and the causal relationships among them (Wilson and Cleary, 1995; Ferrans *et al.*, 2005). This is the first study, as far as I am aware, to test the Wilson and Cleary biopsychosocial model in sickle cell disease. This thesis contributes to research on quality of life by demonstrating the applicability of Wilson and Cleary model in sickle cell disease.

2. Globally, few studies have examined the factors that determine HRQL in SCD populations (Fisak *et al.*, 2011). Few studies have examined HRQL in Nigeria, and this is the first study to characterize predictors of HRQL in adults with sickle cell in Nigeria.

3. This study is also the first to investigate preference-based health-related quality of life in adult with sickle cell disease in the Nigerian population; only one study has derived utility for SCD previously, in a UK population (Anie, Steptoe and Bevan, 2002).

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1.7 What is health?

Health is a multidimensional construct (Kalnins and Love, 1982; Eberst, 1984; Laffrey, 1986) and both health and illness are difficult concepts to define (Curtis, 2000). This is because individuals have different ideas of health and illness which influence their health attitudes and behaviours (Boruchovitch and Mednick, 2002).

Health is a valued resource that can prolong duration of life and improve wellbeing and overall quality of life (Curtis, 2000). Health and illness are not distinctly separate concepts but there are degrees of illness and wellness. Antonovsky (1987) viewed these concepts as ends of a continuum and noted that "we are all terminal cases, and we all are, so long as there is breath of life in us, in some means healthy" (p.3).

There have been various definitions of health without consensus. Balog (1979) categorised definitions of health into three major views namely; traditional medical concept, the ecological concept and the WHO or official concept of health.

The traditional medical concept assumes that health and disease are objective and observable phenomena and regards health as a condition free of diseases in which there is no symptoms and signs of ill health (Curtis, 2000). This view was promoted by developments in anatomy, bacteriology and physiology; the drawback of this view is that it conceptualises health by laying emphasis on illness, and only focuses on the body part that is affected with disease but neglects the total individual (Boruchovitch and Mednick, 2002). This is the philosophy behind the biomedical model of health (See 2.2.1).

The ecological concept views health as relative and places emphasis on interrelationships between the environment and the individual's quality of life (Boruchovitch and Mednick, 2002). The focus is on evaluation of the person's level of functioning and adaptation to the environment. Thus health is conceived in terms of an adequate functional capacity that does not hinder performance of daily activities or in terms of quality of life which gives the

individual a sense of happiness, success, fruitfulness and creativity (Hoyman, 1962). This view is criticised because it fails to clearly distinguish between what constitutes a healthy and an unhealthy adaptation. For example, individuals may adapt to sick, morbid or disease-provoking conditions or otherwise, a sick person may still be able to perform some social responsibilities (Lewis, 1953). Furthermore, if terms like normality, proper functioning and adaptation are culturally and socially defined, what is reckoned as healthy in one context might be unhealthy in another (Parsons, 1958).

The World Health Organisation states that "health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" (World Health Organization, 1948, p. 1). The WHO concept of health, freely quoted as the official definition of health, was viewed as more holistic in that it de-emphasises the negative concept of health (absence of disease) and focuses on the presence of absolute and positive qualities. This concept supports the importance of evaluating psychosocial factors in measuring health status and well-being and in identifying health with subjective wellbeing. According to the definition, health and illness are conceptualised as multi-causal such that the components of physical, mental and social domains of life are recognised to influence state of health and illness. The WHO concept of health therefore embodies the social model of health, referring to the multifaceted and holistic view of health. The definition integrates two essential components of a health concept: firstly that man is an entity of biological, psychological and social elements and secondly that health is based on the individual's perspectives (Barenthin, 1975). This definition therefore has been widely accepted as presenting the holistic view of health and regarded as a significant milestone in the development of quality of life studies within healthcare (Galloway, Bell, Hamilton and Scullion, 2006; Gurková, 2011). The definition gives a positive dimension of health as a complete wellbeing and has shifted attention away from preoccupation with disease to give recognition to the interaction between individual and their environment in determining

health such that health is viewed as an interaction between biological processes and psychological and social factors (Edelmann, 2000). However, the wide acceptance of WHO's definition has not insulated it from criticism; there are those who described the definition as being over ambitious (Downie, Fyfe and Tannahill, 1990). The criticism has been based on three major issues: difficulty with measurement, impossible to attain, and not relevant to changing disease demographics (Larson, 1999; Bowling, 2001; Jadad and O'Grady, 2008).

The concept was perceived as difficult to measure because the definition is broad and vague, without specificity to be defined operationally (Lewis, 1953; Bowling, 2001). This limits its use in practice because 'complete' is neither operational nor measurable. The idea of complete perfect state of health is argued to be unrealistic and unattainable (Banyard, 1996). According to Huber and colleagues, this is an unintentional contribution to the medicalisation of society because setting complete health as the norm will mean that most people will almost perpetually be in a state of ill-health (Huber *et al.*, 2011). Huber et al., have further argued that persistent emphasis on complete physical wellbeing would identify many people in the population as eligible for screening and expensive interventions, when perhaps only one person might benefit. Additionally, the demographic shift in disease nature has also contributed to the near obsoleteness of the WHO concept today. Disease patterns have transformed over the years from acute to chronic nature leading to a global increase in the number of people living with chronic diseases and many countries now carry significant burden of chronic diseases compared to seven decades ago when the definition was first published (Kanungo *et al.*, 2010; Huber *et al.*, 2011). For example, in developed countries, over 50% of all adult deaths are caused by three chronic diseases: cancer, heart disease and stroke (WHO, 2004). Huber et al. insisted that the WHO definition has declared, "people with chronic diseases and disability definitively ill" and has by so doing "minimised the role of human capacity to cope autonomously with life's ever changing physical, emotional and

social challenges and to function with fulfilment and a feeling of wellbeing with a chronic disease or disability (Huber *et al.*, 2011, p. 2).

In the light of the perceived weaknesses of the WHO definition, there have been various calls for a new conceptual framework of health that will characterise a widely accepted direction that could serve as reference (Huber *et al.*, 2011). The Ottawa charter for health promotion (WHO, 1986) has suggested a definition that emphasises social and personal resources and physical capacity. Huber and colleagues also supported the Dutch's approach which views health as: "the ability to adapt and self-manage". The implications of this lack of agreement is that health research is better approached using a conceptual framework which should encompass the physical and mental and social domains of health (Huber *et al.*, 2011).

1.8 Models of health

Three major health models are discussed in this section. They are the biomedical, the psychosocial and the biopsychosocial models.

1.8.1 The Biomedical model

The biomedical model was the dominant concept in medical science in the twentieth century arising from the influence of Rene Descartes (1596-1650) who theorised that mind and body were separate entities. The biomedical model of health and illness rested on several assumptions.

One of the assumptions was that health and illness are opposing state of bodily functioning where health indicates 'normal' biological functioning and illness is a deviation from the norm. Based on the doctrine of specific aetiology, the causes of illnesses are known and knowable; they are mainly pathogen, such as virus or bacteria or genetic defects (Naidoo and Wills, 2005) and the only means of treatment is by rectifying or restoring biological functioning by chemical means or removing the faulty parts by surgery or radiation. Current

knowledge has rendered this assumption faulty in that diseases like diabetes and heart disease result from causes which may interact with one another, for instance, heart disease may be caused by a combination of genetic factors, diet and lifestyle/behaviour and each contributes to the treatment process (Curtis, 2000). Another assumption was the mind-body dualism, from the Cartesian postulate which regarded the body as separate from the mind. This assumption reduced illness to merely biochemical process devoid of any social or psychological processes. This 'reductionist' approach explained a complex phenomenon only in terms of disordered biological functioning while ignoring the multiplicity of factors which combine with biological processes to cause illness. Attention was on failing or failed health and identification of treatment without considering promotion and maintenance of health (Engel, 1977; Antonovsky, 1987; Boruchovitch and Mednick, 1997; Curtis, 2000). The reality is that the mind influences the body and vice-versa.

Though the biomedical model has greatly enhanced our understanding of biological causes and treatment of disease, it has several limitations. Research has shown that health is not only determined by disease and biology but partly by social factors such as living condition and personal habit such as smoking, while social and psychological factors have been found to influence treatment efficacy. In addition, there have been cases of people who seek medical help for distress or illness associated with 'problems of living' without any identifiable disease process (Kellner, 1985; Barsky *et al.*, 1993). Furthermore, patient's experiences of illness are poorly addressed in biomedicine. This often increases the patient's level of distress especially when disease processes are not evident, for example, more than 50% of GP visits are for the non-disease based complaints (Carson *et al.*, 2000). Thus, a biomedical approach to resolve such complaints might result in unsatisfactory treatment and a continuation of patient's illness.

The biomedical model ignores the social, psychological and behavioural dimensions of illness (Engel, 1980) and is therefore criticised because it is considered to rely on costly and

sometimes harmful treatments and fails to promote prevention, health enhancement or individual responsibility for health (Gordon and Fadiman, 1984). Also, it has been argued that biomedical models treat only the agents of disease and ignore the hosts, Blaxter (2010) argued that the concept of health and ill-health are asymmetrical; they are not simply opposites as conceptualised by the biomedical model, he opined that the absence of disease may be part of health, but health is more than absence of disease.

1.8.2 The psychosocial model of health

The psychosocial model of health presents health as a product of social, biological and environmental factors with less focus on the role of specialists but more attention on why people are healthy, emphasis on self-help and environmental activity and people being helped to take control over their own health (Naidoo and Wills, 2016).

In a study of the combined mortality from scarlet fever, diphtheria, whooping cough and measles among children up to 15 years, Illich (1976) noted that about 90% decline in mortality between the years 1860 and 1965 was outside the introduction of antibiotics and widespread immunisation. He claimed that improved housing and better nutrition were responsible for reduced mortality. He also identified poverty and poor nutrition as factors responsible for frequent occurrence of diarrhoea and upper respiratory tract infections in poor countries. Illich insisted that environment is the primary determinant of the state of general health of any population. He identified food, water, and air as correlates of the level of socio-political equality and the cultural mechanisms that keep the population stable and argued that these are the factors responsible for determining how healthy grown-ups feel and at what age adults die (Illich, 1976). In line with the submission of Illich, social scientists who belonged to his school of thoughts argued that the biomedical model was not adequate to provide understanding of health and illness, they therefore emphasised the need for

alternative approaches to enhance understanding of the concept of health and illness as it affects the individual (Curtis, 2000).

The concept of social health recognises social factors such as poverty, lifestyle or behaviour as important in a model of the causes of ill health. The social model locates biological processes within their social context and considers the person as a whole rather than a series of distinct bodily systems (Illich, 1976). Antonovsky's (1979) 'salutogenic' concept of health involves focusing on what facilitates health, rather than what causes or prevents disease, that is, to focus on successful physical and mental coping. In other words, Antonovsky identified why some people remain healthy and how they cope despite adverse circumstances, change and stress he labelled as 'sense of coherence' the human ability that involves understanding, managing and making sense of change and suggesting that these human abilities could be nurtured or hindered by the wider environment (Antonovsky, 1979, 1987; Naidoo and Wills, 2016). The social model projects health as a positive state of wholeness and wellbeing explained by an integration of multiple factors which include the absence of disease, illness or physical and mental impairment as well as social and spiritual dimensions (Madjar, 1992). In addition, the psychosocial model encourages prevention and health promotion rather than relying on medical intervention which often carry high financial burden and health risk. The psychosocial model has been described as a more realistic model because of the role that lifestyles play in disease (Sheridan and Radmacher, 1992). For example, studies have shown that behavioural factors are involved in seven of the ten leading causes of death in the US (Raub, 1989).

1.8.3 The Biopsychosocial model of health and illness

The biomedical model and the psychosocial model follow different paths in their concepts of health. Observing the gaps, Engel (1977) has proposed a biopsychosocial model to harmonise the divergent health concepts in the biomedical and psychosocial models to

provide a better understanding of health. According to Engel, to properly understand and adequately respond to patients' suffering, and to give them a sense of being understood; it is important that clinicians attend simultaneously to the biological, psychological, and social dimensions of illness (Engel, 1977). His holistic model draws attention to the interrelatedness of body, mind and environment emphasising that no single one of these factors can sufficiently influence health or illness but rather in conjunction with the others. The model recognises health as an illness-wellness continuum thus creating a balance of the negative and positive perspectives.

Engel's biopsychosocial framework outlines the complex interplay of biological, psychological and social factors in the determination of wellness or disease outcomes. The biological system, including the immune and nervous systems, consists of organs, tissues and cells; the psychological system which include experience and behaviour is made up of cognitions, emotions and motivation while the social system includes society, community and family as subsystems. As systems, they are constantly changing and have components which interrelate. Health then operates as a complex interplay of factors within these factors (Engel, 1977).

A better understanding of health and illness can be achieved by examining the interactions between social and individual factors with biological elements. Health is determined by behaviour, attitudes and affective state, which is in turn influenced by aspects of the broader environment, such as employment and living standards. Evidence showed that social and environmental factors have impact on health (Khanna *et al.*, 2007). Therefore, any model or explanation which does not take into account this multiplicity of factors is likely to provide an inadequate representation of health and illness (Engel, 1977, 1980; Kazarian and Evans, 2001).

Engel viewed biopsychosocial model as a more complete and inclusive conceptual framework necessary to guide clinicians in their everyday work with patients. He wrote:

> Biopsychosocial thinking aims to provide a conceptual framework suitable for developing a scientific approach to what patients have to tell us about their illness experiences (Engel, 1997, p. 523)

In summary, a biopsychosocial model can be applied to study health in order to understand the whole person or adopt a holistic approach. A holistic model of health implies that professional health workers can only address some and not all aspects of health or ill-health which necessitates that health workers work in collaboration with others in order to achieve optimum results (Naidoo and Wills, 2016). The biomedical model diagnoses the disease to show the required intervention and summarises the morbidity and mortality, while the psychosocial model reveals the impact of disease condition and intervention on the patient's health. The integrated concept then makes it possible to clearly understand the condition of the individual and interventions offered will be directed towards meeting the patient's needs (Bowling and Ebrahim, 2005).

The usefulness of the biopsychosocial model in health research and practice has been acknowledged in literature. Wilson and Cleary (1995) described health as a continuum of increasing biological, social and psychological complexity and employed the principle to develop a conceptual framework to link clinical variables to patients' perspectives.

1.9 Sickle Cell Disease Overview

The following section provides a general overview of the sickle cell disease

1.9.1 Definition and aetiology

Sickle cell disease (SCD) belongs to a group of diseases caused by inherited disorders of haemoglobin. These disorders are generally referred to as haemoglobinathies (genetic defect,

i.e. abnormal haemoglobin in the blood). Approximately 5-7% of the world population are affected with heameoglobinopathies (Modell and Darlison, 2008). SCD is the most severe and common haemoglobinopathy affecting over 5% of the world population (WHOQOL group and others, 1995; World Health Organization, 2008).

Haemoglobin is an iron rich protein that transports oxygen in the blood and give the colour to the red cells. Haemoglobin molecule has two subunits namely alpha globin and beta globin. The problem in sickle cell was brought about by a mutation in the beta (β) globin gene at position 6 of the beta subunit, and a replacement of the normal glutamic acid with the amino acid valine takes place at this position (Sant'Ana *et al.*, 2017). The disease damages and alters the shape of the red blood cells into a crescent (sickle) form. The sickle haemoglobin (HbS) is insoluble when deoxygenated. As the oxygen uptake of the cell is low, the shape of the cells is distorted from a healthy round disc to a crescent or sickle shape, a distortion referred to as sickling (Pauling *et al.*, 1949). Thus, the disease is known as sickle cell disease. The rigid sickle shaped cells are hard (insoluble) and sticky compared with normal healthy cells. The hardness may obstruct blood vessels, or they may stick together and obstruct blood vessels. These obstructions are responsible for harsh painful complications (vaso-occlusive crisis). The disease is also referred to as sickle cell anaemia (SCA) as a result of the frequent breakdown of the red blood cells (haemolysis) resulting in anaemia.

Due to haemolysis, survival of the blood cells may be reduced to as little as 20 days (Wilson, Krishnamurti and Kamat, 2003) compared to normal blood cells which lives between 110-120 days in the blood stream (Allison, 1960). The consequence of haemolysis also includes jaundice, aplastic crisis (red blood cells unable to mature resulting in worsening anaemia) and retarded growth.

As an autosomal recessive disease (Pack-Mabien *et al.*, 2001), SCD is determined at conception. The genes that children carry are inherited from their parents, hence having a sickle cell is a consequence of the type of genes the parents pass on to their children. If the child inherits a 'sickle gene' from one of the parents and a normal gene from the other, he is a carrier for the sickle cell disease or said to have sickle cell trait (SCT)

1.9.2 Sickle cell trait

Children who inherit one copy of the sickle haemoglobin (HbS) from one of the parents and a normal gene (HbA) from the other parent are said to have a carrier status (HbAS). This carrier state is known as sickle cell trait (SCT). Though people with SCT live normal, healthy life, recent discovery has shown that some complications could be present in people with SCT under conditions of severe biological stress. For example, SCT has been indicated as a risk factor for sudden death during physical training (Eichner, 2010).

In a study of causes of sudden death in athletes ages 8 to 39 years, Harris et al.(2012) reported that 0.9% of deaths in a cohort of 2,462 sudden deaths was associated with SCT and 2.6% of footballers died suddenly of SCT-related complications. They suggested that vigorous exercise and elevated temperatures may trigger sudden death in people with SCT (Harris *et al.*, 2012).

Individuals with SCT (HbAS) have been found to exhibit higher resistance against malaria when compared with those with normal gene (HbAA). This survival advantage (discussed below) is linked to the high prevalence of the HbS in malaria endemic regions of the world, for instance, HbS occurs in 8% Americans and in 24% Nigerians (Harris *et al.*, 2012). This discovery gave rise to the malaria hypothesis which is discussed later in this chapter.

1.9.3 Pattern of inheritance

The pattern of inheritance in sickle cell disease follows the principles of heredity as proposed by Gregor Mendel (1822 - 1884). If one of the parents has SCT and the other has normal genes the child cannot have SCD but has 50% chance of having SCT. If both parents have SCT, the child has 25% of having SCD and 50% of having SCT (Mendel, 1965; Mendel, Stern and Sherwood, 1966) (see Figure 1-1).

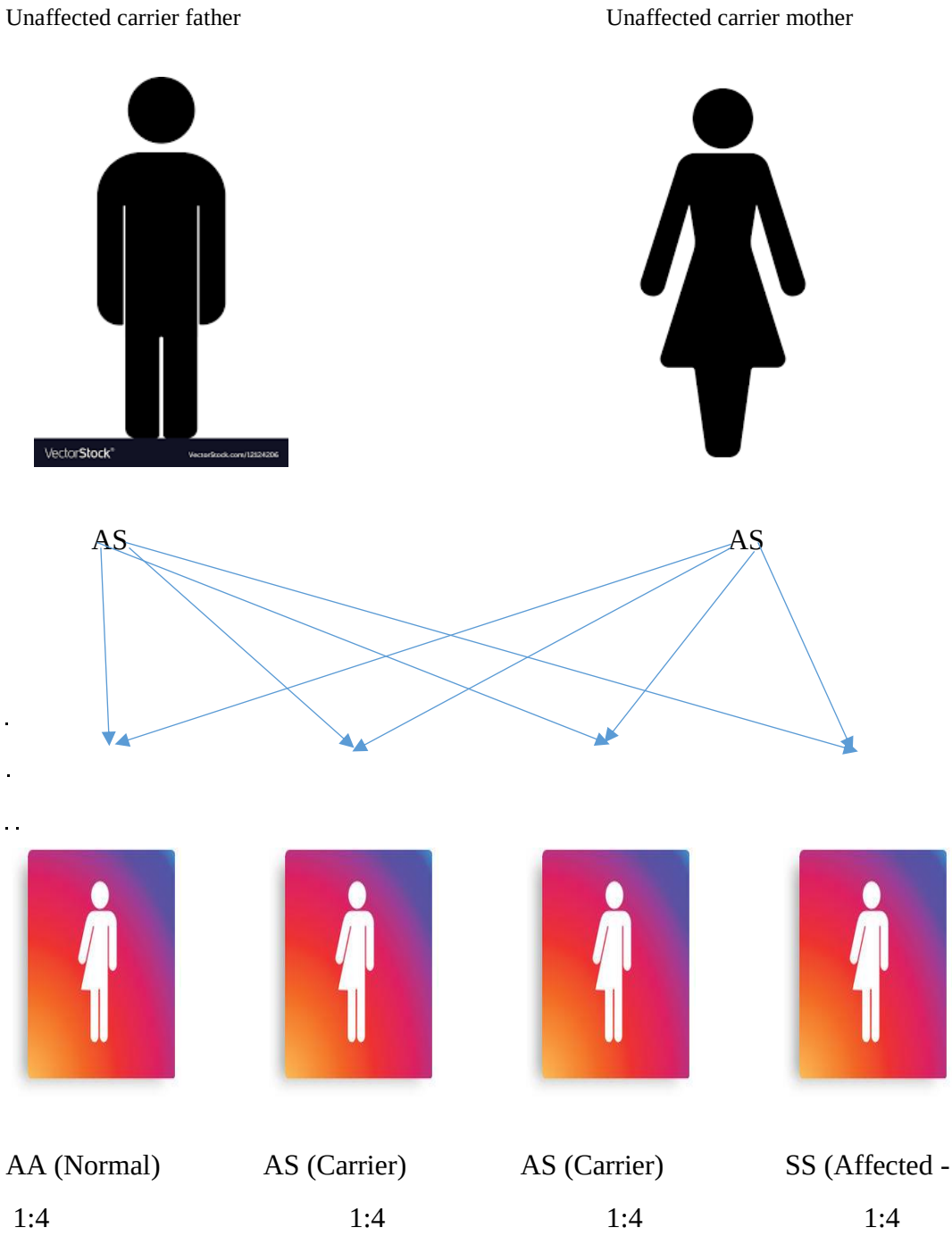


Figure 1-1: Pattern of Inheritance.

1.9.4 Classification

The chromosome structures of the SCD are referred to as haplotypes. There are four main African haplotypes and one Asian haplotype of the beta-globin chain genes. The African haplotypes are, Bantu, Benin, Cameroun and Senegal haplotypes. The Bantu (Central-African Republic) haplotype is the most severe disease phenotype reputed to have twice increased risk of complications (which include higher incidence of organ damage, and renal failure) and early mortality when compared with other haplotypes (Powars and Hiti, 1993). The Asian or Arab-Indian haplotype has a mild disease phenotype associated with higher foetal haemoglobin (HbF) which has been indicated to be responsible for reduced severity of the disease and improved survival (Tewari and Rees, 2013). Several forms of SCD are related to these chromosome structures.

The most common form is the homozygous (HbSS) often referred to as sickle cell anaemia (SCA). This is a condition in which the individual affected inherits the sickle haemoglobin (HbS) from both parents. The resultant HbSS genotype is the most severe form of SCD and accounts for 70% of causes of the disease in African population (Rees, Williams and Gladwin, 2010). The other common but milder form of SCD is the HbSC which is a co-inheritance of the β^s and β^c alleles to form HbSC. The HbSC is present in 25-30% of African population (Modell and Darlison, 2008; Rees, Williams and Gladwin, 2010). The HbS /β-thalassaemia is another form of SCD found in people of the Mediterranean origin. Other variants include HbC, HbD common in Punjab HbO among the Arabs. In a study of 143 patients with SCD in Jamaica, 70% had HbSS, 24% HbSC and 6% HbSβ – thalassaemia (Gibson *et al.*, 2013). In a longitudinal study of 230 African-American people with SCD Soghutlu et al. (2011) reported that 71.7% had HbSS while 24.5% had HbSC. They are often classified as severe, moderate, mild or very mild as depicted on Table 1-1.

Table 1-1: Classification of Sickle Cell Disease

Sickle cell disease	Characteristics	Population where found
A. SEVERE		
HbSS	Inheritance of the double 'S'(homozygous). Most common form of sickle cell disease generally known as sickle cell anaemia (SCA)	Africa especially sub-Saharan Africa
HbSβ^0 thalassaemia	Most prevalent in the. Almost clinically indistinguishable from sickle cell anaemia.	Eastern Mediterranean region and India
Severe HbSβ^+ thalassaemia	Most prevalent in the 1-5% HbA present	Eastern Mediterranean region and India
HbSO Arab	Rare	North Africa, the Middle East, and the Balkans, occurs worldwide but predominant in Northern India
HbSD Punjab		
HbSC Harlem	Resembles HBSC but clinically severe, double mutation in β-globin gene, very rare	
HbC/S Antilles	Double mutation in β-globin gene results in severe SCD when co-inherited with HbC, very rare	
B. MODERATE		
HbSC	25-30% of SCD in population of	African origin
Moderate HbSβ^+ thalassaemia	6-15% HbA present	Mediterranean region
HbAS Oman	Dominant form of SCD caused by double mutation, rare	Arabian origin
C. MILD		
Mild HbSβ^+ thalassaemia	16-30% HbA present	African population
HbSE	Uncommon and mild	Southeast Asia
HbA/Jamaica plain	Double mutation results in low Hb with oxygen affinity, very rare	
D. VERY MILD		
HbS/HPFH	Group of disorders caused by large deletions of the β-globin gene complex, typically 30% foetal haemoglobin. symptom-free	
HbS/other Hb variants (**r**are combinations of HbS with HbD Los Angeles, HbO Arab, G-Philadelphia, among others)	Hbs is co-inherited with many other Hb variants	

Source: Rees, D.C., Williams, T.N. and Gladwin, M.T., 2010. Sickle-cell disease. *The Lancet*, *376*(9757), pp.2020.

Note: ***HbSS*** *- homozygote for the beta S globin,* ***HbS*** *β^0* ***(beta0) thalassaemia*** *– double heterozygote for HbS and beta0 thalassaemia,* ***HbSC*** *- double heterozygote for HbS and HbC, HbSβ^+* ***beta+ thalassaemia*** *- double heterozygote for HbS and beta+ thalassaemia,* ***HbS/hereditary persistence of fetal Hb (S/HPHP), HbS/HbE syndrome.***

1.10 History of SCD

SCD was discovered in 1910 when a dental student, Walter Noel, who originated from Grenada but studying in Chicago, presented to Dr Herrick with complaints of pain and symptoms of anaemia. The blood from Noel was examined by Dr Irons, who described it as 'having the shape of a sickle'. A subsequent paper from Herrick used the term 'sickle shaped cell' to describe the irregular-shaped red blood cell. This was the first published scientific article to describe the shape of the cells responsible for the disease. However, in 1874, 36 years prior to Herrick's paper, a Dr Horton from Sierra Leone had given a written description of clinical signs and symptoms of what is now referred to as SCD (Adewoyin, 2015). Additionally, there had been cultural references in Africa for centuries to an illness referred to as 'rainy season rheumatism' which appeared to be hereditary in families (Konotey-Ahulu, 1991). The 'rainy season' coinage was probably due to their observation of colder temperature, associated with rainy season period as a precipitant of pain crisis in the affected. This was supported by a multicentre study across Virginia in the US which reported that adults with SCD experienced worsening disease condition during colder seasons (Smith *et al.*, 2008). In the South-Western part of Nigeria, the Yorubas normally referred to this illness as 'arun aromoleegun' which translates to a disease accompanied with 'aches and pains in the bones'. This is similar to a vivid description of the bone pain crisis that patients with SCD experience. This means that the disease has been known to people of African origin before the discovery by Herrick in 1910.

Further insight into SCD continued in 1927 when Hahn and Gillepsie observed that by removing oxygen (deoxygenation), the blood of the person with the disease could be made to sickle, thus concluding that deoxygenation played a crucial role in the sickling of the cell. In 1949, two articles were published independently, one by Col Beet, a military doctor in Mozambique and the second by James Neil of the University of Michigan. Both articles revealed that SCD was hereditary and that people with SCT were heterozygous (HbAS) or

carriers for the gene while those with the disease were homozygous, had two copies of the gene (HbSS). In 1951, Dr Pauling and Itano discovered the association of the disease with haemoglobin by demonstrating that the chemical structure of haemoglobin in a person with SCD is different from that in the person without the disease. In 1956, Ingram, made a discovery of the actual amino acid substitution which differed from the normal haemoglobin (HbA). Ten years later, Welch and Goldberg introduced and described much of the modern terminology associated with sickle cell disease with respect to ocular changes. In 1971, Goldberg proposed a classification for sickle cell retinopathy (Goldberg, Charache and Acacio, 1971). In 1972, the US 92nd congress passed the National Sickle Cell Control Act which paved way for the commencement of the first state-wide screening programme for SCD in the US in 1975.

The first reported case of cure was in 1986 with a bone marrow transplantation in a child with sickle cell. The cure was accidental as the transplantation was carried out to treat acute leukaemia, but the child was discovered to be free from the symptoms of SCD after the transplantation. Further interventions are noted in that Gaston et al. (1986) demonstrated the value of oral administration of penicillin in reducing morbidity and mortality in children with SCD. In 1995, a multicentre study of Hydroxurea (Hu) in sickle cell anaemia was completed revealing that Hu has the potential to prevent complications in SCD (Charache *et al.*, 1995). The study of SCD, its clinical manifestation, search for cure and management of the disease has since engaged the attention of researchers, policymakers, health care practitioners and international organisations.

1.11 Epidemiology of Sickle Cell Disease (Incidence and Prevalence)

Sickle cell disease is the most predominant haemoglobinopathy in the world (Modell and Darlison, 2008; World Health Organization, 2008). The disease occurs in 193 countries of the world (Modell and Darlison, 2008; Center for Disease Control and Prevention., 2016).

SCD has been described as the fastest growing and most frequent inherited disorder in England (Pizzo *et al.*, 2015). The prevalence is 1 in every 2400 births (National Institute for Health and Care Excellence NICE, 2016) about the same range as Cystic Fibrosis (NHS, 2006). France has about 12,000-15,000 people affected with the disease about the same as UK (Brousse et al, 2014; NICE, 2016) and a prevalence of 1 in 2472 births in USA (Center for Disease Control and Prevention., 2016). Approximately 80,000-100,000 US citizens are affected compared with 30,000 people with Cystic Fibrosis (Smith *et al.*, 2006; Brousseau *et al.*, 2010). In India, around 40, 000 children are born annually with the condition and 10,000 in Eastern Mediterranean (Piel *et al.*, 2013). The prevalence in Africa is 2% or 1 in 50 births representing approximately 240,000 births annually (WHO, 2007; Modell and Darlison, 2008). While the Democratic Republic of Congo accounts for 40,000 of the annual birth (Piel *et al.*, 2013; Brousse, Makani and Rees, 2014), Nigeria with a prevalence of 2-2.39% (WHO, 2007; Nwogoh *et al.*, 2012) is responsible for between 90,000-150,000 of this population of children born with SCD (W H O, 2006; Aliyu *et al.*, 2008; Modell and Darlison, 2008; Frederic B Piel *et al.*, 2013; Brousse, Makani and Rees, 2014; Carey, 2014) This figure has been projected to increase to 140,000-200,000 by the year 2050 (Piel *et al.*, 2013).

The sickle cell trait or carriers is present in 5% of the world population (Modell & Darlison 2008; WHO 2011). Sickle cell carriers are at risk of passing the gene to their children (See Figure 1-1). Globally, over 300 million people have the sickle cell trait (Grant *et al.*, 2011). There are 240,000 people in UK (NICE, 2016) and an estimated three hundred thousand in USA (NCBDDD, 2011). Cuba has 3-7% prevalence of carriers (Granda *et al.*, 1991), while Brazil has approximately 4% (Santos and Gomes Neto, 2013). The prevalence of SCT ranges between 10% and 40% across Africa but less than 2% in North and South Africa. In some West African countries, the carrier prevalent is between 15% to 30% and up to 45% among the Bantu people of Central Africa. In Nigeria, the estimated carrier prevalence is 24% (W

H O, 2006; Aliyu *et al.*, 2008; Modell and Darlison, 2008; Frederic B Piel *et al.*, 2013; Brousse, Makani and Rees, 2014; Carey, 2014) which translates to over 40 million people.

1.12 Factors responsible for the HbS allele frequency

Two major factors are discovered to be responsible for the frequency and geographical spread of the sickle cell gene (HbS). They are the malaria factor and the migration factor.

1.12.1 The malaria factor

Alison (1954) suggested that sickle cell trait offered protection against malaria infection. Further research has documented substantial evidence to support the possible role of malaria in the mutation of the gene. For example, it has been discovered that a significant correlation exists between incidence of malaria and the prevalence of the HbS gene (Rees, Williams and Gladwin, 2010). In addition, carriers are found to exhibit resistance to all forms of *plasmodium falciparum* malaria (Serjeant and Serjeant, 1992). Those who survived malaria did pass on the gene to their children thus acting like a selective factor that resulted in increased prevalence of the gene. The prevalence of SCD in people from the malaria endemic regions of Africa and the Mediterranean seem to support this hypothesis (Galadanci *et al.*, 2013). However, the protection against malaria is only in people with sickle cell trait. Malaria has been found to be a risk factor for people with the double sickle gene HbSS (W H O, 2006) and contributes to mortality, anaemia and other crises in SCD (McAuley *et al.*, 2010; Williams and Obaro, 2011).

1.12.2 The migration factor

Human migration especially across continents has been increasing since the 1960s (OECD, 2014). In 2015, 244 million people (3.3% of the world population) lived outside their country of origin due to the demand for their economic skills, escape from crisis and better education (United Nations Population Fund, UNFPA, 2015). This, along with slave trade has been

responsible for the incidence of SCD in countries like UK, US and parts of Europe (Modell *et al.*, 2007).

SCD is found with varied incidence and prevalence in over 70% of the countries of the world (Modell and Darlison, 2008) but traced to people from particular regions of the world indicating that the spread may be due to migration especially since SCD is not a contagious disease. SCD is particularly common in sub-Saharan Africa; Spanish-speaking regions in the Western Hemisphere, South and Central America, the Caribbean, India, and Mediterranean countries (Center for Disease Control and Prevention., 2016) but there are current evidence of rising population of people with SCD in countries like the Ireland, Scandinavia, Australia and South Africa which were previously free from incidence of the disease (Ware, 2013).

1.13 Pathophysiology

Sickle cell disease occurs as a result of a single-point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of haemoglobin (Schnog *et al.*, 2004). This process results in a mutant form of haemoglobin referred to as sickle haemoglobin (HbS) (Kanter and Kruse-Jarres, 2013). People who inherit two copies of the HbS mutation are homozygous (HbSS) and have the sickle cell disease phenotype but the heterozygous carriers (HbAS) referred to as sickle cell trait do not exhibit clinical disease (Kanter and Kruse-Jarres, 2013). Other forms of SCD result when mutations associated with other aberrant type of haemoglobin (C or E) or β-thalassemia combine with HbS as a compound heterozygous mutation (haemoglobin genotypes SC, SE, $S\beta^{+}$ or $S\beta^{0}$). People with HbSS and $Hb\beta^{0}$ have been known to demonstrate the most severe form of SCD (Kanter and Kruse-Jarres, 2013).

1.13.1 Pathological processes

Events behind severe morbidity and mortality in SCD are complex and yet to be fully understood. However, current knowledge has identified two major pathological processes. They are vaso-occlusssion and haemolysis.

Vaso-occlussion occurs as a result of the sticky nature of the sickle cells. When these cells stick together they block blood vessels and obstruct the flow of blood. This phenomenon (vaso-occlussion) results in what is known as acute vaso-occlusive crisis or painful crisis (Galadanci *et al.,* 2013). This event has been found to be the cause of acute and chronic ischaemia which is responsible for acute pain, organ damage and related complications in people with SCD.

Haemolysis (the breakdown or destruction of the red blood cells) is responsible for anaemia, vascular endothelial damage resulting in many complications including pulmonary hypertension, priapism and stroke. In childhood, the major cause of mortality is bacterial infections especially pneumococcus (Barrett-connor, 1971; Gill *et al.*, 1995).

1.13.2 Clinical manifestations or Symptoms of SCD

The clinical manifestation of SCD range from mild symptoms to very severe symptoms across the ages (See Figure1-2). While it has been difficult to explain these irregular patterns, genotype, the volume of foetal haemoglobin (HbF) and comorbidities have been suggested as factors responsible for degree of severity (Ballas *et al.*, 1982; Nagel and Ranney, 1990; Powars and Hiti, 1993; Gill *et al.*, 1995; Chang *et al.*, 1997; Thomas, Higgs and Serjeant, 1997; Ohene-Frempong *et al.*, 1998; Ashley-Koch, Yang and Olney, 2000). Some of the acute and chronic clinical manifestations include painful crisis, vaso-occlusive episodes, stroke, anaemia, hand-foot syndrome, jaundice, frequent infections, delayed growth, vision problems, aplastic crisis, acute chest syndrome, leg ulcers, priapism, pulmonary hypertension and organ damage (Powars, 1990; Hernigou *et al.*, 1991; Castro, D J Brambilla,

et al., 1994; Ohene-Frempong *et al.*, 1998; Oliveira, Ciasca and Moura-Ribeiro, 2008; Scheinman, 2009; Ladizinski *et al.*, 2012).

Vaso-occlusive episodes. Vaso-occlusion or acute pain crisis are common features in SCD for all age groups (Smith and Scherer, 2010) sometimes triggered by physical and emotional stress (Westerdale and Jegede, 2004). Pain crisis is the leading cause for visit to emergency departments and frequent hospitalisation both for children and adults, these pain episodes with varied degree of intensity often occur in any part of the body system but most common in the lower back, knee and hip (McClish *et al.*, 2009; Smith and Scherer, 2010). The pain can last from a couple of hours to weeks (Yusuf *et al.*, 2010; Cope and Darbyshire, 2013; Brousse, Makani and Rees, 2014). Pain was found to be common among patients ages 10-30 years; a study revealed that adults had pain in over 50% of days and people above 20 years are more likely to die during painful crisis (Kanter and Kruse-Jarres, 2013; Brousse, Makani and Rees, 2014). High frequency of pain is an indication of the severity of the disease and vary between subjects and within genotypes. The Pain in Sickle Cell Epidemiology Study (PiSCES) which focused on adults with SCD reported pain in 54% of 31,017 days surveyed with 29% of respondents reporting pain in more than 95% of the days. The PiSCES study classified pain into three categories of severity using a numeric scale of intensity. The first category (mean intensity, 5.9±0.1) led to emergency departments or hospitalisation; the second category (mean intensity, 5.0±0.1) was regarded as a crisis but without use of medical care; the last category (mean intensity, 3.9±0.1) was not described as a crisis (Smith and Scherer, 2010). In a study of adults with SCD in Illinois USA, painful crisis was responsible for 97% of hospital admissions (Woods *et al.*, 1997). Pain in SCD is associated with depression, anxiety disorder and has negative effect on the health-related quality of life (Brandow *et al.*, 2010; McClish *et al.*, 2016).

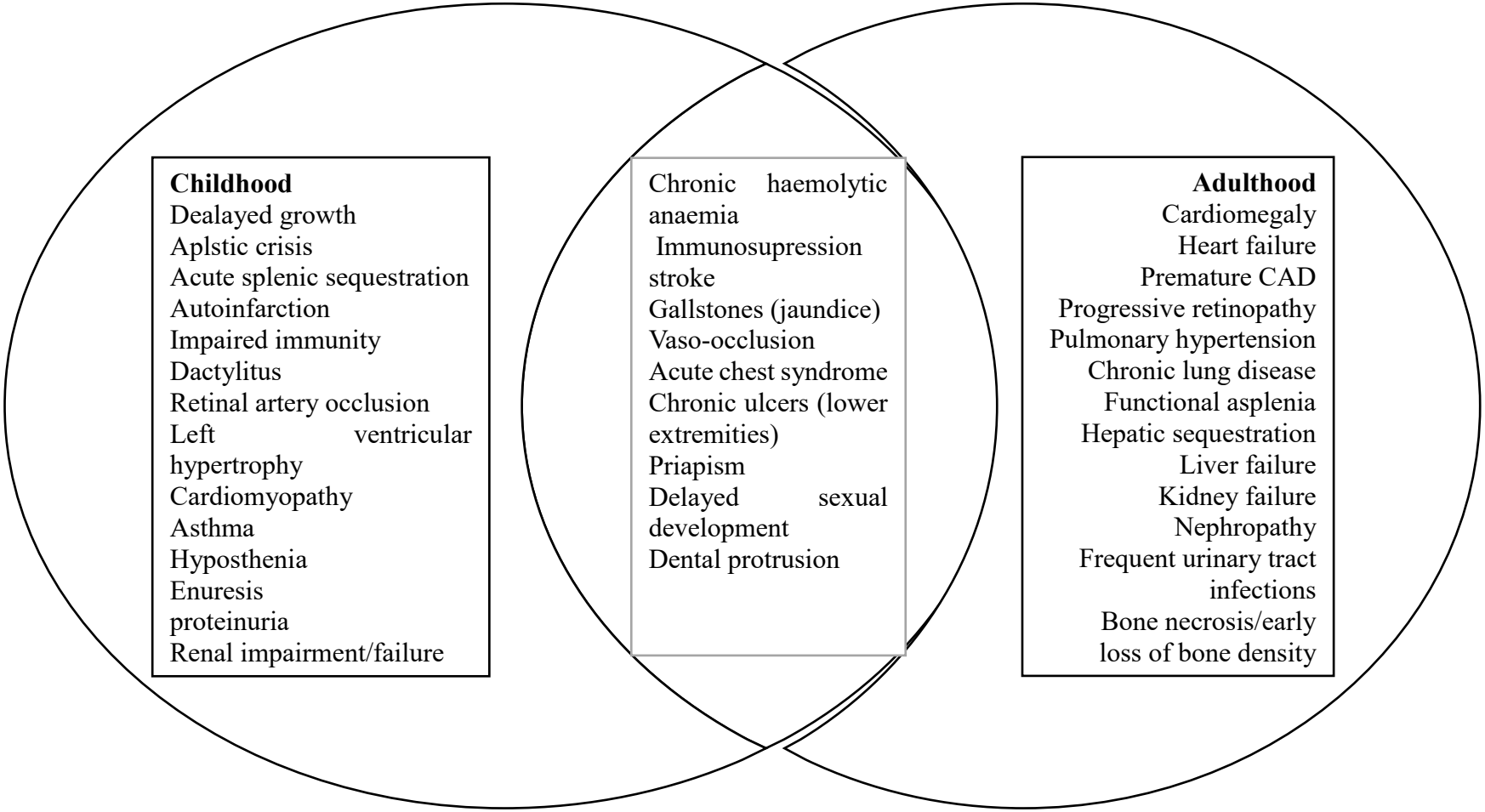


Figure 1-2: SCD Complications in Children and Adult

Source: Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. Blood Rev. 2013;27:279–87

Acute chest syndrome (ACS). ACS is often triggered by infections (29%) and fat embolism (9%), the complication occurs at all ages and is the second most common cause of hospital admission, for example, 95% of patients were hospitalised on their first experience of ACS (Ashcroft and Serjeant, 1981; Vichinsky and Lubin, 1994; Stuart and Nagel, 2004) . In a study of 3751 patients, Castro et al. (1994) found that 29% of the subjects had at least one episode of ACS during the period of the study and an average of 1.9 episode per person. High incidence of ACS is associated with HbSS and is a predictor of shorter survival or early death in adults with SCD (Powars *et al.*, 1988; Castro, Donald J Brambilla, *et al.*, 1994). The syndrome is a major cause of death in young adults (Stuart and Nagel, 2004), a leading cause of death in SCD patients in US (Quinn *et al.*, 2010), and responsible for 25% of all deaths of SCD patients in Jamaica (Serjeant *et al.*, 1986) and in Nigeria (Ogun, Ebili and Kotila, 2014). ACS occurrence is affected by seasons of the year with a 3-times more likely in winter than in summer (Vichinsky, 1991). The syndrome is associated with pleuritic or chest pain, cough, fever, shortness of breath, wheezing and chills. Fever, cough and chest pain are the most common symptoms found to account for 67% in a first event of ACS (Vichinsky *et al.*, 1997). Patients may also develop chronic lung disease as a result of repeated episode of ACS (Powars *et al.*, 1988).

Stroke. Stroke occurs in SCD without warning at least with a chance of 10% in people with HbSS and HbSβ^0. This can result in severe disability, research has shown that 50% of cases have long-term neurocognitive deficit with long term impact on the child and family (Cope and Darbyshire, 2013). In addition, stroke has been indicated as a leading cause of morbidity and mortality in children with SCD, studies showed that 11% of SCD patients would have had stroke by age 20yrs, while there is a 50% chance of reoccurrence in patients who have suffered one stroke (Pegelow *et al.*, 1995; Ohene-Frempong, 2001; Inati, 2009). Stroke prevalence

among SCD children in Nigeria is between 4.3% and 5.2% (George and Frank-Briggs, 2011; Oniyangi *et al.*, 2013).

Priapism. This is a painful penile erection not associated with sexual pleasure in males. This manifestation is common in adolescents and adult males with SCD. Nwogoh et al. (2012) found the prevalence of priapism to be 44.9% in Nigerian SCD patients.

Chronic leg ulcers is a complication in SCD that affects 10% of adults, especially males in US, 50-75% in Jamaica and 22.4% in Nigeria (Bazuaye, Nwannadi and Olayemi, 2010).

Infections. Infections in SCD could be bacterial, viral or mycoplasma. In a study of autopsy at the University College Hospital Ibadan, Nigeria, Ogun et al.(2014) reported that 78% of deaths was due to infection alone or in combination with other factors.

Asthma. A common complication in People with SCD is asthma with a prevalence of 8-53% (Knight-Madden *et al.*, 2005). Asthma is associated with increased risk of hospitalisation for ACS and predicts mortality in SCD patients.

Anaemia. One major complication in SCD is shortage of the red blood cells which normally results in symptoms of fatigue, shortness of breath and paleness (Schnog *et al.*, 2004; Brown, 2012; Kanter and Kruse-Jarres, 2013)

Aplastic crisis. This manifests as a complication due to sudden acute decrease of haemoglobin because of infection (Schnog *et al.*, 2004; Brown, 2012)

Osteomyelitis. This is a common skeletal complication in people with SCD found in about 29% of Nigerian SCD patients (Ebong, 1986).

Musculoskeletal. The occurrence of musculoskeletal complications is high among adults with SCD patients, 31.4% of adults with SCD in Nigeria experience musculoskeletal pain (Balogun *et al.*, 2010).

Pulmonary hypertension. This complication occurs in 3.6% Nigerians with SCD (Aliyu *et al.*, 2008; Dosunmu *et al.*, 2013).

Heart disease. Heart disease is a complication found in adult with SCD. Thirteen percent of adults with SCD suffer from left-sided heart disease (Gladwin *et al.*, 2004; Rees, Williams and Gladwin, 2010).

Renal complications. Renal damage is common in patients with SCD and potentially present from childhood. Chronic renal failure has been responsible for many deaths in SCD and has been found to be present in 30% of adults with SCD (Platt *et al.*, 1994).

Pregnancy. Red blood cells play significant role in pregnancy, but the sickling process may reduce the amount of oxygen going to the foetus. Morbidity and mortality is therefore high in pregnant women with SCD. Complications include increased risks of painful crises and pre-eclampsia, low birth weight, and heart enlargement. There is a 19% risk of spontaneous abortion, 21% stillbirth, 32% risk of premature birth and 42% of intrauterine growth restriction (poor foetal growth) (Oteng-Ntim *et al.*, 2008).

1.14 SCD and Infectious Diseases

The SCD gene confers an increased susceptibility to infection which in turn promotes a cascade of SCD-specific pathophysiological changes. For example, repeated episodes of sickness and ischaemic damage lead to multiple infarcts of spleen tissue.(Booth, Inusa and Obaro, 2010)

Pathogens such as malaria, invasive salmonellosis, immune deficiencies, urinary tracts infections and respiratory infections have important effects on SCD and contribute to a whole range of complications in SCD. For example, while the single HbS confer protection against malaria, the homozygous HbSS is highly susceptible to malaria infection which associates with increased morbidity and mortality. Malaria causes anaemia through a number of mechanisms (Menendez, Fleming and Alonso, 2000)

Low levels of zinc have been suggested as a contributary factor in susceptibility to infection. These infections may lead to the development of comorbidities. The number of comorbidities has been identified in this study as measure of bio-physiological factor. Additionally, during infection with any pathogen, changes occur at a cellular level which corresponds to Wilson and Cleary's bio-physiological function. These cellular changes predispose to crises which often lead to pain frequency, hospitalisation and sometimes blood transfusion which make up the measure of diseases severity index in this study.

1.15 Mortality and Life Expectancy

SCD is a leading cause of high infant mortality rate in Africa. The disease is responsible for above 5% of all under-five deaths in Africa rising to 9% in West Africa and up to 16% in individual West African countries (W H O, 2006; Aliyu *et al.*, 2008). Dacie (1960) described SCD as "disease of childhood" apparently because those affected hardly survived into adulthood. This statement was supported by a study carried out 13 years later where Diggs (1973) calculated the median age of survival to be 14.3 years. However, decrease in early childhood mortality has been achieved due to newborn screening (NBS), prophylactic penicillin, vaccination and parent education. These have been responsible for the survival of 90-95% of children with SCD into first decade (Quinn, Rogers and Buchanan, 2004) especially in high resource countries.

The increase in survival of children due to SCD has been gradual. Quinn et al. (2010) reported that survival to age 5 increased from 96.8% in the period 1983-1987 to 99.2% in the period 2000-2007. In East England, 99% of children with SCD now survive to adulthood (Telfer *et al.*, 2007), corresponding estimates were 97% in Paris (Couque *et al.*, 2016) and 94% in US (Quinn *et al.*, 2010). In Africa, education and medical interventions such as screening, vaccine and antibiotics have contributed to the increase of survival rate of children with SCD from less

than 2% four decades ago to nearly 50% (Makani *et al.*, 2011; Brousse, Makani and Rees, 2014).

Life expectancy has significantly increased in the last four decades from a median of 14.3 years (Diggs, 1973) to 42 years for males and 48 years for females in 1994 (Platt *et al.*, 1994). Recent estimates have also confirmed improvements in life expectancy, however, this increase is still low when compared with people with the normal gene (See Table 1-2). The life expectancy of people with SCD was found to reduce by 20-30 years when compared to people with the normal haemoglobin (NCBDDD, 2011).

The risk of premature and sudden death is high in SCD patients in spite of medical efforts (NCBDDD, 2011). Risk factors for premature death include low foetal haemoglobin (HbF), acute chest syndrome, high white blood count, seizures, acute pain episodes, acute anaemia, renal insufficiency and infection in patients less than 20 years of age (Platt *et al.*, 1994). In addition, adults 20 year and older are at risk of premature death as a result of accelerated organ damage (renal failure, congestive heart failure and stroke) occasioned by sickling and weaker ability of adults to tolerate or withstand painful episode and ACS (Platt *et al.*, 1994).

Table 1-2: Median Survival of Individuals with Sickle Cell Disease

Genotype	**US**	**UK**	**Jamaica**	**Nigeria**
HbSS / HbSβ^0	58	67	53- 58.5	21
HbSC / HbSβ^+	66	72		24
General population		80-83		55-56
Authors	Elmariah et al., 2014 (Elmariah *et al.*, 2014).	Gardner et al., 2016 (Gardner *et al.*, 2016).	Wirenga et al, 2001 (Wierenga, Hambleton and Lewis, 2001)	Chijioke & Kolo, 2009 (Chijioke and Kolo, 2009) .

1.15.1 Shift in mortality rate

While the increase in child survival rate is a welcome development, researchers opined that the mortality has only been shifted to adulthood as the adult mortality rate is still high. In addition,

patients surviving into adulthood carry increasing burden of the disease throughout their adult life as no universal cure for the disease has been discovered yet. This poses challenges to researchers and healthcare practitioners to develop comprehensive management strategy that will reduce the burden of the disease. Studies have shown that the chronic disease condition predisposes the affected individuals to several adverse conditions including disability, chronic end organ complications and other diseases associated with older age (Aliyu *et al.*, 2008; Yanni *et al.*, 2009). Furthermore, the psychosocial complications of the disease are pronounced and research has shown that patients with SCD have poor health-related quality of life (HRQL) which worsen with increasing age (Anie, 2005).

1.16 Sickle cell disease in adults

SCD is determined at conception. Once known as disease of children (Dacie, 1960), this life-threatening disease has evolved in the last four decades to a chronic disease of adults (Chaturvedi and DeBaun, 2016). Better health care and nutrition has led to the increase in the survival rate for instance, SCD-related deaths among African-American children below 4 years fell by 68% between 1983 and 2002 (DeBaun, 2014). Medical interventions include neonatal screening for early detection (Wang *et al.*, 2011), use of penicillin prophylaxis (Cober and Phelps, 2010), pneumococcal immunization (Hardie *et al.*, 2009; Ellison *et al.*, 2012), transcranial Doppler screening to detect patients at risk of stroke, blood transfusions (Malouf Jr *et al.*, 2001; Lee *et al.*, 2006), other therapies like hydroxyurea (Charache, 1991), bone marrow transplantation (Bhatia *et al.*, 2015); these along with better nutrition, hygiene and public health practices have contributed to increase in the life span of people with SCD.

Currently, more people with SCD could live into adulthood for instance, 95%-99% of children now survived into adulthood in developed countries such as UK and USA because of these interventions (Telfer *et al.*, 2007; Quinn *et al.*, 2010; Ware, 2013). In US, the average life span

has increased to 42 for males and 48 for females (Yanni *et al.*, 2009; Lanzkron, Carroll and Haywood Jr, 2013). Recent studies have also shown that people with SCD now live beyond five decades especially in the high resource countries such as UK and the USA. An example is a qualitative study of 15 adults with SCD in USA (Jenerette, Leak and Sandelowski, 2011) where the age range of participants was 48-73 years. This underscores the growing population of adults with SCD. The disease has thus taken a chronic form which requires a comprehensive life-long management (DeBaun, 2014). Also, SCD in adults has additional complications with those found in children and adolescents with SCD. Because transition to adulthood is more challenging for people with SCD compared to the general population, people with SCD must learn to cope with multiple increased complications and restrictions associated with the illness (Thomas and Lipps, 2011).

Moreover, as patients with SCD grow older, they become susceptible to further disease complications such as vasculopathy, systemic and pulmonary hypertension, chronic organ dysfunction or severe organ damage, renal failure, thromboembolism and iron overloads (Powars *et al.*, 2005; Aliyu *et al.*, 2008; Ogun, Ebili and Kotila, 2014). These experiences might result in unexpected high stress level and negative emotions especially because the disease condition also predisposes to a life-long treatment regimen which in most cases are complex and multi-focused (Thomas and Lipps, 2011). The emerging adult population is then faced with the challenge of coping with the effects of the disease and its treatment.

This has serious implications for the quality of life of the patients which cannot be ignored. Therefore, the need to understand quality of life associated with the disease has become more important and understanding factors responsible for HRQL in the patients may inform further research that may lead to advances in medical care.

1.17 Psychosocial impact

Edwards et al. (2005) observed that SCD is complicated with psychosocial and physiological challenges which affects the patients, their families or caregivers. Adegoke and Kuteyi (2012) in a study of 225 caregivers of children with SCD treated at the Paediatric Haematological Clinic of the University Teaching Hospital, Ado-Ekiti, Nigeria, observed that caregivers carry significant financial, interpersonal and psychological burden. For example, caregivers, reported their inability to engage in gainful activities, the neglect of other members of the family, loss of financial benefits as a result of time spent on caring, and presence of tension and hostility in the homes (Adegoke and Kuteyi, 2012). In the transactional model of stress and coping (Lazarus and Folkman, 1984), SCD is regarded to be a potential stressor to which individual and family try to adapt (Anie, 2005). Studies also showed that SCD patients are predisposed to low esteem, feelings of hopelessness due to frequent pain, hospitalisations, loss of schooling (in children and adolescents) and loss of employment (in adults); these are conditions that predispose to depressive symptoms (Anie, 2005).

Psychological complications in SCD was associated with pain and perceived attitude of the society (Anie, 2005; Edwards *et al.*, 2005). Depression has been found to be a common psychological reaction to pain in affected subjects. In a study of 39 patients age 6-19 years, 13% reported depression symptoms, 10% anxiety, and 8% behavioural problems (Cepeda *et al.*, 1997). Depressive symptoms such as sadness, guilt, hopelessness and helplessness were associated with pain in SCD. Other psychological problems include social withdrawal, aggression, poor school attendance and/ or performance in children and loss of employment in adults (Anie, 2005).

1.18 Public health implications

SCD presents a significant challenge to public health due to the under-five mortality which was estimated to be over 5% and as high as 16% in individual West African countries (SCAF, 2016;

WHO, 2006). Added to this is the high rate of deaths due to SCD-related complications in adolescents and pregnant women in Africa (Dennis-Antwi, Dyson and Frempong, 2008). Globally, the chronicity of the disease and high rate of hospital utilisation increases burden on health facilities. Moreover, the disability-adjusted life years (DALY) from SCD has been found to compare with the DALY from cervical cancer and greater than DALYs of chronic kidney disease related to diabetes mellitus or hypertension (Ware, 2013).

1.18.1 Burden of SCD on the health care system

One of the factors that made SCD a public health issue is its high rate of health care service utilisation indicated by admission rate, number of hospitalisation, emergency department visits and demand on time of health care personnel. For instance, SCD is less common but has higher hospital rate of utilisation than diabetes, cardiovascular disease and cancer (Davis, Moore Jr and Gergen, 1997; AlJuburi *et al.*, 2012).

In UK, admission rate for SCD increased by more than 50% from 21.2 per 1000 in 2001/02 to 33.5% in 2009/10 (AlJuburi *et al.*, 2012). In US, it was reported that emergency departments visit due to SCD was approximately 200,000 per year translating to average of two visits per person per year, the number of hospitalisation was put at 83,149 adults with SCD aged 18-44 (Healthcare Cost and Utilisation Project (HCUP), ARHQ 2004). This accounted for 66% of hospitalisation. In another study, Yang et al. (1995) discovered that 33.5% of SCD patients who did not use the comprehensive health care clinics were responsible for 71.4% of visits to the emergency department and 42.3% of hospital admissions. Hospitalisation per year was put at 75,000 SCD patients in US (National Heart, Lung and Blood Institute, NIH, 1994). The health seeking behaviour of SCD patients due to disease-related complications put significant pressure on utilisation of healthcare facilities.

1.18.2 Health cost of SCD

In US, the health cost associated with SCD has been estimated at $2 billion annually (Kauf *et al.*, 2009), medical expenditure for children with SCD in 2005 averaged $11,702 for children with medical coverage and $14,772 for children with employer sponsored insurance (Mvundura *et al.*, 2009), in fact, it would cost an average of $8.7 million to care of an SCD patient from age 0-50 years in the country without taking into consideration other non-transparent costs such as social workers time and efforts (Ballas, 2009). In 2010-2011, England recorded 6,077 admissions of SCD patients with crisis as primary diagnosis at a total cost of over £18 million, 91% of which was spent on emergency admissions, while estimated costs for all SCD-related cases was put at over £20 million (Pizzo *et al.*, 2015). In the Democratic Republic of Congo (DRC), cost of care in a paediatric ward was estimated at $1,000 per patient (WHO, 2014). A recent study in Nigeria revealed that the average cost of blood transfusion among paediatrics with SCD was above $3,000 (Lagunju, Brown and Sodeinde, 2013). In another study of 73 children with SCD at the paediatrics ward of Ekiti State Teaching Hospital, Nigeria, the cost of care per hospitalisation was $132.67 with an average of 2.5 hospitalisation per child (Adegoke, Abioye-Kuteyi and Orji, 2014). This is high considering that Nigeria is a low-income country where the minimum wage is $120 and 70% of the population earn less than 1USD per day (World Bank report, 2011). Estimated cost for care of adults with SCD was found to be twice the cost for children with SCD (Pizzo *et al.*, 2014).

1.19 Clinical Management of SCD

The complications in SCD are complex in nature. Various methods used in the management of the disease are briefly discussed.

Newborn screening (NBS) has been institutionalised especially in high-resource countries to identify children who may be affected early enough. The screening programmes has been responsible for reduction in the mortality rate of children affected with the disease.

Pneumococcal immunisations and use of prophylactic penicillin have been embarked upon as preventive measures. These measures have been found to be responsible for significant reduction in incidence of infections in paediatrics SCD (Quinn, Rogers and Buchanan, 2004).

Transcranial Doppler (TCD) screening has been used to detect early signs of organ damage. There have been recommendations that TCD be carried out annually in patients aged 2-26 years to detect the possibility of stroke and initiate preventive therapies (Kanter and Kruse-Jarres, 2013).

Education of healthcare providers on attitude to pain in SCD and parents and patients on early recognition and the medical complications have also contributed to reducing the burden of the disease (Pack-Mabien *et al.*, 2001).

Therapies for the treatment of SCD include the use of Hydroxyurea, blood transfusion and stem cell transplantation. Hydroxyurea (Hu) has been established as preventive treatment for patients with SCD. According to the Multicentre Study of Hydroxyurea in sickle cell anaemia (MSH), Hu was found to reduce number of acute VOC and hospitalisations (Lanzkron *et al.*, 2006).

Blood transfusion has been shown to reduce the risk of stroke and prevent repeated ACS (DeBaun *et al.,* 2012). However, patients may be exposed to the risk of iron overload which may damage vital organs such as the liver in the patients.

Allogeneic Haemopoietic Stem Cell Transplantation (HSCT) has been proved in some conditions to be the only therapy for now that has potential for the cure of SCD. In a study of 31 Nigerian children transplanted from their identical human leucocyte antigen (HLA) sibling donors, Isgro et al.,(2015) reported that the probability of those who survived without the symptoms of the disease after transplant was 90% while the probability of transplant-related mortality was 10%. However, challenges with HCST include finding matched donor especially

for adults with SCD, the cost and the association of the therapy with increased risk of morbidity including infertility, gonadal failure and graft-versus-host disease (Isgro *et al.*, 2015).

1.20 Holistic Management of SCD

Managing SCD as a chronic disease requires a comprehensive approach to address not just the clinical symptoms but also the psychosocial manifestations of the disease. The need to evolve strategies that integrate the objective clinical measures with subjective psychological and social variables to solve health problems has been well documented in literature (Edelmann, 2000; Anie, Egunjobi and Akinyanju, 2010; Panepinto, 2012), subjective measures of social functioning and measures of psychological well-being have been found to be better and reliable in their accuracy to predict long term morbidity and mortality for example, in rheumatoid and arthritis, (Jenkinson, 1995) than traditional clinical measures. Moreover, it has been posited that these measures may have greater impact and relevance to the society and the individual (Rosenberg, 1995). This subjective measure is conceptualised as quality of life as it relates to health functioning.

1.21 Management of SCD in Nigeria

As in other developing countries, SCD patients in Nigeria - especially those living in rural areas - have little access to medical care.

In high resource countries, factors responsible for improved lifespan include the availability of comprehensive care encompassing newborn screening for early diagnosis (Wang *et al.*, 2011), pneumococcal vaccination (Hardie *et al.*, 2009; Ellison *et al.*, 2012), penicillin prophylaxis (Cober and Phelps, 2010), and use of Transcranial Doppler (TCD) ultrasound to identify patients at risk of stroke who are then placed on chronic transfusion programmes (Malouf Jr *et al.*, 2001; Lee *et al.*, 2006). Hydroxyurea has also been used to reduce frequency of painful crisis, acute chest syndrome and anaemia in children and adults with SCD (Charache, 1991; Heeney and Ware, 2010).

However, despite the high burden of SCD in Nigeria (Akinyanju, 1989; Aliyu *et al.*, 2008), many of the standard management practices are lacking (Galadanci *et al.*, 2013). A survey conducted by the Nigerian SCD network (NSCDN) in 2011, a body which brings together Nigerian physicians, non-governmental organisations and other relevant bodies within and outside Nigeria reported "deficiencies in the management of SCD in Nigeria" (Galadanci *et al.*, 2013, p. 4). The survey which covered 18 responses from 8 teaching hospitals, a general hospital, a Federal Medical hospital and an NGO-run hospital showed that while all clinics administered folic acid and malaria prophylaxis, only 8 of the 18 clinics prescribed penicillin prophylaxis (Galadanci *et al.*, 2013). The report also showed that none of the centres offered pneumococcal vaccine routinely but some clinics encourage patients who can afford it to get it. Furthermore, 8 clinics prescribed hydroxyurea and a local herbal medicine, Ciklavit, is prescribed by 8 clinics. It is important to note that all these clinics are in tertiary or secondary institutions where SCD patients are generally cared for and where the best care for the patients is expected to be available, however reports show a suboptimal care (Galadanci *et al.*, 2013). In addition, despite the disease being among the priority top 10 non-communicable diseases, the country is yet to have a national policy on SCD. Despite a policy on SCD being sent for consideration by the National Assembly, it is still awaiting passage more than four years after it has been presented.

1.22 The Nigerian Healthcare System

Apart from inadequate facilities and absence of policy, the Nigerian healthcare system is also a main factor for the suboptimal management of the disease.

Healthcare delivery in Nigeria is structured along the widely-used three levels of care. Primary care is delivered by the local government, state government delivers the secondary care while tertiary care is delivered by the Federal government(Asuzu, 2004). However, government commitment to improved and affordable healthcare delivery is low (WHO; 2004). The 2000

World Health Report ranked Nigeria as the 187 of the 191-member nations for its health systems performance (Asuzu, 2004). This results from many factors including inadequate government allocation to health, high out-of-pocket expenditure and lack of integrated system for disease prevention, surveillance and treatment and low supervision of healthcare providers (Obansa and Orimisan, 2013). Most of these spending at all the three-tiers of government is on personnel (World Bank CRS, Nigeria, 2005).

Delivery of healthcare is regarded more as a personal affair which means assessing healthcare depends on patients' ability to pay for basic laboratory and physicians services which have worsened disease burden (FMOH, 2004). The high out of pocket spending has kept people in the poverty trap and hinders access to quality medical care (Aregbeyen, 1992).

According to the publication of the World Health Organisation, in 2015 the out of pocket spending on health was 70% in Nigeria compared with UK 15% and US 11% (http://who.int/nha/database/). Out-of-pocket health expenditures presents a large and sometimes catastrophic burden on a household; patients find consultations and medications as the most costly relative to other health related expenses (Ogunbekun, Ogunbekun and Orobaton, 1999). The social insurance available, the National Health Insurance Scheme (NHIS) currently applies only to employees of the Federal government.

Furthermore, absence of integrated system for disease prevention, surveillance and treatment is reflected in the lack of targeted efforts at outreach, health promotion and disease prevention activities designed to reach the people where they are (Obansa and Orimisan, 2013).

1.23 Quality of Life

The notions of quality of life are not new, for example in the Bible, the concept of the abundant life as proposed by Jesus Christ (John 10:10) emphasised quality of life as the goal of his ministry and divine-human relationship. His disciple, John Zebedee expanded the concept

many years later explaining that the abundant life of his master included prosperity, sound health, spirituality and satisfaction (3John1:2).

The term ‘quality of life’ entered the American’s dictionary after the Second World War to connote good life which goes beyond wealth (Campbell, Converse and Rodgers, 1976). This concept has since become an important construct in research, clinical practice and policy making as well as being a useful parameter for evaluating the quality and outcomes of health care (Moons, Budts and De Geest, 2006).

Quality of life as a concept emerged in the mid-1950s (Rosenberg, 1995) and was introduced as a key term in medical indexes in 1975 while its systematic study started with oncology in 1980 (Berlim and Fleck, 2003). This was to investigate individual’s view on his or her health status beyond what signs and symptoms may indicate in the process of measuring treatment outcome. According to Marks (2003), quality of life is basically a public health concern as the purpose of health goes beyond increased duration of life but should enhance a more satisfying meaningful life and to enjoy a better quality of life. Health should correlate with one’s ability to work, maintain activities of daily life and be independent as long as possible (Marks James, 2003). In addition, recognition has been given to the study of quality of life and the need for its promotion in patients (US Department of Health and Human Services, 2010; WHO African Region, 201). This aligns with the goal of medical care to improve and maintain the global functioning and general health of patients beyond the traditional focus on physiological and anatomical conditions (Jenkinson, 1995) as targets of diagnostic and treatment procedures. Measures of objective indicators like morbidity and mortality have been relied on to evaluate the effects of diagnosis and treatment. However, the need to incorporate patient-based assessment along with clinicians’ judgements in evaluating medical interventions or effectiveness of therapy became a growing discuss among researchers and practitioners. The consensus was that such evaluations will provide more accurate assessment of individual’s or

population's health with the potential benefits and possible harms that may result from medical care (Jenkinson *et al.*, 1995; Fitzpatrick *et al.*, 1998).

Quality of life is a broad range measure of health status compared to the clinical measures (which use only morbidity and mortality as indicators. Quality of life has the potential to act as an adjuvant and is useful in documenting the impact of illness (Schweizer, 1995). In practice, quality of life studies has been found to discriminate between different patients or groups of patients and helps to evaluate the effectiveness of medical interventions and predict individual outcomes (Berlim and Fleck, 2003).

Healthcare professionals need to consider the views that patients are more concerned about how they feel rather than what clinical evidence dictate they ought to feel. For example, the experiences of people with SCD are influenced by multiple social and psychological factors (Barbarin and Christian, 1999). These have impact on all aspects of their experience which play out in their physical, social, psychological and occupational well-being including their self-esteem and levels of independence (Caird, Camic and Thomas, 2011). Some of the concerns may be whether the various treatments in any way help relief these burdens; thus, the evaluation of quality of life puts patients in any way at the centre of inquiry and gives due weight to their opinion (Berlim and Fleck, 2003). This is the motivation for employing subjective indicators like health-related quality of life (Bowling, 1995b, 1995a) as a key factor in the management of chronic diseases. Furthermore, thee World health Organisation (WHO) defined health as:

> a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1948 pg.1).

This definition was recognised as a significant milestone in the development of quality of life studies within healthcare (Galloway *et al.,* 2006; Gurková, 2011). The definition highlighted

the positive aspect of health and the importance of evaluating psychosocial factors in measuring health status and well-being.

However, a major challenge is the absence of a widely acceptable definition of quality of life and whether the construct can be or should be measured (Wolfensberger, 1994). There are also individual and cultural differences as to what constitutes quality of life.

1.23.1 Definitions of quality of life

Quality of life is a broad concept that borders on the evaluation of the impact of all aspects of the life on a persons' general well-being. The World Health Organisation Quality of Life (WHOQOL) Group defined quality of life as:

> 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, and standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment" (WHOQOL Group, 1993 p. 153).

This definition shows that quality of life is about the way individuals perceive how satisfied they are with their lives including health status and this may have little resemblance to his her actual physical health status (Curtis, 2000). Curtis (2000) further argued that the subjective nature of the concept highlights the need to allow patients to express how they feel about their state and treatments, rather than for caregivers to infer how they must feel. Additionally, the definition underlines the need to recognise individual and cultural differences in the study of quality of life (Szabo, Orley and Saxena, 1997) and to properly define relevant elements of quality of life both in a global and local parlance.

More challenging is the lack of consensus as to a widely-accepted definition for quality of life. Different authors used different definitions, and some were rather ambiguous (Tyrrell *et al.*, 2005). There is however a popular agreement that the term is a multidimensional construct that includes subjective measures of both positive and negative features of life (CDC, 2012) Researchers in quality of life have viewed the concept as elusive, multidimensional with diverse operational definitions (Felce and Perry, 1995) and without consensus agreement on its operational definitions. The definitions of quality of life are many and diverse (Liu, 1976; Baker and Intagliata, 1982). The lack of agreement arose in part from the academic orientation of the proponents. The 1970s witnessed researchers from economics, healthcare and the social sciences working independently to develop conceptualisations of the population 'life quality' (Cummins and Lau, 2006). The quality-adjusted life years (QALY) concept has emerged from the disciplines of economics and medicine; the health-related quality of life (HRQL) has resulted from the discipline of medicine while subjective well-being (SWB) has emerged from the disciplines of the social sciences (Gurková, 2011). Although these approaches are all related to health, the methodologies are so different from one another such that obtained indexes had little in common (Cummins and Lau, 2006; Gurková, 2011). There is however a general consensus that HRQL is a dynamic, subjective and value-based multidimensional construct which require conceptual models to describe its various aspects and determinants (Banerjee, Gurland and Graham, no date; group and others, 1995; Wilson and Cleary, 1995; Testa and Simonson, 1996; Haas, 1999; Vallerand and Payne, 2003; Padilla, Frank-Stromborg and Koresawa, 2004; Ferrans *et al.*, 2005; Speight and Shaw, 2007).

1.23.2 Multidimensional nature of quality of life

There are two broad approaches to studies in quality of life: the social science approach which regards quality of life as a measurable phenomenon that can change and so can be improved upon; and the philosophical approach with a eudemonistic view concerned with the nature of

human beings and their environment, searching for better conditions in which human beings can be happy or flourish (Draper, 1997). The focus of the social scientist was to fashion out a distinction between happiness and satisfaction the two major concepts describing quality of life (Ferrans and Powers, 1992).

For the health researchers and providers, the concept must be applied to their population of interest or patients. The term 'health-related quality of life' then takes on different connotations which include, well-being, psychological adjustment, physical functioning, symptoms and health status (Ferrans *et al.*, 2005).

As quality of life is being used like an umbrella coinage (Feinstein, 1987), encompassing various dimensions such as health status, life satisfaction, socioeconomic status, physical health, life goals, affect, perceived stress, life goals, housing and neighbourhood, city and nation, self-esteem, depression, coping, and happiness among others (Ferrans and Powers, 1985; Simko, 1999). This term was seen as too broad to be considered appropriate when making a health care claims (Bradley, 2006) because it evaluated non-health-related aspects of life as well; health-related quality of life' was therefore to refer to quality of life within the specific context of health, illness and treatment (Ferrans *et al.*, 2005; Galloway *et al.*, 2006), the impact of disease on important areas of one's life (Phillips, Davis & White, 2001). In this sense, quality of life is viewed as a broad concept that focuses on whether one's ability to fulfil a normal life role is limited due to disease or impairment (Carr, Gibson and Robinson, 2001). Thus HRQL does not consider cultural and political factors or societal attributes (Ferrans *et al.*, 2005).

1.23.3 Quality of life in Medicine

Quality of life in medical literature is viewed from different perspectives. There is the philosophical approach which examines the the nature of human existence and the meaning of the good life (Holmes, 1989). Another approach is the methodological approach which focuses

on the subjective or objective nature of quality of life and describes ways in which it could be measured (Felce and Perry, 1995; Anderson and Burckhardt, 1999; Cella and Stone, 2015). There is also the relationship approach which directs efforts at investigating relationship of quality of life to health status (Pearlman and Uhlmann, 1988; Padilla *et al.*, 1990) and the resource allocation approach which discusses the role of quality of life in the allocation of scarce medical resources (Grabowski and Hansen, 1990; Anderson and Burckhardt, 1999). These different approaches underline the importance and usefulness of quality of life as complementing clinicians' efforts at enhancing well-being.

Quality of life in medicine provides useful information to complement data on the life-preserving properties of medical intervention. Najman and Levine (1981) suggested that regarding increasing longevity as the main goal of medical intervention will be true only for a small proportion of care delivered; they submitted that medicine aims to relieve symptoms, improve mental health, restore functioning, or reduce pain and discomfort, therefore evaluation of healthcare should be based on its impact on the quality of life.

1.23.4 Growth of interest in quality of life in medical literature

In 1966, when the index of medical literature, *Index Medicus*, introduced quality of life as a category, only one article was published on the subject. Between 1981 and 1986 the number of publications rose to 1902 and to 8,820 between 1991 and 1996 (Draper, 1997). Moons et al. (2006) reported a total of 76, 698 articles containing 'quality of life' in a Pubmed search from 1966 to 2005, they showed that proportion of quality of life publications increased from 0.002% to 1.36%. A search through the Discover database of the University of Sunderland (November 10, 2016) showed a growth of 552% to 973% in publications in twenty years on quality of life and health-related quality of life respectively. (See Table 1-3)

Table 1-3: Growth of Interest in the Study of Quality of Life

Year	Articles containing Quality of Life anywhere in the Publication	Articles containing Quality of life in the Title	Growth	Articles containing Health-related quality of life in the Title	Growth
1996-2000	258,467	8, 368	-	1,309	-
2001-2005	484,294	20,287	242.4	4,134	315.8
2006-2010	759,153	31,209	153.8	7,680	185.8
2011-2015	1,059, 684	46,213	148.1	12,733	165.8
20 years growth			552.3%		972.7%

Source: Search of Discover database, November 10, 2016.

Several explanations have been given for this growing interest in quality of life in health research and practice. In the first instance, life expectancy has generally increased due to improved medical therapies, better nutrition and other health promotion activities such that many terminal diseases have transformed to life life-long chronic diseases (Moons, Budts and De Geest, 2006). Therefore, those who otherwise would have died had remained alive which implies that mortality had reduced but the number of people with chronic diseases have consequently increased. Diseases otherwise tagged terminal have now transformed to lifelong chronic diseases. Such chronic diseases are now being clinically managed to avoid early death. Therefore, quality of life measure is a critical outcome measure for this group of patients (Moons, Budts and De Geest, 2006). Additionally, some researchers have insisted that quality of life should be used together with mortality and morbidity to assess outcomes in healthcare (Macduff, 2000; Moons, Budts and De Geest, 2006).

Secondly, the need to consider the benefit-burden ratio of equally effective therapies has informed the requirement for quality of life measurement to assess the benefits of different medical interventions, health programmes and to evaluate both human and financial costs and benefits - a practice that has influenced policymakers in resource allocation to healthcare (De Geest and Moons, 2000; Galloway *et al.*, 2006). Furthermore, other international bodies have

focused on activities that encourage quality of life assessment and research, for example, the United States Food and Drug Administration has included quality of life measurements in its process of approving new drugs, in addition to increased advocacy by national and international groups to employ quality of life assessments in clinical trials research (Grant and Dean, 2003).

Other reasons include the evolution of quality of life assessment into a primary outcome measure in health services research, acute care and chronic illness which has coincided with economic changes and pressures to reconcile quality care and cost effectiveness as well as the current routine use of quality of life assessment to evaluate human and financial costs and benefits of different health programmes and medical intervention (Grant and Dean, 2003; Galloway *et al.*, 2006). These have resulted in rapid growth of research on quality of life (Gurková, 2011).

1.24 Health-related quality of life (HRQL)

Quality of life became operationalised in medicine and allied professions via the health-related quality of life construct (Gurková, 2011). Interests in the study of Health-Related Quality of Life (HRQL) emerged in the 1970s as a construct to define quality of life in terms of the impact of an illness, its complications, and its treatment on the patient (Ferrans *et al.*, 2005; Panepinto, 2008). The term health-related quality of life first appeared in titles of published articles in the mid-1980s (Post, 2014). The concept of health-related quality of life is commonly used to describe quality of life in relation to the effects of illness and treatment (Ferrans *et al.*, 2005; Palermo, Riley and Mitchell, 2008; Gurková, 2011), that is, the aspects of overall quality of life associated with physical or mental health (CDC, 2000).

It has been suggested further that, clear description and explanation of the patient's overall health condition will help clinicians in their assessments of the burden of disease (Fayers and Machin, 2000; groSSe Schlarmann, Metzing-Blau and Schnepp, 2008; Gurková, 2011) beyond

clinical measures. This in part, is a furtherance of the WHO's definition of health (WHO, 1948).

HRQL as a component of quality of life may help to advance the knowledge that relief from symptoms is not sufficient to measure success in care-giving meaning that possible impairment of the functional status, psychosocial and socio-economic conditions of the patient should be addressed as well. The Centre for Disease Control and Prevention (2003) considered HRQL as a construct to identify and track the health status of vulnerable subgroups and older adults in the USA. This would inform the need to develop and support programmes that reduce the impact of chronic diseases and disability, maintain the ability of older adults to live independently and improve quality of life (CDC, 2003). Marks (2003) opined that HRQL must transform to a core means of measuring progress in health.

The main domains of HRQL are physical, social and psychological. The physical domain details the patient's perceived ability to expend energy on daily activities; the social domain focuses on relationship and integration with other people while the psychological dimension is concerned with emotions and mental well-being. Spitzer (1987) has argued that we must include physical, and social functions, emotional or mental states and perception or sense of well-being to peoperly define the domain of HRQL. In the case of patients with SCD the unremitting pain and complications caused by the disease can interfere with many aspects of the patient's life, including education, employment and psychosocial development (World Health Organisation, 2010) resulting in low health-related quality of life in the patients (Trzepacz *et al.*, 2004; WHO, 2007; Dampier *et al.*, 2010; McClish *et al.*, 2016) and their families and caregivers (Anie, 2005; De, 2005). Hence, investigating factors that influence HRQL in people living with SCD and discovering the pattern and path of influence could contribute to reducing the burden of the disease and improve its management by designing appropriate interventions.

Research in HRQL is important due to its effects on the individual, the healthcare providers and healthcare policy. At the individual level, HRQL can be used to improve the quality of life and treatment of individuals with chronic disease because this is the major goal of health care (Omery and Dean, 2004). At the healthcare providers level, evaluating HRQL in clinical trials help to differentiate between therapies, and may suggest to the health care providers the need to modify or alter prescribing habits, treatment regimens and/or decision to cease treatments (Gurková, 2011). Quality of life is also useful in national healthcare policy to improve the allocation of scarce healthcare resources to address health issues.

There are several reasons for including quality of life assessment in healthcare. They are used for the evaluation in clinical trials of treatments with curative or palliative purpose, to reduce symptoms or improve care or rehabilitation (Gurková, 2011). Additionally , they are used to document information about several problems associated with specific disease in the patients, such information have been observed to have potential to facilitate patient communication and help to determine patient preferences (Fayers and Machin, 2013) and establish therapeutic relationship (Gurková, 2011).

Many clinical trial organisations have now introduced the assessment of quality of life as being a standard part of new trials. Such assessments have also been reported to have had a significant role in the interpretation and conclusions of randomised clinical trials (RCTs), in fact some RCTs have recognised that quality of life may be the principal outcome of interest. In addition, quality of life is important as some treatments have shown that, in some instances, the cure might be worse than the disease. It is also useful in understanding treatment preference by patients, to identify problems of psychological adaptation and aid medical decision-making

Quality of life has been discovered to be an important outcome in evaluation of curative treatments, palliative care, rehabilitation and in facilitating communication with patients

(Fayers and Machin, 2013). Results of such evaluations have shown their usefulness to distinguish between two equally effective and safe therapies but with substantial and different changes in quality of life. Rehabilitation programmes can be improved or modified or completely discarded in response to results from quality of life measures, for example, Jews and West (1996) found that rehabilitation programmes used in psychological therapy, counselling, relaxation theory and stress management seemed to offer little benefit to myocardial infarction patients.

Furthermore, quality of life can be a predictor of treatment success. Several studies have shown that overall quality of life, physical wellbeing, mood and pain are of prognostic importance in cancer patients (Davis *et al.*, 2007; Takeuchi *et al.*, 2011). Patient's HRQL has also been found to be a strong predictor of morbidity and mortality. A study has shown that quality of life was strongly predictive of survival and recovery process in surgery (Jenkins, 1992) in addition to the prognostic value of quality of life scores during treatment (Gotay and Moore, 1992).

Researchers have observed that within a target population, HRQL can be used to benchmark diseases across population to provide a better understanding of the burden of disease that patients experience, and this is informative to healthcare providers, patients, families and others (Fayers and Machin, 2000; Grant and Dean, 2003; Omery and Dean, 2004; Panepinto, 2012; Panepinto and Bonner, 2012). Impact of treatment on the patient can easily be measured using HRQL measurements and hence tailor therapies.

There has been an exponential increase in the use of HRQL measures in clinical research since 1973 (Testa and Simonson, 1996), especially in a clinical trial setting in patients with cancer (Basch *et al.*, 2007; Davis *et al.*, 2007; Takeuchi *et al.*, 2011) and other chronic diseases (Panepinto and Bonner, 2012) including SCD (Thornburg *et al.*, 2009).

Some usefulness of the HRQL concept has been highlighted. For example, it has been suggested that HRQL could be considered as central to measuring the efficacy and effectiveness of treatment interventions to predict outcomes and resource use and direct therapy (Panepinto, 2012; Panepinto and Bonner, 2012). Additionally, the use of HRQL has been shown to improve patient-provider communication and to create a more patient-oriented environment; several studies have shown that the use of HRQL data improves patient's physician's communication, is acceptable to patient and providers and aids in the care of patients with chronic illnesses (Basch *et al.*, 2007; Davis *et al.*, 2007; Takeuchi *et al.*, 2011; Panepinto and Bonner, 2012; Fayers and Machin, 2013; Cella and Stone, 2015). Employing HRQL as part of medical protocol can help patients to become more aware of their functioning and symptoms when they are actively involved in providing HRQL information to their providers and they are thus better able to advocate for themselves to improve their HRQL. This, according to Panepinto (2012), can also help providers to react quickly to change in HRQL to tailor treatment especially when significant worsening of HRQL is noted from visit to visit. HRQL can be used in a home setting and can provide a means to track functioning over time and alert providers to any worsening in HRQL as Davis et al., (2007) demonstrated in cancer patients.

1.24.1 The Modelling apparoach to Health-related quality of life

The need to properly measure and develop a knowledge base for HRQL requires reference to a conceptual model (Sousa and Kwok, 2006). Conceptual clarification and accumulation of empirical data will help understanding of fine details of quality of life issues and guide the design of comprehensive care protocols. A conceptual model will assist to understand the relationships among the concepts and consequently translate the clinical relevance of HRQL (Wilson and Cleary, 1995; Sousa and Kwok, 2006; Bakas *et al.*, 2012).

Models are of central importance in understanding scientific phenomena (Rosenblueth and Wiener, 1945) especially for understanding health and illness (Engel, 1977; WHO, 2001; Wade and Halligan, 2003, 2004). In quality of life research, the use of a conceptual model is important because it can advance the selection of appropriate measurement variables and make it possible to identify potential links between variables with complex construct of quality of life (Saban *et al.*, 2007a). Heo et al. (2005) opined that researchers and clinicians can work better to improve HRQL outcomes if they know which variables are associated with HRQL and which variables are of less importance to HRQL. They submitted that there is high possibility of committing errors if assumptions were not tested. They cited the example of clinicians' belief that the HRQL of heart failure patients was largely determined by the severity of the illness which they measured with the ejection fraction. Various studies have however, contradicted this belief as such studies showed that ejection fraction had not been associated with HRQL (Heo *et al.*, 2005). Such outcomes supported HRQL as a complex phenomenon and assumptions must be subjected to test when in the process of developing intervention to improve HRQL (Heo *et al.*, 2005). There is a consensus among researchers that conceptual or theoretical models that clearly indicate the elements of HRQL and their determinants are needed (Wilson and Cleary, 1995; Wood-Dauphinee, 1999; Ferrans *et al.*, 2005; Sousa and Kwok, 2006) and without a theoretical approach, identifying patterns in relationships between the concepts and interpreting their meanings will be difficult, and the ability to properly assess the mediators and moderators of predictors, whether by the person, disease or treatment-related factors will be limited (Haase and Braden, 1998; Sousa, Tann and Kwok, 2006). A theoretical model provides scientific ground for generating and testing hypothesis and may help to explain important phenomenon like HRQL which may likely have impact on interventions and practice. Haase and Braden (1998) highlighted several ways in which a non-theoretical approach fails. First, it is difficult to assess if or how domains are related to one another; second,

one cannot interpret the meaning of relationship patterns; third, one has no basis for specifying whether the dimensions are moderated or mediated by persons, the disease, treatment-related factors or all three, relative to cost and quality of care outcomes (Haase and Braden, 1998). Such models must be valid to achieve the following: (i) clarify predictors, (ii) understand the factor that has the greatest impact on a patient's life (iii) evaluate the relative importance of different approaches and/or interventions to patient care, and (iv) establish clinically relevant measures (Sousa, Tann and Kwok, 2006).

1.24.2 Models of Health-related quality of life

In a systematic review of 100 studies that used HRQL models, Bakas and colleagues (Bakas et al, 2012) reported that three models presented the greatest potential to guide HRQL research and practice; they are the Wilson and Cleary model used in 16% of the studies, the World Health Organisation International Classification of Functioning Disability and Health (WHO ICF) used in 5% of the studies and Ferrans et al.'s revised version of the Wilson and Cleary model used in 4%. Bakas et al. recommended the use of one of these three global models in research to more quickly advance the science in the area of HRQL. All the three models emerge from the two paradigms of biomedical and social sciences and are briefly described as follows.

The World Health Organisation International Classification of Functioning Disability and Health (WHO ICF).

The WHO ICF model was designed to provide a description of health and health states while providing a unified standard language that can be used across disciplines and cultures (WHO, 2001). The model is made up of components within two parts; one part focuses on functioning and disability (body functioning and structures, activities, and participation) while the other part addresses contextual factors (environment and personal). The drawback of this model is that it is not specific to HRQL (Bakas *et al.*, 2012) , but also focuses on disease classification.

According to Cieza and Stucki (2008), the model's categories under functioning can serve as the basis for operationalisation of HRQL but are not the only potential application of the model. The model serves more as a mapping and classification framework than a model in the area of HRQL. This model was therefore not considered useful to achieve the objectives of this thesis.

The Wilson and Cleary Model of Health-related Quality of Life

The Wilson and Cleary model (Wilson and Cleary, 1995) is a global model of HRQL, which has been used to guide literature reviews and the development of models and instruments, also, the model focuses specifically on explaining HRQL and can be applied in real-world settings (Bakas *et al.*, 2012). Moreover, the model has clearly defined concepts and has been to be found applicable to individuals across all ages, lifespan, health and disease conditions as well as across cultures (Bakas *et al.*, 2012). The model was the first and currently the major model that integrated the biomedical and the social science models of health. The model highlighted five domains of bio-physiological factors, symptoms, functioning, general health perceptions and overall quality of life (see Figure 1-3a). The aim was to understand the pattern of relationships among different levels of patient outcomes as well as pathways of their influence on the overall quality of life (Wilson and Cleary, 1995). This information could be used in planning healthcare interventions directed to improving patients' quality of life. Clinicians and researchers need to consider and test potential causal relationships among the biological, psychological and social variables of health in order to contribute to the design of an 'optimally effective' therapeutic intervention (Wilson and Cleary, 1995).

The model considers five main factors in a multilevel continuum which linked objective, biological variables at the start of the framework to the subjective overall quality of life outcome at the end of the continuum. The model hypothesizes that the biological and physiological variables affect symptoms; while symptoms affect functional status; the functional status affects general health perceptions; and the general health perceptions affect

the HRQL (Figure 1-3a). Individual characteristics and environmental characteristics affect all the variables except the biological and physiological variables. Although, the model portrays a linear, one directional link, Wilson and Cleary admitted that the relations between variables could be bidirectional and the causal pathway may not be as simple as illustrated. There could also be relationships between nonadjacent levels though there were no arrows to illustrate such, hence the need to test the model with empirical data (Wilson and Cleary, 1995). Each level of the model was clearly defined. The biological and physiological variables are assessed by the functional status of cells, organs and organ systems, considerations are also given to factors whose effect are mediated by variability in cell or organ, or organ system functions. Second, the symptom status shift to the organism as a whole and describe the patients' subjective perceptions of an abnormal state of physical and mental, and cognitive conditions. Third the functional status refers to the ability of the individual to perform physical, social, emotional role and psychological functions. Fourth, the general health perceptions was defined by the patients' global perceptions of their health, i.e. a subjective ratings integrating the other health concepts including others such as mental health (Wilson and Cleary, 1995). The overall quality of life evaluates overall satisfaction (Wilson and Cleary, 1995; Moi and Nilsen, 2012). This has been described as the discrepancy between a person's expectations or hopes and their present experiences (Calman, 1984). Environmental characteristics refer to available supports from the family, friends and others while individual characteristics, though not defined by Wilson and Cleary could be inferred to consist of the demographic and psychologic characteristics of patients (Heo *et al.*, 2005).

The Revised Wislon and Cleary model

Ferrans *et al.* (2005) developing a conceptual model of health-related quality of life, revised the Wilson and Cleary model. They retained the five major domains of the Wilson and Cleary model but broadened the scope by expanding on characteristics of the individual and

characteristics of the environment. They agued that the characteristics of the individual and the characteristics of the environment should have affect the bio-physiological factor. They therefore drew paths from the characteristics of the individual to the bio-physiological factor and from the characteristics of the environment to bio-physiological factor (see Figure 1-3b).

1.24.3 Justification for model selection

Several factors were considered before selecting the Wilson and Cleary model (WCM) for empirical test in this study. First, WCM is a global model specifically designed to explain HRQL unlike the WHO ICF which is more of a mapping and classification framework than a model in the area of HRQL.

Second, WCM is the most frequently used model and has been validated across all ages, life span, disease conditions and across cultures unlike the revised model which has received little study. While WCM has been tested empirically in many disease conditions such as in patients living with heart disease / failure (Heo *et al.*, 2005; Krethong *et al.*, 2008; Carlson *et al.*, 2014; Lee and Larracoechea, 2015), stroke (Mayo *et al.*, 2015), adult Pompe disease (Kanters *et al.*, 2015), HIV/Aids (Cosby *et al.*, 2000; Sousa and Kwok, 2006), Cancer (Wettergren, Björkholm, Axdorph, Langius-Ekiöf, *et al.*, 2004), Parkinson's disease (Chrischilles *et al.*, 2002), diabetes (Shiu *et al.*, 2014), generalized anxiety disorder (Wyrwich *et al.*, 2011), asthma (Eilayyan *et al.*, 2015) and obesity (Brunault *et al.*, 2016); only one study has attempted to fully test the revised model in patients with haemodialysis (Kring and Crane, 2009).

Third, a systematic review of the application of Wilson and Cleary model in chronic diseases has shown that the WCM demonstrates a good fit and proved useful in identifying relationships among the health constructs, and predictors of HRQL in the studied disease populations. These findings demonstrate the robustness of the Wilson and Cleary model as a conceptual framework to characterise predictors of HRQL in chronic diseases (see Chapter 3). These provide a basis

for compring the findings in my study which currently is not possible with the revised version due to lack of studies that have used this version.

Fourth, a major revision by Ferrans and colleagues (Ferrans *et al.*, 2005) was to draw path linking characteristics of the individual and characteristics of the environment to the bio-physiological factor. In SCD, one characteristic of environment that triggers crisis in SCD is cold weather, however, this study did not collect data on weather condition other than that the period of data collection fell in the warm season. Low income/poverty is an environmental variable that may have affected the biological variables. For example, poverty could limit the ability of patients to purchase vitamins and drugs for medications that could inhibit the progression of the disease or development of new co-morbidities. However, it is unclear how an environmental factor like having a confidant can affect thedevelopment of co-morbidities. In addition, it is unclear how a personal characteristic like gender can affect genotype, a biological factor because SCD is autosomal. These unexplored relationships did not allow this thesis to investigate the path between biological factors and the characteristics of the individual and the characteristics of the environment as hypothesised by Ferrans et al. Also, Kings and Crane (2009) did not find any relationship between characteristics of the individual, characteristics of the environment and the bio-physiological factor. Further studies would be required to establish direct relationships between the characteristics of the individual, the charactertics of the environment and bio-physiological factor in SCD. The Wilson and Cleary model is therefore considered more useful to achieve the objectives of this study.

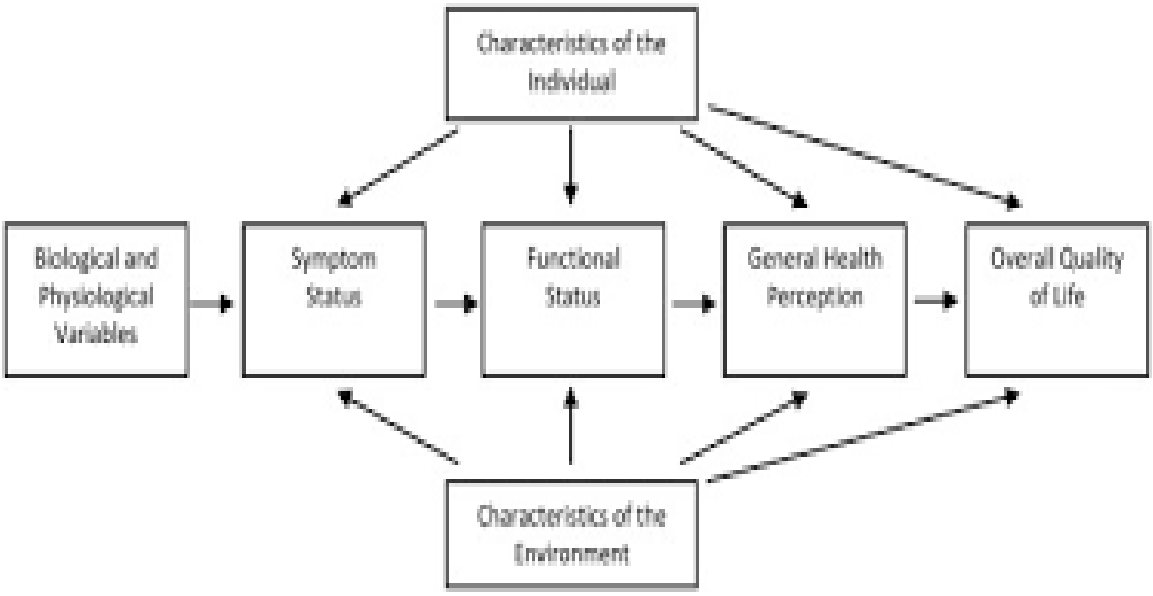


Figure 1-3a: Wilson and Cleary Model of Health-Related Quality of Life

Source: Linking clinical variables with health-related quality of life. A conceptual model of patient outcome. JAMA 1995;273(1):59–65. © 1995 American Medical Association.)

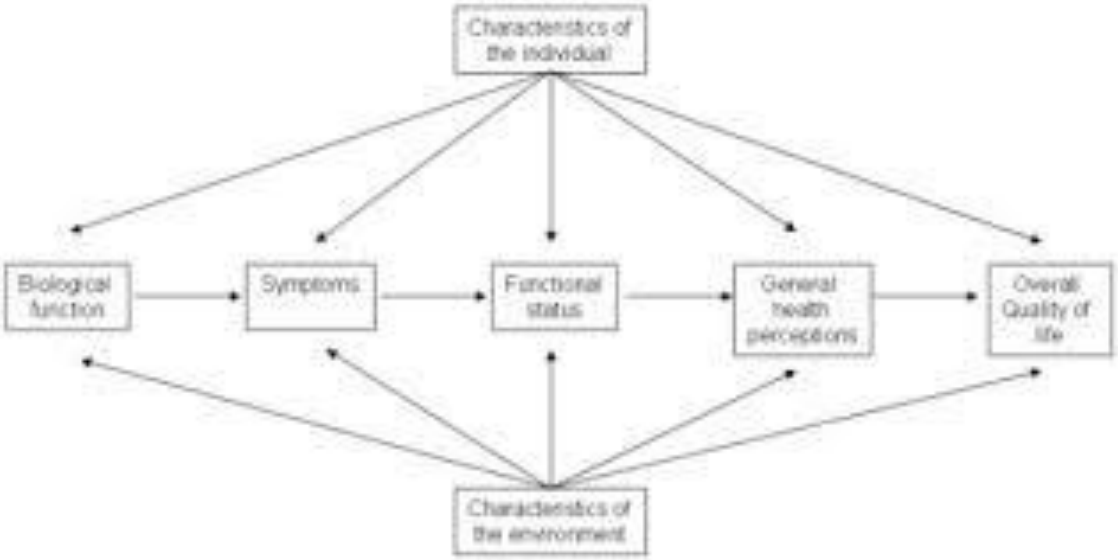


Figure 1-3b: Revised Wilson and Cleary Model of Health-Related Quality of Life

Source: Ferrans, C. E., Zerwic, J. J., Wilbur, J. E. and Larson, J. L. (2005) 'Conceptual model of health-related quality of life.', *Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing / Sigma Theta Tau*, 37(4), pp. 336–342. doi: http://dx.doi.org/10.1111/j.1547-5069.2005.00058.x.

1.25 The Wilson and Cleary Conceptual Model of HRQL

Wilson and Cleary(1995) proposed a conceptual model of HRQL that provides a link between biological and psychological aspects of health outcomes and with the potential to guide quality of life studies and provide theoretical core. This holistic model focuses on two ends of health concepts, namely the clinical approach and the social science approach and proceeds to integrate both. The Wilson and Cleary model was the first theoretical model to address HRQL concept and has contributed significantly to a better understanding of HRQL concepts since its publication about three decades ago, transforming HRQL concept from a purely descriptive phenomenon to an explanatory model with clear explanations of causal relationships among the components (Bakas *et al.*, 2012).

The use of HRQL has been on the increase in clinical trials research, effectiveness and quality of care because of abundant evidence that measures of HRQL are valid, reliable (McDowell and Newell, 1987) and responsive to important clinical changes (Wilson et al., 1991; Bombadier et al., 1986). The importance of HRQL in medicine and as a measure of health outcomes has been discussed previously (see section 2.4). However, despite HRQL being recognised as an important complement to physiological and biological measures of health status, there has been limited understanding of its determinants. An improved understanding of the underlying causes of HRQL is useful to optimise interventions to target these causal factors to improve patients' perceived HRQL (Wilson and Cleary, 1995).

Wilson and Cleary's conceptual model integrates clinical variables of the biomedical model with the HRQL of the social science model. The goal of the authors was to specify a series of critical concepts on a causal pathway, hence the model describes specific causal relationships among health concepts (Sousa and Kwok, 2006). The model uses most variables typically included in HRQL assessments and brings together the two different health paradigms

belonging to two academic traditions, one belonging to the clinicians and basic science researcher, and the other belonging to the social scientist.

These two academic traditions differ in purpose, methods and intellectual history. For the biomedical approach, the focus is on etiologic agents, pathological processes and clinical outcomes with the primary aim of understanding causation to guide diagnoses and treatment of diseases; the intellectual foundation was in biology, chemistry and physiology. The social science or quality of life concept has its focus on dimensions of functioning and overall well-being (Sousa and Kwok, 2006) with the goal of accurately measuring behaviour and feelings and has its roots in sociology, psychology and economic concepts and methodologies unfamiliar to physicians and clinical researchers.

The social science concept aggregates and evaluates all factors that contribute to the illness and identifying the way the various social structures and institution influence individuals. Wilson and Cleary suggested that a clear understanding of causal relationship of clinical variables to measures of HRQL would be necessary in designing optimally effective clinical interventions (Wilson and Cleary, 1995).

1.25.1 Description of the model

The Wilson and Cleary model is a biopsychosocial model that makes it potentially possible to have a single unifying approach to understanding health issues. The model identified five levels of patient characteristics which include, biological and physiological factors, symptoms status, functional status, general health perceptions and overall quality of life. In addition, characteristics of individuals and environmental factors were included as non-specific predictive variables of symptoms status, functional status, general health perceptions and overall quality of life (Wilson and Cleary, 1995; Ferrans *et al.*, 2005). The model conceptualised health as a linear progression across the five concepts on a continuum of

increasing biological, social and psychological complexity (see figure 2). Arrows were used to indicate higher levels of complexity from the cells to individual person and the society. The authors, having recognised the inadequacy of unidirectional models in explaining causality posited that the relationships could be bidirectional between and among the concepts notwithstanding the fact that there were no arrows in the model to so indicate. A longitudinal study of 108 patients in Norway who underwent heart surgery using structural equation modelling supported that bidirectional causal paths existed between general health perception and overall HRQL (Mathisen *et al.*, 2007).

1.25.2 Constructs of the Wilson and Cleary model

The latent constructs of the Wilson and Cleary model are discussed in the following sections

Biological and Physiological Factors

The biological and physiological factors form the first construct of the model located at the initial end of the continuum. This construct focuses on the function of cells, organs and organ systems. They are mostly laboratory values of the diagnosed disease. Included at this level are health effects of characteristics that are mainly mediated by changes in cell organ or organ system function. In SCD, biological and physiological factors include the foetal haemoglobin (HbF), genotype, comorbid diseases, frequency of pain and history of blood transfusion. Frequency of hospitalisation and visit to emergency departments are also regarded as measure of the severity of the disease.

Symptoms Status

Symptoms status was defined in the model as "patient's perception of an abnormal physical, emotional or cognitive state" (Wilson and Cleary, 1995 p ref). The assessment of symptoms moves from the continuum of cells and organs to the whole person to identify the underlying

factors behind deviation from normal functioning and the cause of the perceived imbalance. They suggested that symptoms can be classified into (1) physical symptoms (2) psychological symptoms and (3) symptoms that are not clearly physical or psychological such as emotional distress, fear, worry and frustration. In addition, Mechanic (1977) categorised symptoms as visible, severe, interfering and frequent insisting that each characteristic affects the individuals and their response to illness in different ways for instance, a visible symptom is apparent and may stimulate precautionary behaviour in the individual while symptoms that interfere with daily living may influence the patient to seek medical help.

Symptom is a subjective experience conditioned by the complex interaction of biological, social and environmental process. The magnitude of a symptom varies in severity or its persistence (Mechanic, 1995; Wilson and Cleary, 1995; Ferrans *et al.*, 2005) and recognising the severity of symptoms may encourage a person to seek treatment.

The model depicted symptoms as being influenced by biological and physiological factors, Wilson and Cleary described this influence as complex and ambiguous because a person may exhibit symptoms without a clinically identifiable biological and physiological abnormality while it is also possible for a person to show signs of biological and physiological changes without experiencing symptoms. Pain acute and chronic is the major symptom in SCD (Anie, Steptoe and Bevan, 2002). Pain has been responsible for frequency and length of hospitalisation as well as visit to emergency departments (Yusuf *et al.*, 2010) and is a source of depression for patients (Levenson *et al.*, 2008; Anie *et al.*, 2012; Ola, 2016).

Functional Status

Functional status occupies the next level of the continuum being influenced by symptoms status. Functional status, according to Wilson and Cleary, is the ability of the individual to

perform specific tasks and adjust to their environment, a concept that is measurable, subjectively or objectively, over a given time (e.g. ability to walk upstairs or walk a distance).

The variable is assessed by four domains which include physical functioning, social functioning, emotional functioning and role functioning. These are recommended as the minimum areas that can be evaluated (Ware, 1997; Cleary et al, 1991). Other factors that may influence functional status include the individual's personal and social environment such as perceived self-efficacy, family relationship, and access to health care and medical treatment.

Physical activity in people with sickle cell disease has been a subject of research showing that SCD patients are severely limited in their functioning due to the presence of the disease (Ohaeri *et al.*, 1995; Anie, Steptoe and Bevan, 2002; Adegoke and Kuteyi, 2012). This includes their inability to get employment or keep employment as a result of frequent sickness absence.

General health perceptions

General health perception refers to a subjective self-rating of one's overall general health. Two components are seen here: subjective ratings and health components. While general health perceptions assess symptoms and abilities, they also consider satisfaction.

The ways in which people rate their health are subject to many factors which include physiological processes, symptoms and functional ability that have been found to be consistent predictor of general health perceptions (Bjohner, 1996). To assess general health perceptions, question asking people to rate their health based on a Likert scale rating from poor to excellent has been recommended as a measure of general health perceptions (Ware Jr and Sherbourne, 1992; Ferrans *et al.*, 2005). In extant literature, self-rated health has been shown to be a more powerful predictor of mortality and morbidity than many objective measures of health (Dominick *et al.*, 2002; Eton *et al.*, 2003; DeSalvo *et al.*, 2006; Gotay *et al.*, 2008; Chase *et al.*, 2012; Sloan *et al.*, 2012; Cella and Stone, 2015). The single health transition question and

the General Health domians of SF-36 were used in this study to measure general health perception.

Overall Quality of Life

Overall quality of life stands at the end of the model. The concept refers to how happy or satisfied a person is with their life as a whole. Overall quality of life should be related to HRQL but is influenced by other salient characteristics and experience (Wilson and Cleary, 1995). Changing circumstances can also reflect in the way people perceive things in the light of current values, preferences, expectations and aspirations. Hence, general measures of life satisfaction or happiness or overall quality of life do not always relate to objective life situation in the expected manner (Diener, 1984). For example, lower functioning may not necessarily relate to lower levels of satisfaction; a disease condition or impairment which poses a burden to one individual may not necessarily be to another, and the level of satisfaction six months ago might be lower compared to the present, not necessarily because disease condition has improved but because outlooks and expectations have been adapted (Patrick and Erickson, 1993; Wilson and Cleary, 1995).

Individual Characteristics and Environmental Characteristics

Wilson and Cleary hypothesised that patients' responses to clinical conditions and the way they value their HRQL may be limited to factors such as biophysical attributes or medical treatments but can also be extended to the way they interact with individual and environmental factors. These are referred to as characteristics of the individual and characteristics of the environment often measured with sociodemographic variables. Sousa et al. (1999) viewed characteristics of the individual as referring to specific traits or qualities that identify human beings and the characteristics of the environment as external conditions that influence or are influenced by

human beings. Wilson and Cleary have stated that these characteristics influence the symptoms, functional status, general health perceptions and overall quality of life.

The interaction of the individual with the environment can affect their biological functions. For example, a habit of long-term exposure to smoking might affect the human-gene environment of the individual who might then develop lung cancer or chronic obstructive lung disease (Ferrans *et al.*, 2005). Socioeconomic status has been regarded as an environmental factor with a potential to influence HRQL in patients with chronic disease. Studies have shown that parental income level and education affect the HRQL of children and adolescents with SCD: worse socioeconomic status (lower parental education, low family income) is associated with worse HRQL (Palermo, Riley and Mitchell, 2008; Hijmans *et al.*, 2010; Amr, Amin and Al-Omair, 2011). A study has reported that SCD in adults predisposes the patient to poor socioeconomic status (Jenerette, 2008; Santos and Gomes Neto, 2013).

1.26 Health-related quality of life in sickle cell disease (SCD)

There has been a growing interest in the study of SCD (W H O, 2006) and more importantly in the study of HRQL in SCD (Barakat *et al.*, 2008; Dampier *et al.*, 2010; Panepinto and Bonner, 2012; Ahmed *et al.*, 2016; McClish *et al.*, 2016). In the last three decades, health outcomes research on chronic illness has witnessed a growing concern with patients' evaluations of the effectiveness of care and treatment using quality of life (QOL) as an important indicator (Garratt *et al.*, 1993; Galloway *et al.*, 2006).

SCD in the last four decades has evolved from a life-threatening disease of children to a chronic disease of adults (Chaturvedi and DeBaun, 2016). Medical interventions and some public health practices has enabled most people with SCD to live into the fifth decade (Platt *et al.*, 1994; Grosse *et al.*, 2009; Lanzkron, Carroll and Haywood Jr, 2013). This has shifted the priorities from survival to long-term quality of life concerns (DeBaun, 2014).

Acute pain episodes in SCD which often result in frequent hospitalisation and other complications have impact on the quality of life of the patients (Anie and Green, 2000; Ellison and Shaw, 2007; Smith *et al.*, 2008; Anie *et al.*, 2012). Studies have shown that the quality of life of SCD patients are significantly impaired (Palermo *et al.*, 2002; Asnani *et al.*, 2008; Amr, Amin and Al-Omair, 2011; Dampier *et al.*, 2011; McClish *et al.*, 2016). Studies have therefore advocated the inclusion of QOL assessment as outcome measures in the management of the disease to better understand the burden that patients experience (Anie, Steptoe and Bevan, 2002; Palermo, Riley and Mitchell, 2008; Panepinto, 2012).

1.27 Impact of SCD on HRQL

It is worthy of note that there has been significant volume of studies on the quality of life in people with sickle cell disease to investigate the impact of the disease on the quality of life of the patients (Brown, Armstrong and Eckman, 1993; Anie, Steptoe and Bevan, 2002; Dampier *et al.*, 2010, 2011; Sogutlu *et al.*, 2011; Coleman *et al.*, 2016; McClish *et al.*, 2016). Such studies have taken place mostly in high-income countries and expectedly reflected the characteristics and cultural norms of the society where they took place. However, the findings may not always be applicable to other countries (Caird, Camic and Thomas, 2011) especially the low-income countries of Africa where access to healthcare facilities and affordable healthcare is poor.

To examine the impact of SCD on HRQL of patients and the determinants of HRQL in people with SCD, a systematic review of literature was conducted. This is presented in Chapter Two.

CHAPTER TWO

A SYSTEMATIC REVIEW OF PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE IN PEOPLE WITH SICKLE CELL DISEASE

2.0 Introduction

The aim of this chapter is to systematically review and synthesise studies that explored HRQL in people with SCD to identify the determinants of HRQL in SCD.

A search of literature was carried out using the Discover database of the University of Sunderland. The procedure and result are presented below.

2.1 Methods.

The review follows the format of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff and Altman, 2009). The electronic databases searched included Science Direct, MEDLINE, CINAHL and PsyARTICLES. Search terms combined keywords such as health-related quality of life OR HRQL OR HRQOL OR quality of life OR QOL OR health status OR patient-reported outcome OR Well-being) AND (Sickle cell anaemia OR sickle cell disease OR haemoglobinopathies OR HbSS OR HbSC OR SCD OR SCA OR sickle cell disorder) AND (predictors OR factors OR determinants). The findings are presented in Table 2.1 and Table 2.2.

The inclusion criteria were:

Articles published in English language.

Articles that focused on SCD.

HRQL measured with a validated instrument.

Any reported variable associated with HRQL.

Articles published between on the subject up to December 2016.

Peer-reviewed articles with full-text accessible online or from the author.

The exclusion criteria were:

Articles that did not measure HRQL as outcome variable

Articles that focused on instruments for measure

Studies which were not written in English

Search result.

The initial search yielded a total of 13,414 articles. A filter ‘quality of life’ reduced the articles to 91. These were further screened on titles and abstracts. Duplicates and articles that did not meet the inclusion criteria were removed leaving 24 (14 paediatrics and 10 adults 18 years and older) articles for review. Additional articles (two paediatrics and one adults) were added through searching of reference lists (See Figure 2-1).

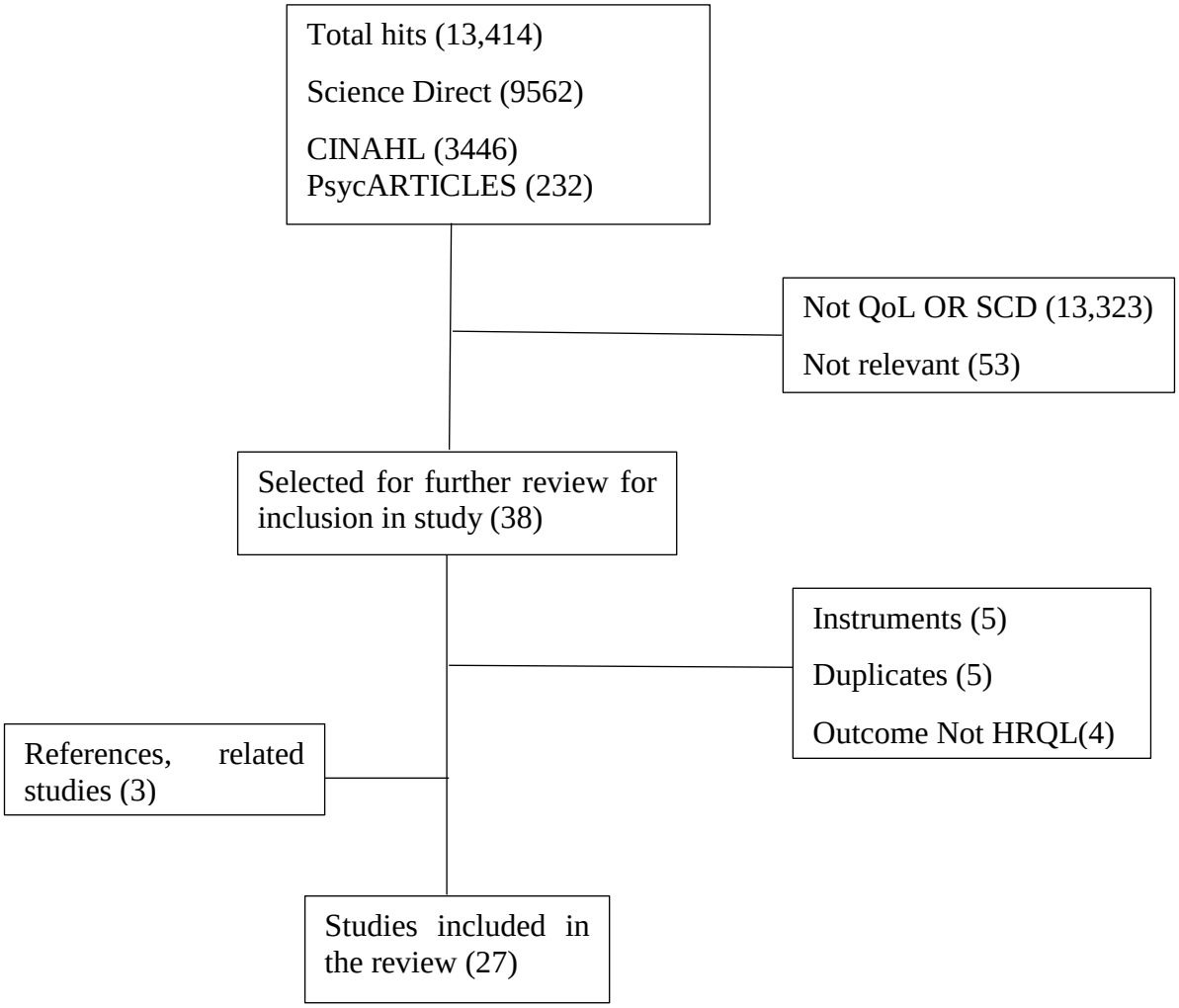


Figure 2-1: Flow Chart of Study Selection Pprocedure

2.2 Characteristics of studies reviewed

The articles originate from USA (16), UK (2), Jamaica (2), Saudi Arabia (2), Brazil (2) and one each from India, Netherlands and Nigeria. The mean ages of participants range from 8.97±5.28 to 16.9±1.7 for children and adolescents and 25.7±1.4 to 36.4±12.67 for adults. Three of the studies focused specifically on adolescents while 13 combined children and adolescents together. Three of the studies were longitudinal, one a prospective study, seventeen cross-sectional, four case-control studies and one each of randomised double blind and qualitative studies. The percentage of participants with HbSS phenotype was

above 70% in most of the studies, showing that the HbSS genotype was predominant in the study population.

2.3 HRQL in people with SCD

The Tables (2.2 and 2.3) show that the HRQL was affected in the patients with SCD when compared with the healthy peer or healthy siblings and have impaired HRQL which were either similar or worse when compared with other chronic diseases. SCD in children and adolescents was associated with limitations in most aspects of HRQL (Menezes *et al.*, 2013). In addition, SCD in adults had negative effects on the biological and social functioning which got worse with increase in age (Caird, Camic and Thomas, 2011) and predisposed to high stress level and negative emotions (Thomas and Lipps, 2011).

Comparison with a healthy group.

Children and adolescents with SCD showed more limitations in physical, social and psychological functioning with significant impairment in 13 of the 14 health dimensions of the CHQ-PF50 subscales (Palermo *et al.*, 2002) and five domains of the HRQL measure (Hijmans *et al.,* 2010). Dale et al. (2011) reported that 53% and 63% of children and adolescents with SCD were 'at risk' for impaired overall HRQL and physical HRQL respectively. In adults, the HRQL was poor in all subscales of SF-36 (Anie, Steptoe and Bevan, 2002), their average quality of life scores were lower at 83.6 compared to the scores of the healthy population at 90 (Mann-Jiles and Morris, 2009).

Socio-demographic profiles (education and income) of parents of adolescents with SCD were lower, while educational delay (excessive failing and school retention) and absenteeism were common among adolescents with SCD (Amr, Amin and Al-Omair, 2011). The disease in adults predisposed the patients to poor socioeconomic status (Jenerette, 2008), low sociodemographic profile such as low income and impaired access to healthcare services (Santos and Gomes Neto, 2013). Children and adolescents with SCD

were also reported to have poorer behaviour, worse mental health, and lower self-esteem and significantly poorer academic performance (Palermo *et al.*, 2002; Sehlo and Kamfar, 2015).

Comparison with other chronic diseases.

The quality of life of people with SCD were compared with published HRQL scores of other chronic diseases.

When compared with HRQL scores of people with juvenile rheumatoid arthritis (JRA) group, children and adolescents with SCD had similar physical health summary scores of HRQL but worse psychosocial health summary scores of HRQL also, when compared with peer group with epilepsy, children with SCD showed comparable psychosocial health summary score but worse physical HRQL score (Palermo *et al.*, 2002). Furthermore, when compared with other non-communicable chronic disease children and adolescents with SCD reported worse impaired overall HRQL (Bhagat *et al.*, 2014). Moreover, the literacy, socio-economic status and duration of disease, were comparable to those of congenital heart disease, nephrotic syndrome and diabetes while seeking for medical attention was higher in SCD patients (Bhagat *et al.*, 2014).

In adults with SCD, the HRQL was similar or worse than adults with other chronic diseases such as arthritis (Ballas et al., 2006) and comparable to the rheumatic disease group (Mann-Jiles and Morris, 2009). Adults with SCD also reported reduced HRQL in all domains except mental health when compared with adults with cystic fibrosis (Santos and Gomes Neto, 2013) and their overall quality of life was significantly lower than non-SCD patients (Thomas and Lipps, 2011).

Comparison with published normative data.

Both children with SCD and their parents' ratings of HRQL were significantly lower (Dale *et al.*, 2011). The level of depression and depressive symptoms (32%) was higher in adults with SCD compared with 9.5% in the general population (Jenerette, Funk and Murdaugh, 2005).

Comparison with healthy siblings.

Children with SCD had lower HRQL scores on physical wellbeing (Hijmans *et al.*, 2010). SCD also had negative effect on caregivers who were more impacted emotionally, in personal time and family activities (Palermo *et al.*, 2002).

Gender comparisons.

Irrespective of age, studies have shown that females with SCD had worse HRQL than males with SCD and higher level of depression in adult females than the male counterpart (Jenerette, Funk and Murdaugh, 2005). One of the causes of depressions in females may be attributed to inability to marry or raise children as a result of the illness. For example, in a qualitative study of older adults with SCD aged 48 years and older, Jenerette and Sandewlsky (2011) reported a participant describing her life as 'half-full' for lack of children and husband. Adult females with SCD also reported higher frequency of somatic symptoms burden that the males (Sogutlu *et al.*, 2011).

The low quality of life associated with people with SCD therefore deserves that efforts be intensified and directed towards improving their quality of life. This requires investigating the factors that affect the HRQL to understand the impact of clinical and psychosocial factors (DeBaun, 2014).

2.4 Predictors of Health-Related Quality of Life in Children and Adolescents with SCD.

The review identified ten main determinants (along with their markers) of HRQL in children and adolescents with SCD (Table 2-1). They were disease severity/complications (7 studies), comorbidities (2 studies) hospitalisation (4 studies), frequency of pain (3studies), depression/anxiety (3 studies), stigma (1 study), parental support (1 study), treatment adherence/barriers to treatment adherence (2 studies), child demographics (5 studies) and socioeconomic status of parents (5 studies).

Disease severity/complications.

Disease severity/complications was found to be a predictor of overall HRQL (Palermo *et al.*, 2002; Palermo, Riley and Mitchell, 2008; Panepinto *et al.*, 2008; Amr, Amin and Al-Omair, 2011; Fisak *et al.*, 2011; Adeyemo *et al.*, 2015; Sehlo and Kamfar, 2015), psychosocial HRQL domains (Palermo, Riley and Mitchell, 2008) and total number of disease-related complications correlated with worse physical health (r=-0.91) (Palermo *et al.*, 2002) while the presence of SCD predicted 4 times higher odds of having worse HRQL (Panepinto, Hoffmann and Pajewski, 2009). In addition, disease complications had been found to predict the physical functioning, physical role limitation, emotional role limitation, emotional well-being and general health of the SF-36 HRQL subscales (Amr, Amin and Al-Omair, 2011) and influenced 7 out of the 8 subscales of the SF-36 measure of HRQL except the mental/emotional well-being subscale (Adeyemo *et al.*, 2015). Disease severity also combined with social support and depression to affect HRQL of the study population (Sehlo and Kamfar, 2015).

Comorbidities.

Medical co-morbidity and neurobehavioral co-morbidity were both associated with worse HRQL (Panepinto *et al.*, 2008) while behavioural comorbidity predicted physical health of the HRQL (Wrotniak *et al.*, 2014).

Hospitalisation.

The frequency of hospitalisation predicted lower overall HRQL (Amr, Amin and Al-Omair, 2011; Dale *et al.*, 2011), physical health summary and mental health of the HRQL (Wrotniak *et al.*, 2014) along with school functioning scores and the psychosocial domain (Dale *et al.*, 2011). The frequency of hospitalisation had also predicted worse HRQL in the patients in all the 8 domains of SF-36 HRQL subscales (Adeyemo *et al.*, 2015). While increased emergency department visits was associated with higher scores on the emotional role dimension of the HRQL subscales (Dale *et al.*, 2011).

Pain episodes

Pain has been described as the hallmark of SCD, in the review, frequency of pain predicted change in HRQL (Schlenz *et al.*, 2012), physical functioning and self-esteem (Barakat *et al.*, 2008), and low HRQL in the patients (Menezes *et al.*, 2013).

Depression

The review had discovered that depression had been a determinant of the psychosocial HRQL domain (Palermo, Riley and Mitchell, 2008) and was associated with poor quality of life (Sehlo and Kamfar, 2015). Mediator variables consisting of internalizing symptoms and disease-related parenting stress also correlate with HRQL domains, depression predicted self-esteem while anxiety predicts physical functioning (Barakat *et al.*, 2008).

Stigma

Health-related stigma was characterised by discrediting of individuals and populations due to a health condition, this normally results in adverse effects on health (Weiss, Ramakrishna and Somma, 2006). Stigma was associated with worse HRQL in all domains of the SF-36 HRQL measure (Adeyemo *et al.*, 2015).

Parental support

A high level of parental support significantly reduced depression in children and adults with SCD and predicted better HRQL in them (Sehlo and Kamfar, 2015).

Treatment adherence/barriers to treatment adherence

Treatment adherence had unexpectedly predicted poor HRQL in the study population (Barakat *et al.*, 2005) while barriers to treatment adherence (e.g. transportation problems, financial problems, access to medication) predicted HRQL (Fisak *et al.*, 2011). Normally, treatment adherence was expected to predict better HRQL, the unexpected negative association that Barkat and colleagues reported might be due to measures of adherence used which they agreed were neither standard nor objective as mentioned in the limitations of their study.

Child /adult demographics

Age had inversely predicted overall HRQL in the patients (Palermo *et al.*, 2002; Panepinto *et al.*, 2008; Amr, Amin and Al-Omair, 2011; Adeyemo *et al.*, 2015), and worse psychological HRQL (Panepinto *et al.*, 2008). Furthermore, all domains of HRQL on the SF-36 were negatively associated with increasing age of the patients (Amr, Amin and Al-Omair, 2011). Female gender had also been associated with worse overall HRQL and general health, physical role functioning and body pain domains of HRQL (Palermo *et al.*, 2002; Amr, Amin and Al-Omair, 2011; Wrotniak *et al.*, 2014). Moreover, lower BMI had

been associated with higher scores on the body pain subscale of HRQL (Wrotniak *et al.*, 2014). The association of age had shown that the HRQL was worse with increasing age apparently also because older patients had additional complications associated with the disease (Dampier *et al.*, 2011). Females were also found to have poorer HRQL than their male peers.

Socio- economic status

Individual/family socioeconomic status were found to be determinants of functional disability, lower physical and psychosocial HRQL in the study population (Palermo, Riley and Mitchell, 2008). Higher parental education had predicted better physical HRQL (Palermo, Riley and Mitchell, 2008; Amr, Amin and Al-Omair, 2011). Also, neighbourhood socioeconomic distress had predicted physical HRQL and low family income predisposed the patients to 2.88 times higher odds of worse HRQL (Palermo, Riley and Mitchell, 2008), while low socio-economic status of the patient population had associated with low HRQL (Hijmans *et al.*, 2010). Moreover, rural residence was a negative predictor of vitality and pain of the HRQL subscales (Amr, Amin and Al-Omair, 2011).

Understanding these determinants, their interrelationships with one another and with HRQL is important to design therapy and disease management strategies to improve the quality of life. For example, the non-modifiable factors such as age and gender may be addressed in the management of the disease by considering age-stratified and gender-sensitive approach that will enhance quality of life.

Table 2-1: HRQL of SCD in Children and Adolescents

Authors Year Country	Design	Sample size SCD	Sample size Non-SCD	Mean age with SD	Main focus	Investigated Determinants	Predictors/ Correlates	Outcomes	Association/ Predictors
Adeyemo et al., 2015 Nigeria	Cross sectional	80	80	16.0±1.5 16.6±1.4	To identify sociodemographic and clinical factors impacting on HRQL of adolescents with SCD and effects of SCD-related stigma on quality of life	Child demographics, Stigma	Disease complications, hospitalisation, education status, age	Adolescents with SCD have significantly impaired HRQL in all the subscales of the SF-36 compared with healthy group	Disease complications, hospitalisation and stigma were predictors of HRQL in adolescents with SCD
Amr et al., 2011 Saudi Arabia	Cross sectional	180	202	16.8±3.6 16.9±1.7	To assess the impairment of the different domains of HRQL among adolescents with SCD compared to healthy peers.	Socio-demographic factors, disease-related factors, family income	Rural residence, Female gender, Family income, Disease-related complications	Domains of HRQL were significantly deteriorated in adolescents with SCD compared to their peers. Increasing age was negatively associated with HRQL	Rural residence was a negative predictor of vitality subscales and pain subscales HRQL. Low family income was hypothesized to be a risk factor for lower HRQL.
Barakat et al., 2005 USA	Cross sectional	21	43	10.5±4.55.	To investigate the association of treatment adherence with QOL in children with SCD	Treatment adherence Disease complications	Treatment adherence	Treatment adherence was found to be, unexpectedly, associated with poorer quality of life in the children.	Treatment adherence significantly correlated with the child self-rated and parent-rated QOL.
Barakat et al., 2008 USA	Cross sectional	42	42	15±1.82 44.1±10.19 (caregiver)	To examine association between pain, psychological adjustment and family functioning with HRQL	Pain frequency, anxiety, depression, family functioning difficulty	Anxiety, pain, depression, disease-related parenting stress.	A complex association of pain with HRQL was observed along with the existence of potentially modifiable concomitant variables.	Existence of potentially modifiable concomitant variables (anxiety, depression, disease-related parenting stress) that when addressed, could improve HRQL
Bhagat et al., 2014 India	Case – Control	105	105	11.78±2.67 10.98±4.23	To determine HQROL in SCD patients and compare	emotional problems chronic fatigue	n/s	Compared with the matched control patients with chronic	Emotional problems may be related to chronic fatigue and

					same with those of other chronic non-communicable diseases	small physical size		illness, the overall HRQL of patients with SCD was found to be significantly lower	small physical size in SCD patients
Bhatia et al., 2015 USA	Mixed Longitudinal	17	23	8.97±5.28	To physical, psychological and social functioning in SCD subjects before and after Allogeneic Hematopoietic Stem Cell Transplantation (allo-HCT)	Effect of treatment with allo-HCT	Treatment with allo-HCT	Self-reported overall baseline HRQL was found to be lower, falling below published at risk cut off scores for chronically ill children. Also, parent-proxy report showed that the overall HRQL was lower than the population mean for chronically ill children.	Overall HRQL score was found to significantly increase at 1 year of allo-HCT. This was also observed for the physical, psychosocial and emotional domain except for the social domain where the increase was not significant.
Dale et al., 2009 USA		124	143	13+3.3	To assess HRQL in in children and adolescents with SCD compared with healthy children and adolescents	Hospitalization, Emergency visits	No of hospitalisations, ED visits	53% and 63% respectively of the children and adolescents with SCD were classified as "at risk" for impaired overall and physical HRQL and they were found to have lower overall HRQL and all the subdomains except emotional functioning compared with their healthy counterpart.	There was a significant difference between parent and child rating of their overall HRQL. A weak inverse relationship was observed between number of hospitalisations, ED visits and overall HRQL. Increased hospitalisation correlated with lower HRQL
Fisak et al., 2011 USA	Cross sectional	78	n/a	11.4±3.9	To evaluate factors associated with HRQL in a paediatric SCD sample	Barriers to treatment adherence	Disease type, Frequency of pain and Barriers to treatment adherence	Pain episodes and barriers to treatment adherence were found to be robust predictors of HRQL in the paediatric SCD sample	Barriers to treatment adherence was a mediating factor between HRQL and treatment adherence
Hijmans et al., 2010,	Case Control	40	36	11.7±3.1 11.6±3.4	To examine whether reduced HRQL in children with SCD is	Parents SES	SES	Children with SCD had significantly lower HRQL compared to	Low HRQL was related to low SES of

Netherlands					related to consequences of the disease or to the low SES of most patients.			their healthy siblings only on physical well-being domain but scored significantly lower in 5 domains compared to the normative population.	the patient population.
Menezes, 2012 Brazil	Cross sectional	100	50	n/s	To assess the quality of life in children and adolescents with SCD and those of their relatives	Pain, care overload	Pain, Care overload	SCD was found to be associated with limitations in HRQL particularly the physical, social, emotional and school domains. The HRQL of parents were also impaired compared with healthy children and their parents.	Low HRQL was associated with pains in the patients and possibly due to overload of care in their parents.
Palermo et al., 2002 USA	Case-control	58	120	10.97±3.4	To provide information on HRQL and parental burden of children with SCD and describe relationships between demographic and disease related factors and children HRQL	Demographic factors, Disease related factors	Disease complications, age, female gender	Caregivers of children with SCD were reported to be significantly more impacted by the child's health emotionally, personal time and family activities than those of healthy children. They also reported that children with SCD demonstrated more limitations across the physical, psychological and social functioning domains of the HRQL compared to their healthy counterpart.	Disease complications were important predictors of children's physical health after controlling for socio-demographics factors.
Palermo et al., 2008 USA	Cross sectional	56	n/a	12±2.5	To investigate if individual distress and residence in neighbourhood of	Depression, diseases severity, individual/	Depression, diseases severity, individual/family SES and parent	Greater depression was associated with greater pain and disability while higher family	Depression, diseases severity, individual/family SES and parent

					economic distress would predict children level of pain-related functional disability and health-related quality of life .	family SES parent education	education, neighbourhood	income was associated with low child-reported disability and higher physical HRQL	education were found to predict psychosocial HRQL while living in a distressed neighbourhood, parental education predicted physical HRQL.
Panepinto et al., 2009, USA	Cross sectional	104	74	Range: 2-18	To determine the impact of family income and SCD on HROL	Family income Disease severity, comorbidities		Children with SCD reported worse HRQL than children without SCD. Moreover, children with SCD had a 4.0 (parent-report) and 3.33 child report) times higher odds of having worse overall HRQL than their healthy counterpart	Low family income indicated worse HRQL (OR=2.88) while disease severity indicated worse HRQL (OR=4.0). Severity of disease significantly predicted physical HRQL. Older children having medical or neurobehavioral comorbidities were associated with lower psychosocial HRQL
Schlenz et al., 2012 USA	Prospecti ve	90	n/a	11.04±4.34		Frequency of pain episodes	Pain episode frequency between Time1 and Time2	Caregiver proxy reports were found to be responsive to pain-related changes in HRQL	Pain episode frequency between Time1 and Time2 were predictors of changes in physical, psychosocial and overall HRQL.
Sehlo & Kamfar 2015 Saudi Arabia	Cross sectional study (case control)	60	60	11.93±1.72 11.77±1.96		Social support, Disease severity, Depression	Parent support, Depression, Disease severity	Higher level of parent support was associated with lower depressive state and better ratings of quality of life.	Higher level of parent support predicted better quality of life while higher depression and increased disease severity were predictors of lower quality of life.

Wrotniak et al., 2012 USA	Longitudinal, randomised, controlled trial	47	66	8.6±2.4	Hospitalisation, comorbidity, age, gender, haematocrit status	Hospitalisation, Behavioural comorbidity, female gender	Children with SCD had lower HRQL, compared to their healthy counterpart in general health, overall physical health and parental emotional stress but higher mental health	Predictors of lower HRQL scores were: • Hospitalisation: a predictor of physical health, mental health. • Behavioural comorbidity: a predictor of psychosocial health, mental health, general health and associated with parental emotional stress, role functioning and parental time. Gender predicted general health

Table 2-2: HRQL in Adults with SCD

Author, Year and / Country	Designs	Main focus	Setting	Hypothesised Predictor variables	Findings	Significant Predictors
Adegbola, 2011, USA	Correlational	To explore the relationships among spirituality, self-efficacy and Quality of life.	SCD Association, mail-out surveys	Spirituality and self-efficacy	Correlations were found among Spirituality and self-efficacy and quality of life. Self-efficacy accounted for 34% and spirituality 6.6%	Self-efficacy (+ve) Spirituality (+ve)
Anie et al., 2002, UK	Cross-sectional	Compare pattern of pain, health service use and psychological coping with observed USA pattern Assess the HRQL of adults with SCD	Sickle Cell clinic (2 main hospitals)	Demographic variables Disease severity markers Health service utilisation, pain, coping	Poorer HRQL on all subscales of SF-s6 compared to the general population Clinical and demographic variables associated significantly with physical function Pain associated with physical function, social function, role limitation(phy) and general health	Demographic Clinical (number of complications, haemoglobin concentration) Pain Affective coping
Ballas et al. 2006, USA	Randomised double blind	To examine the clinical benefits of treatment with hydroxyurea on HRQL as well as the effct of other factors like Hb-F level mean.	Multicentre Study of Hydroxyurea in Sickle Cell Anaemia	Hydroxyurea	Quality of life in adults with SCD was similar or worse than patients with other chronic diseases such as arthritis. Those who responded to hydroxyurea therapy had improvement in social function, pain recall and general health perception and were far better that the placebo group or non-responders. increase in HbF level reduced frequency of painful episodes and improved certain measures of HRQL	Baseline body pain Hydorxyurea HbF
Caird et al. 2011, UK	qualitative	To assess lived experiences of SCD	Sickle cell society meetings	Coping, building resilience,	SCD in adults has negative effect on biological,	Age Physical suffering

		patients above 30 years and develop a conceptual framework to understand the impact of biopsychosocial functioning on this			psychological and social functioning. The effects get worse with age	Social support (+ve) Loss of control Emotional suffering Spirituality (+ve)
Gibson et al, 2013, Jamaica	Cross sectional	To explore the interplay of locus of control on depression and quality of life in SCD adult patients.	Outpatient clinic	Demographic, diseases-related, locus of control (LOC)	A strong association between locus of control and both depression and quality of life. High level of external LOC found in adults with SCD	Internal locus of control (LOC) ((+ve))
Jenerette C.M 2008, USA	Cross-sectional	To examine relationships among types of social support and HRQL in adults with SCD	2 South-Eastern SCD clinics	Social support: Affectionate, emotional, positive interaction, tangible	SCD in adults predisposes them to poor socio-economic status. Overall social support and all its four subscales were associated with each time point of HRQL and overall HRQL	Affectionate social support Tangible social support
Jenerette et al., 2005, USA	Cross-sectional	To describe depressive symptoms among adults with SCD	2 South-Eastern SCD clinics	Depression	Higher levels of depression and depressive symptoms (32%) compared to the general population (9.5%). Females reported higher level of depression than males Significant correlation between depressive symptoms and frequency of SCD crisis	Physical and emotional complications (-ve)
Mann-Jiles & Morris, 2009, USA	Cross-sectional	To examine QOL in adult patients with sickle cell anaemia	Outpatient clinic	Disease type Gender differences	Average QOLS scores of participants (83.6) were found to be lower than those of healthy population (90) and comparable to other rheumatic disease group. No significant difference in gender HRQL but in spirituality	No significant relationships were found. Spirituality was however suggested to be a potential factor in coping

Santos and Neto, 2013, Brazil	Cross sectional	To describe the sociodemographic profile and the impact of the disease on the quality of life of SCD patients	Association of sickle cell anaemia patients, Bahia	Sociodemographic variables	Adults with SCD have reduced quality of life in all domains except mental health when compared with cystic fibrosis patients. Sociodemographic profiles eg low income and impaired access to healthcare services	
Sogutlu et al. 2011, USA	Longitudinal	To examine the impact of somatic symptoms burden on pain. Depression, anxiety, healthcare utilization and quality of life	Pain ins Sickle Cell Epidemiology Study (PiSCES) project, Virginia	High somatic symptoms burden	Somatic symptoms burden negatively correlated with all subscales of SF-36 High somatic symptoms burden were more frequent in women than men	Somatic symptom burden (-ve)
Thomas and Lipps, 2011, Jamaica.	Cross-sectional	To examine overall life satisfaction and its components and their positive and negative affect in adults with homozygous sickle cell (HbSS)compared to healthy adult peers	Sickle Cell Society, Greater London	Demographics Socioeconomic status Positive affects Negative affects	Subjective well-being is compromised in adults with HbSS as Overall life satisfaction was significantly lower in SCD patients than their non-sickle cell peers. Positive affect was also lower in SCD patients but surprisingly had similar negative affect score	Work status & occupation SCD status overall life satisfaction health functioning

2.5. Predictors of Health-Related Quality of Life in Adult with SCD

In adults with SCD, some of the determinants of HRQL in children and adolescent with SCD were present and more that are peculiar to adulthood. Some of these included spirituality, self-efficacy, clinical and demographic variables, and social support. Table 2.4 shows the summary of included studies on determinants of HRQL in adults with SCD.

In a cross-sectional study of 96 adults with SCD in UK, Anie et al. (2002) discovered that number of complications, haemoglobin concentrations and pain had effect on the HRQL of participants. They stated that the physical functioning, social functioning, physical role limitations and general health were impaired due to pain episodes in the patients. Caird et al. (2011) supported this in a qualitative study of 15 adults with SCD in UK and reported that biological, psychological and social functioning of adults with SCD are impaired. In addition, Ballas et al. (2006) revealed that increase in foetal haemoglobin (HbF) level reduced frequency of pain episodes and improved HRQL. These studies showed that clinical variables have effects on the HRQL of adults with SCD.

Adegbola (2011), in a study of 90 adults with SCD in the USA revealed that spirituality and self-efficacy associated with better HRQL. Caird et al. (2011) also reported that spirituality predicted better HRQL. Though Man-Jilles and Morris (2009) did not find significant relationship between spirituality and HRQL, they however suggested that spirituality could be a potential factor in coping with the disease which was in line with the findings of Adegbola.

Sogutlu et al. (2011) using the data on the Pain in Sickle Cell Epidemiology (PiSCES) project, Virginia revealed that somatic symptom burden negatively correlated with all the subscales of SF-36. Also, depressive symptoms correlated positively with frequency of SCD crises (Jenerette, Funk and Murdaugh, 2005), and resulted in low HRQL.

Locus of control associated with HRQL (Caird, Camic and Thomas, 2011; Gibson *et al.*, 2013), additional findings also showed that social support was associated with HRQL (Jenerette, 2008; Caird, Camic and Thomas, 2011) reflecting the positive effect of support from family and friends on HRQL.

Sociodemographic characteristics predicted HRQL in adults with SCD (Anie, Steptoe and Bevan, 2002; Thomas and Lipps, 2011) and HRQL worsened with increasing age (Caird, Camic and Thomas, 2011). Using a univariate analysis of variance, Thomas and Lipps discovered that the interaction of work status, occupation and SCD had significant effect on the subjective well-being of adults with SCD; for instance, unemployed adults with SCD showed less satisfaction with their health and functioning, social and economic situation, and psychological functioning compared with adults with SCD who were employed (Thomas and Lipps, 2011).

Adults with SCD are vulnerable adults with elevated risk for negative psychological outcomes (Thomas and Lipps, 2011) hence their situation requires targeted intervention efforts to relief the patients of the burden of the disease. The opinions of care providers alone cannot be sufficient to evaluate patients' outcomes, but patients themselves must be involved in such evaluation, in fact many researchers have argued that the patients are in a more vantage position to report on their experiences and to judge their satisfaction with the quality of their lives (Panepinto, 2012; Cella and Stone, 2015). Intervention efforts could also be reliably based on the information provided by patients with respect to the care and treatment they receive and the effects of therapy.

This chapter has reviewed studies on the HRQL of people with SCD from which factors predicting HRQL have been identified. These include clinical, psychosocial and demographic factors. Evidence from the review showed that the predictors are multifaceted and significantly affect the HRQL either individualy or in combination with

other predictors This gives rise to a potential need to characterise these factors to properly understand interrelationships and possible mediator variables as well as establish the relative importance of the predictors. Such efforts require employing a model of HRQL. A conceptual model that has been found useful in modelling HRQL in chronic disease is the Wilson and Cleary model (see 1.24.2). A systematic review of the application of the Wilson and Cleary model in modelling predictors of HRQL is presented in Chapter Three.

CHAPTER THREE

A SYSTEMATIC REVIEW OF THE APPLICATION OF WILSON AND CLEARY HEALTH-RELATED QUALITY OF LIFE MODEL IN CHRONIC DISEASES.

3.1 Introduction

In order to understand the application of the Wilson and Cleary conceptual model in practice, a systematic review of its use in determining the predictors of HRQL in chronic disease was conducted. This chapter reports a systematic review of literature on the application of Wilson and Cleary's model in chronic diseases to examine the paths and pattern of relationships of the concepts as well as determine their relative importance (See Ojelabi *et al.*, 2017). Three important research questions are proposed:

1. Does empirical evidence show the causal relationship of the dominant concepts as proposed in the Wilson and Cleary model?
2. Does the Wilson and Cleary model follow a strictly linear unidirectional path?
3. What is the relative effect of each latent factor?

3.2 Methods

This study followed the format of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, *et al.*, 2009). The electronic databases searched consisted of Science Direct, MEDLINE, CINAHL and PsyARTICLES. The search term used was "Wilson and Cleary" (free text). Further related search terms such as, "Wilson and Cleary model", "Wilson and Cleary conceptual model", "(Health-related quality of life OR HRQL OR HRQOL) AND (Wilson and Cleary OR Wilson and Cleary model)", were also used, but did not yield any additional studies. The search covered a period from 1995 (when the model was published) to December 2016.

3.2.1 Inclusion and exclusion criteria

The inclusion criteria were as listed below:

Inclusion criteria

1. Chronic disease
2. Articles published in English language
3. HRQL measured with validated instruments
4. Empirical study
5. Wilson and Cleary model was used or tested
6. Peer-reviewed articles with full-text accessible.

Exclusion criteria

1. Articles based on instrument development
2. Articles that did not apply the model
3. The disease could not be clearly defined as a chronic disease.

3.3 Quality assessment of selected articles

The Quality Assessment Tool for Quantitative Studies designed by the Effective Public Health Practice Project (EPHPP) was used to evaluate the quality of included articles (Effective Public Health Practice Project, 2010). The EPHPP tool was designed to assess quality of observational and clinical studies. The tool was used to rate each article on a three-point scale (strong, moderate and weak) in six components: selection bias, study design, confounders, blinding, data collection methods, and withdrawal and drop-outs. A global rating was allocated to each study.

3.4 Results

The initial search yielded a total of 2,018 full text peer reviewed articles (Figure 3-1).

Duplicates were removed and articles were screened on titles and abstracts. The full-texts of the selected 78 articles were screened. Of these, 59 articles were excluded: 14 because they were based on instrument development, 18 did not apply the model, 14 were not empirical studies and 11 could not be categorised as focusing on chronic disease. Five additional articles were added through searching of reference lists of the selected studies. The total number of articles reviewed was 26 (Sousa *et al.*, 1999; Cosby *et al.*, 2000; Wettergren, Björkholm, Axdorph and Langius-Eklöf, 2004; Arnold *et al.*, 2005; Phaladze *et al.*, 2005; Portillo *et al.*, 2005; Heo *et al.*, 2005; Hofer *et al.*, 2005; Sousa and Kwok, 2006; Mathisen *et al.*, 2007; Baker, Pankhurst and Robinson, 2007; Krethong *et al.*, 2008; Ulvik *et al.*, 2008; Halvorsrud *et al.*, 2010; Nokes *et al.*, 2011; Wyrwich *et al.*, 2011; Ade-Oshifogun, 2012; Kanters *et al.*, 2012; Schulz *et al.*, 2012; Saengsiri. *et al.*, 2014; Shiu *et al.*, 2014; Carlson *et al.*, 2014; Mayo *et al.*, 2015; Santos *et al.*, 2015a; Brunault *et al.*, 2015; Eilayyan *et al.*, 2015).

The flow chart of the included studies is displayed in Figure 3-1.

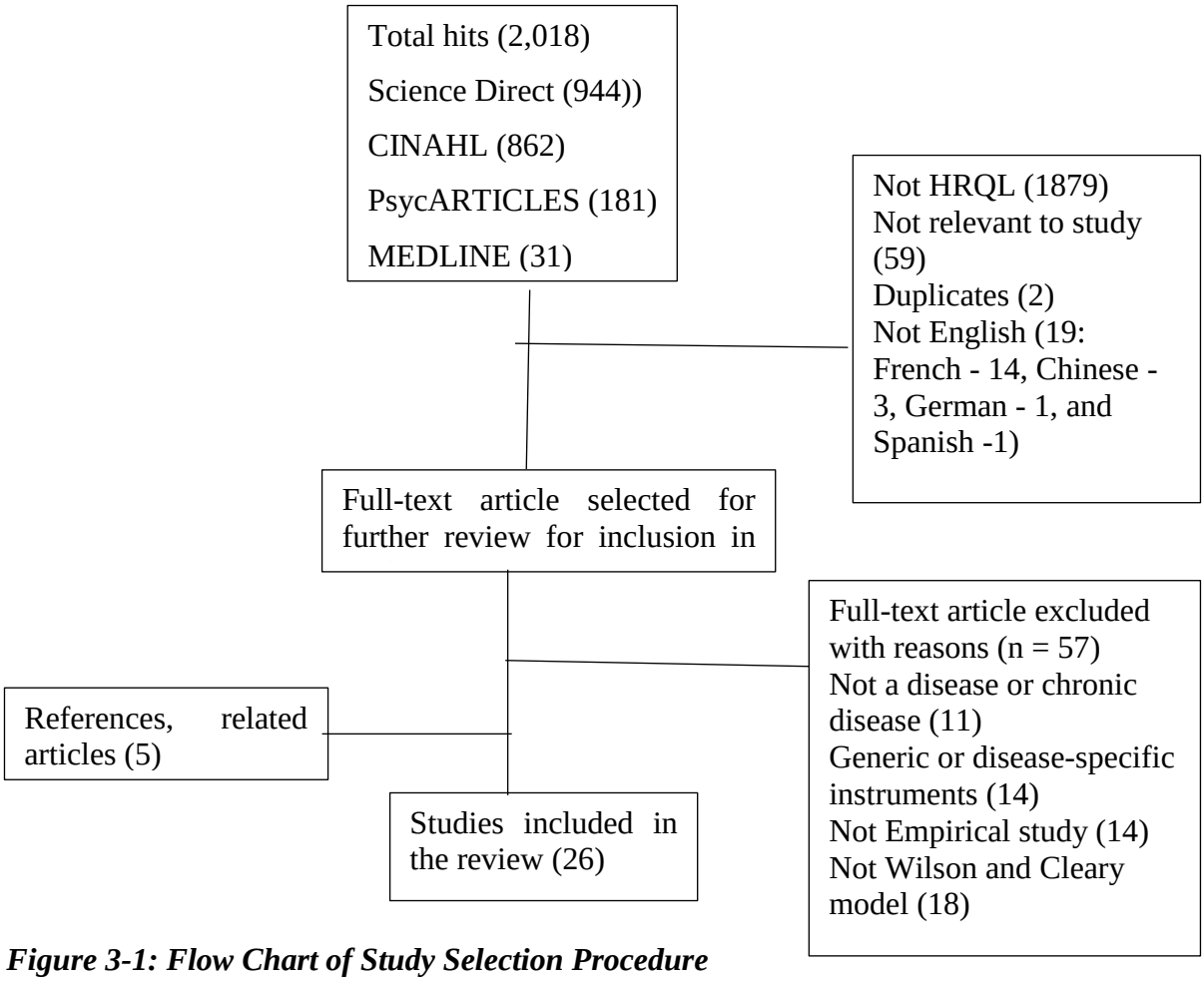


Figure 3-1: Flow Chart of Study Selection Procedure

3.5 Characteristics of Studies Reviewed

The 26 studies took place in 15 countries with one study based across four countries in Sub-Saharan Africa (Botswana, Lesotho, South Africa and Swaziland) (Table 2-5). The other countries were: USA (n=9), Norway (n=3), Canada (n=2), Netherlands (n=3), Thailand (n=2), UK (n=1), France (n=1), Austria (n=1), Sweden (n=1), Brazil (n=1) and Hong Kong (n=1).

Thirteen different types of disease were studied: heart failure/surgery (n=5), HIV/AIDS (n=6), coronary artery disease (n=3), oral health disease (n=2), obesity (n=2), chronic obstructive pulmonary disease (n=2) and asthma, diabetes, Hodgkin's lymphoma, kidney, Pompe disease, generalised anxiety disorder and stroke (all n=1). Study designs were

either cross sectional (n=20) or longitudinal (n=6). The total number of participants was 11,849, with a mean age of 50.5 years; 43.7% were female.

3.6 Quality assessment

Six studies were rated as strong (23%), 19 studies had moderate rating (73%) and one study had a weak rating (Table 3-1).

Table 3-1: Quality Assessment of Included Studies.

Author	Selection bias	Study design	Confounding	Blinding	Data collection	Withdrawal and drop-out	Overall quality
Ade-Oshifogun	1	3	1	2	1	2	**2**
Arnold	1	2	1	1	1	2	**2**
Baker	1	1	1	1	1	2	**1**
Brunault	1	2	2	1	1	1	**1**
Carlson	1	2	3	2	1	2	**2**
Cosby	1	3	3	2	1	1	**3**
Eilayyan	1	2	2	2	1	2	**2**
Halvorsrud	1	1	2	2	1	1	**2**
Heo	1	1	1	1	1	1	**1**
Hofer	1	2	1	1	1	1	**1**
Kanters	1	2	1	1	1	1	**2**
Krethong	1	3	1	2	1	2	**2**
Mathisen	1	1	2	1	1	1	**1**
Mayo	1	2	3	2	1	1	**2**
Nokes	1	3	2	1	1	1	**2**
Phaladze	1	3	2	2	1	2	**2**
Portillo	1	3	1	2	1	2	**2**
Saengsiri	1	1	2	3	1	1	**2**
Santos	1	1	1	1	1	2	**2**
Schulz	2	2	1	1	1	2	**2**
Shiu	1	3	1	2	1	1	**2**
Sousa (1999)	1	3	1	2	1	2	**2**
Sousa (2006)	1	2	2	2	1	2	**2**
Ulvik	1	3	2	2	1	2	**2**
Wettergren	2	2	1	1	1	2	**2**
Wyrwich	1	2	1	1	1	2	**1**

Note: 1 = low risk of bias, 2 = moderate risk of bias and, 3 = high risk of bias.

3.7 Aims of studies

All the studies in the review applied the Wilson and Cleary model to investigate determinants of health-related quality of life in a specific chronic disease. The primary aim of most of the authors was to empirically test the Wilson and Cleary model to establish the hypothesised link between objective and subjective links in the disease

population in order to identify important predictors to be targeted to improve quality of life of the patients. Eleven of the authors explicitly stated this as their purpose of study. Using such words as: ‘systematically test (Baker, Pankhurst and Robinson, 2007), ‘empirically test’ (Mayo et al., 2013), ‘put to test’ (Brunault et al., 2011), ‘apply’(Hofer et al., 2005; Shiu et al., 2014), ‘test’ (Ade-Oshifogun , 2012; Heo et al., 2005; Krethong et al., 2008; Santos et al., 2015;), ‘explore pathways’(Moi and Nilsen, 2012), ‘identify pathways’(Schulz *et al.*, 2012), estimates pathways’(Sousa and Kwok, 2006), ‘identify determinants’ (Wettergren, Björkholm, Axdorph and Langius-Eklöf, 2004). Others focused on predictors but indicated that they were using the model as proposed by Wilson and Cleary to test the causal pathways of specific components of the model.

3.8 Measure instruments

Measure instruments in quality of life studies are broadly categorised into two; the generic instruments and the disease-specific instruments.

Generic instruments for HRQL

The most widely used instrument was the Medical Outcome Survey (MOS) Short Form 36 (SF-36) (Ware Jr and Sherbourne, 1992), in both the full form SF-36 (n=10) and the shorter form 12 (Ware Jr, Kosinski and Keller, 1996), SF-12 (n=2). Components of the instrument were used to measure symptoms status (n=3), functional status (n=7), general health perceptions (n=9) and global HRQL (n=2). Other generic instrument used to measure HRQL was the Sickness Impact Scale (SIS). To measure depression, Patient Health Questionnaire (PHQ-9) (Kroenke and Spitzer, 2002), Beck’s Depression Index (BDI)(Beck and Steer, 1984) and the Hospital Anxiety and Depression Scale (HADS

)(Zigmond and Snaith, 1983) were used.

Disease-specific instruments for HRQL.

Disease-specific HRQL instruments used in the studies included the MacNew Heart Disease Quality of Life(Hofer *et al.*, 2005), Minnesota Living with Heart Failure Questionnaire (MLFHQ) and the New York Heart Association (NYHA) classification to measure the global HRQL in heart failure (Heo *et al.*, 2005; Krethong *et al.*, 2008; Ulvik *et al.*, 2008). The HIV/AIDS-Targeted Quality of Life (HAT-QoL) instrument (Phaladze *et al.*, 2005; Portillo *et al.*, 2005; Nokes *et al.*, 2011) for HIV/AIDs populations while the Quality of Life, Obesity and Dietetics (QOLOD) (Brunault *et al.*, 2015), Oral Health Impact Profile (OHIP-14) (Baker, Pankhurst and Robinson, 2007; Santos *et al.*, 2015a) were used in diabetes and oral health populations respectively.

Measures of the characteristics of the individual and the environment

There is consensus with regards to age, gender and educational status as markers of the characteristics of the individual, but consensus is lacking among the authors on other indicators of characteristics of the individual and indicators of the environment. For example, marital status was treated by some as an individual characteristic and by others as an environmental characteristic. Hofer et al treated depression as an environmental characteristic in contrast to the general classification of depression as a symptoms variable.

3.9 Analytical tools

In modelling the data (Table 3-2), different analytical tools were used: stepwise/hierarchical regression (n=3), linear mixed model/multiple regression (n=4), logistic regression and/or partial correlation (4). Structural Equation Modelling (SEM)/path modelling was used in most of the studies (n=15), with 67% of those who used SEM/path analysis reporting the fit of the model. SEM has been found to exhibit superior properties compared to regression analysis in overcoming the limitations of regression by decomposing the sources of correlation among independent variables and

make it possible for each variable in a path model to be treated simultaneously as both a predictor and as an outcome (Eilayyan *et al.*, 2015).

Table 3-2: Application of Wilson and Cleary Model: the Predictor Markers

1st Author Year Country	Population	Measures Biological / Physical	Symptoms	Function Status	General health perceptions (GHP)	Individual Characteristics	Environmental Characteristics	Overall HRQL
Ade-Osihifogun 2012 USA	Obesity/Chronic Pulmonary Disease	BMI, FEV1, DLCO, Percent trunk fat (DEXA)	Dyspnoea (CRQ), fatigue (CRQ), sleep apnoea (ESS)	Functional capacity measured by 6-minute walk distance (6MWD)	Functional Performance Inventory (FPI)			
Arnold 2015 Netherlands	1. Chronic Obstructive Pulmonary Disease (COPD) 2. Chronic Heart Failure (CHF)	COPD: FEV_1 VHF: LVEF	Dyspnoea measured by a questionnaire	Physical functioning subscale of SF-36	General health perception subscale of SF-36	Age Gender Marital status Level of education		Perceived health competence scale
Baker 2007 UK	Xerostomia	Salivary flow Clinical signs	Xerostomia Inventory (XI)	Oral Health Impact Profile (OHIP-14)	Global oral health rating (GOH)	n/m	n/m	Hospital Anxiety and depression Scale (HADS)
Beverly 2013 USA	Heart Failure	Number of chronic illness Comorbidity burden (Charlson Comorbidity Index (CCI)as in index of severity of illness Diagnosis of diabetes Diagnosis of chronic atrial fibrillation	Depression measure with Patient Health Questionnaire (PHQ-9) Physical symptoms measured with KCCQ	Physical and social functioning measured with Kansas City Cardiomyopathy Questionnaire (KCCQ)	First item in the SF-36(v2)	Age Gender Race/ethnicity Education Family income		
Brunault 2015 France	Obesity	BMI Type of Surgery	Beck Depression Index (BDI) Bulimic Investigatory Test, Edinburg (BITE)	Quality of Life, Obesity and Dietetics (QOLOD) -Physical QoL -Psychological QoL -Social QoL		Age Gender	Marital status	

				-Sexual QoL -Comfort with food				
Eilayyan 2015 Canada	Asthma		Physical symptoms (MAQLQ-symptoms) Emotional symptoms (MAQLQ-emotion) Self-efficacy (KASE-AQ)	Physical function (MAQLQ-activity)	n/m	Age Gender Beliefs about medication	Smoking status Healthcare utilisation	n/m
Halvorsrud 2010 Norway	Chronic Disease		Geriatric Depression Score (GDS-15)	SF-12 subscale of physical function	Health satisfaction: global item measure from WHOQoL-Bref	Age	Environmental domain of WHOQoL-Bref.	WHOQoL-Old
Heo 2005 USA	Heart failure	Patient interview Medical records Charlson comorbidity Index	Patients perception of Presence and severity of dyspnoea and fatigue measured by Dyspnoea-Fatigue Index Questionnaire	NYHA	SF-36	Age Gender Educational status	Social support (having a confidant: y/n) Marital status	MLHFQ
Hofer 2005 Austria	Coronary Artery Disease (CAD)	Severity of CAD (no of diseased vessel No. of risk factors	Canadian Cardiovascular Society classification of angina pectoris	SF-36 physical function score	SF-36 general health score	Locus of control Anxiety Depression	Social support measured by the German short form of the Social Support Questionnaire	Scores on the three scales (physical, social and emotional) of MacNew Heart Disease Quality of Life

								Questionnaire
Kanters 2015 Netherlands	Pompe disease	Enzyme activity (fibroblasts) Skeletal muscle strength assessed by Medical Research Council (MRC), respiratory function assessed by forced vital capacity (FVC)	shortness of breath, Fatigue assessed by Fatigue Severity Scale (FSS)	Rotterdam Handicap Scale (RHS)	EQ-5D Visual Analogue Scale (EQ-5D-VAS)	Age, gender, disease duration		Mental Component Scale (MCS) and Physical Component Scale (PCS) of the Short-form (SF-36) Utility derived from EQ-5D
Krethong 2008 Thailand	Heart Failure	Medical records- Left Ventricular Ejection Fraction (LVEF)	Cardiac Symptoms Survey (CSS)	NYHA functional classification	100mm horizontal visual analogue scale	Personal information questionnaire	Social support- measured with Enhancing Recovery in Coronary Heart Disease Social Support Instrument (ESSI)	Minnesota Living with Heart Failure Questionnaire (MLFHQ)
Mathisen 2007 Norway	Heart Surgery	n/m	n/m	n/m	General Health subscale of SF-36	n/m		Global Quality of Life (gQoL) Norwegian version of the Quality of Life Survey (QoLS-N)
Mayo 2015 Canada	Stroke	Side of lesion Stroke severity measured using Canadian Neurological Scale (CNS)	Stroke Impact Scale (SIS) Pain: SF-36 (body pain) Vitality: SF-36 (vitality)	*Physical Functioning*: RAND Short-Form (SF-36): SF-36 (PF) SIS (mobility)	EQ-5D VAS SF-36 (General health)	Age gender	OARS Social Resource Scale	

		Charlson Comorbidity Index	Emotional well-being: SF-36 (mental health)	Health Utility Inventory(HUI): HUI (ambulation) HUI (dexterity) *Social Functioning:* SF-36 (SF) SIS 8b *Role:* Worst of SF-36 RE & RP Cognitive: Mini mental State Education (MMSE)				
Moi 2012 Norway	Burns	Total body surface area burn; Extent of full thickness injury; Presence or absence of inhalation injury; Number of operations; Length of hospital stays	Pain and itch (measured by BSHS-N) General health (BSHS-N) Body Image (BSHS-N) Affective ((BSHS-N) Mental health (SF-36) Bodily pain (SF-36) Vitality (Sf-36)	Physical health (BSHS-N) Mobility and self-care (BSHS-N) Role activities (BSHS-N) Physical function (SF-36) Social function (SF-36) Role emotional (SF-36) Role physical (SF-36)	General health (SF-36)	Age Sex Non-burn physical illness Psychiatric illness	Living alone Housing or economic problems Unemployment	Quality of Life Scale (QOLS)
Nokes 2011 USA	HIV/AIDS		Center for Epidemiological Depression Scaled (CES-D) Revised signs and symptom Checklist for Persons with HIV Disease Body Change Distress Scale					HAT-Quality of Life (HAT-QOL)_
Phaladze 2005	HIV/AIDS	Has been give AIDS diagnosis Has Comorbidities	Revised Sign and Symptoms Checklist for	Overall functioning	Health worries	Age Gender	Living environment	HIV/AIDS-Targeted Quality of

Sub-Saharan Africa			Persons with HIV Disease			Years of education Has children	Has enough money	Life (HAT-QoL)
Saengsiri 2014 Thailand	Coronary Artery Disease (CAD)	LVEF Rose Questionnaire for angina Rose Dyspnea Scale (RDS)	Centre for Epidemiologic Studies Depression Scale (CES-D) Cardiac Self Efficacy Scale (C-SES)	Functional Performance Inventory Short-Form (FPI-SF) SF-36 Vitality subscale			Social support questionnaire (SSQ)	Quality of Life Index-Cardiac Version
Santos 2015 Brazil	Oral health	Edentulism (dentate=0, edentulous=1) assessed by clinical examination	Assessed using the question, “are you satisfied with the appearance of your prostheses?”	Assessed with the question, “have you decreased or changed the type of food because of problems with your teeth or dental prostheses?”	Assessed using the question, “compared with others your age, how would you rate the health of your mouth overall?”	Age Gender Geographic location Monthly income schooling		Assessed with the Oral health Impact profile-14 (OHIP-14)
Schulz 2012 Netherlands	Kidney transplant	Number of active comorbidities reported by patients		European Quality of Life -5 dimension (EQ-5D)	EQ-5D Visual Analogue Scale (EQ-5D-VAS)	Index of personal characteristics-Mastery (mastery scale, Optimism (Life orientation test) and Self-esteem (Rosenberg self-esteem scale)		General Health Questionnaire (GHQ-12)
Shiu 2013 Hong Kong	Diabetes	Time since diagnosis Age of onset and type of diabetes HbA1c level, blood pressure and lipid profile	Self-reported comorbidity characteristics and presence of comorbidity and no of comorbidities	Physical functioning subscale of SF-36 Older American Resources and Services Multidimensional Functional	SF-36: general health perception Self-developed ratings	Age Gender Working status Lifestyle characteristics Psychological distress	Marital status Income adequacy Social support measured by	6 subscales of the SF-36: role-physical, role-emotional, mental

				Assessment Questionnaire		measured by Rand Mental Health Inventory	MOS Social Support Survey	health, social functioning, bodily pain and vitality
Sousa 2006 USA	HIV/ AIDS	CD4 Count	Signs and symptoms checklist for persons with HIV disease (SSC-HIV)	The Health Assessment Questionnaire-Disability Index (HAQ-DI)	100mm visual analogue scale Ordinal scale	n/m	n/m	Derived from general health status scales
Ulvik 2008 Norway	Coronary Artery Disease (CAD)	Myocardial disease LVEF	Angina (AFS, CCS) Dyspnoea (NYHA) Anxiety (HADS) Depression (HADS)	Physical function Social function	General health (SF-36)			Overall QoL: measured with a single question.
Wan 2016 Singapore	Rheumatoid Arthritis (RA)	Duration of RA, tender and swollen joint counts	Hospital Anxiety and depression scale (HADS), Numerical rating scale (NRS)	Health Assessment-Disability Index (HAQ-DI)		Age, gender, marital status, employment status, education, ethnicity	Medical Outcomes Study-Social Support Survey (MOS-SSS)	European Quality of Life -5 dimension (EQ-5D)
Wettergren 2004 Sweden	Hodgkin's Lymphoma (HL)	Disease stage (I-IV) Treatment modality (irradiation, chemotherapy or combined modality treatment Time since diagnosis	Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting (SEQoL-DW) Hospital Anxiety and depression (HAD) scale	Measured as part of general health perceptions	Physical Component Summary (PCS) of Short Form 12 (SF-12) Mental Component Summary (MCS) of SF-12	Sense of Coherence (SOC) scale	Respondents' rating of present financial situation.	QoL index of Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting (SEQoL-DW)
Wyrwich 2011 USA	General Anxiety Disorder (GAD)	Clinical Global Impression-Severity of illness (CGI-S)	Hamilton Rating Scale for Anxiety (HAM-A)	Pittsburgh Sleep Quality Index (PSQI)	Quality of Life, Enjoyment and Satisfaction			Quality of Life, Enjoyment and Satisfaction Questionnair

Questionnaire-Short Form (Q-LES-Q(SF)) (items 1-14)	e-Short Form (Q-LES-Q(SF)) (Item 16)

BSHS-N: Burn-Specific Health Scale (Norwegian version). FEV: forced expiratory volume. CRQ: Chronic Respiratory disease Questionnaire. ESS: Epworth Sleepiness Scale. DLCO: carbon monoxide diffusing capacity.

Table 3-3: Application of Wilson and Cleary Model: Study Outcomes

1st Author Year Country	Population	Design	Characteristics of Study Sample size	Age Mean (SD)	% of Female	Aim of study	Analytical Tool	Results/Findings	Percentage of variance explained by model (if calculated)
Saengsiri 2014 Thailand	Coronary Artery Disease (CAD)		303	61.2 (10.9)	26.4%	To explain relationship between cardiac self-efficacy, social support, biological and physiological (LVEF) symptoms of angina, dyspnoea, depression, vital exhaustion, functional performance and quality of life in post-PCI CAD patients	Pearson Correlation Path analysis	• Social support (β=0.31), depression(β=0.24), vital exhaustion(β=0.23) and cardiac self-efficacy(β=0.21) had the most powerful direct effect on quality of life of post-PCI CAD patients • Self-efficacy had indirect effect on quality of life (β=0.21, p<0.001)	
Heo 2005 USA	Heart failure	Baseline data	293	73 (11)	53%	To determine the bivariate relationships between HRQL and other variables proposed by Wilson and Cleary To determine best multivariate model based on these variables To test specific components of the Wilson and Cleary model of HRQL	Multiple regression	• Health perception, symptom status and age predict HRQL • Health perception mediates the effect of symptoms on HRQL • Functional status does not mediate the effect of symptom status on health perception	• Final model explains 29% of the variance
Brunault 2015 France	Obesity	Cohort	126	40.2 (10)	79.4%	To put the Wilson Cleary model to test by determining the predictors of postoperative change in each QoL dimension 12 months after bariatric surgery	Linear mixed model	• Improvement in Psychosocial QoL was associated with lower preoperative depression severity, lower preoperative binge eating severity and higher weight loss • Improvement in Sexual QoL was associated with lower	

								preoperative depression severity, lower preoperative binge eating severity and younger age • Improved comfort with food was associated with lower preoperative binge eating severity	
Phaladze 2005 Sub-Saharan Africa	HIV/AIDS	Cross sectional	743	34.1 (9.6)	61.2%	To increase understanding of the meaning of quality of life for people living with HIV/AIDS in four countries in Sub-Saharan Africa: Botswana, Lesotho, South Africa and Swaziland.	Hierarchical multiple regression	• Daily functioning predicts overall HRQL • Higher level of education associates with lower HRQL • Higher symptom intensity associates with lower HRQL • A close correlation between symptom intensity and functional status	• Overall model explains 53.2% of the variance
Wettergren 2004 Sweden	Hodgkin's Lymphoma	Cross sectional	121	45 (median)	45%	To evaluate HRQL in long-term survivors of |Hodgkin's lymphoma (HL) and to identify determinants of HRQL using Wilson and Cleary's conceptual model with the potential goal of improving care and rehabilitation.	Partial Correlations	• Disease stage correlated with Disease index (SEQoL-DW) • Lower SOC was related to a worse HRQL • Poorer physical health was associated with worse overall quality of life.	
Ade-Osihifogun 2012 USA	Obesity/Chronic Pulmonary Disease (COPD)	Cross sectional	76	69.7 (10.3)	35.5%	To test a theoretically and empirically supported model of the relationship among clinical variables, symptoms, function status and health status of elderly people with COPD	Path analysis	• Function status, symptoms and biological variable DLCO have direct causal effect on health status • DLCO ad dyspnoea predict functioning • The effect of clinical variables on health status is mediated by symptoms • Symptoms, function status and clinical variable indirectly influence health status	• Model explains 29% of the variance • Clinical variables explain 29.6% of symptoms • Clinical variables

									explain 50.5% of function status
Nokes 2011 USA	HIV/AIDS	Cross sectional	1217	41.7 (9.1)	31.5%	To determine if there were age-related differences in symptoms status and HRQL for HIV-positive persons aged 50 years and older compared with younger (aged 49 years and younger).	Stepwise regression	• Age was a predictor for sexual function and provider trust • Less depressive symptoms and less body change distress were related to increase in sexual functioning	
Arnold 2015 Netherlands	1. Chronic Obstructive Pulmonary Disease (COPD) 2. Chronic Heart Failure (CHF)	Cross sectional	COPD:95 CHF:90	65 (9.3) 59 (10)	35.8% 24.4%	To investigate relationship between objective and subjective health in patients with COPD and CHF	Structural equation model (SEM)	• Biological/physiological variables in both diseases are not significantly related to symptoms but predict physical functioning • Symptoms predict physical functioning in both diseases • Physical functioning associate with general health perceptions in COPD and CHF • Symptoms directly associate with general health perceptions only in COPD • In COPD, symptoms, physical functioning explain general health perception • Only physical functioning explains general health perceptions in CHF	• The authors report that there exist direct and indirect relationships between the health parameters. • For instance, proxy for global HRQL explains symptoms and general health perceptio

									ns in both diseases.
Moi 2012 Norway	Burns	Cross sectional	95	43.7 (14.5)	18%	To explore pathways leading to self-perceived general health and overall quality of life in burn patients.	Structural equation modelling (SEM)	• Length of hospital stays, Living alone, and Painitch had indirect effects on general health • Vitality had both direct and indirect effects on general health • Vitality was associated with overall quality of life and shown to be the best indicator of biological and physiological variables	Model explained 43% variance in overall quality of life
Shiu 2013 Hong Kong	Diabetes	Cross sectional	452	71.8 (7.3)	59.1%	To apply the Wilson and Cleary model of HRQL to understand the relationship among clinical and psychological outcomes in community-dwelling older Hong Kong Chinese people with diabetes.	Structural Equation Modelling (SEM)	• Four determinants: general health perception, psychological distress, adequacy of income and social support have direct effect on HRQL • Three determinants: symptom status, physical functional status and psychological status have indirect effects on HRQL through general health perception • Four determinants: symptom status, age, gender and physical activity have indirect effect on HRQL through physical function status	• The model explains between 64% and 72% of variance
Santos 2015 Brazil	Oral health	Cross sectional	578	68 (6.3)	67.3%	To test the Wilson and Cleary model of the direct and mediated pathways between clinical and non-clinical variables in relation to oral health-related quality of life	Structural Equation Modelling (SEM)	• Dissatisfaction with symptom status are associated with worse functional status • Worse functioning predicts poor oral health perception • Poor oral health perception associates with higher worse oral health quality of life	• The comparative fit index is 0.98 indicating adequate fit.

								• Final model shows negative significant direct effect between biological variable and symptom status • Age, gender and geographical location have direct paths to biological variable (edentulism) • Age and gender directly impact oral health-related quality of life	
Ulvik 2008 Norway	Coronary Artery Disease (CAD)	Cross-sectional	753	61.7 (10.2)	26%	To analyse relationship between disease severity and both mental and physical dimensions of HRQL.	Linear and ordinal logistic regression	• Biological variables associate with symptoms • Depression associates positively with LVEF • Symptoms affect physical function • Social function is low in patients with more symptoms of anxiety. • General health is negatively related to anxiety and depression but positively related to physical and social functions • Better overall QOL is associated with less symptoms and depression but related negatively to social function	• The model explains 43% of the variance of overall quality of life.
Halvorsrud 2010 Norway	Chronic Disease	Cross-sectional	89	78.6	73%	To explore the predictors of QOL among community-dwelling older adults receiving community health care	Path analysis: Structural equation Modelling (SEM)	• Environment has direct effects on QOL and indirect effects on QOL with depressive symptoms and health satisfaction (GHP) as mediators • Depressive symptoms had an indirect, negative effects on QOL with physical functions	• The predictor variables accounted for 37% of the variance in depressive symptoms,

								and general health perceptions as mediators • Health satisfaction was a mediator between physical function and QOL	29% in physical function, 44% in general health perception s and 66% of the variance in QOL (the overall model)
Krethong 2008 Thailand	Heart Failure	Cross-sectional	422	58.47	Ns	To develop and test a hypothesized causa model of HRQL in Thai heart-failure patients	Structural equation modelling (SEM)	• Biological/physiological affected functional status (β = -0.34, p<0.05). • Symptom affected functional status (β = 0.45, p<0.05); GHP (β = -0.27, p<0.05) and HRQL (β = -0.48, p<0.05) • Functional status had impact on GHP (β = -0.28, p<0.05); HRQL (β= -0.25, p<0.05) • Social support had impact on symptom (β = -0.25, p<0.05); GHP (β = 0.19, p<0.05) and HRQL (β = -0.17, p<0.05) • The effect of biological/physiological on symptom was not significant.	Model explained 58% of the variance in overall HRQL
Sousa 2006 USA	HIV/ AIDS	Cross-sectional	395	30.4 (8.13)	Ns	To estimate the primary pathways of the Wilson and Cleary HRQL conceptual model using structural equation modelling (SEM)	Structural equation modelling (SEM)	• A significant relationship between status and functional health (r= 0.56) • There is significant relationship between symptoms status and general health perceptions (r= -0.33) and functional health and	• Symptoms explain 49% of functional health • Both symptoms status and functional

								general health perceptions (r=-0.42) • There is significant relationship between symptoms status and overall quality of life (r= -0.20) and between GHP and overall quality of life (r= 0.26) • CD4 count had a negative relationship with symptom status (r= - 0.20, p<0.05)	heath accounted for 62.5% of the variance of general health. • Both symptoms status and general heath perceptions accounted for 38,2% of the variance in overall quality of life.
Beverly 2013 USA	Heart Failure	Cross-sectional	265	62	35.8%	To determine the key predictors of overall perceived health (OPH)	Hierarchical multiple regression	• Age, gender and race/ethnicity were predictors of OPH • Perceived sufficiency of income, social functioning, comorbid burden, symptom stability, black compared to white race were independent predictors of OPH • Physical and social functioning mediated the effect of SOB and fatigue on OPH as well as the effect of symptom on OPH	• 39.2%
Wan 2016 Singapore	Rheumatoid Arthritis	Cross-sectional	108	56.4 (13.2)	79.6%	To examine the level of HRQL and its predictors in patients with Rheumatoid arthritis in Singapore	Pearson correlation & Multiple linear regression	• Pain, functional disability, anxiety, depression, medication adherence, social support and tender joint counts were correlated with HRQL	Model explained 55.5% of the variance.

								• Pain, functional disability and depression were predictors of HRQL	
Kanters 2015 Netherlands	Pompe disease	Cross-sectional	103	49.3	50.6%	To develop a conceptual model for Pompe disease in adults and statistically test it in untreated patients	Random effects linear regression	• MRC and FSS were negatively associated with disease duration • FVC was affected by female gender • RHS was affected by FSS, MRC, FVC and Age • EQ-5D Vas was associated with RHS and disease duration • MCS was associated with EQ-5D VAS • PCS was associated with EQ-5D VAS • Utility was associated with EQ-5D Vas	
Schulz 2012 Netherlands	Kidney Transplant	Cross-sectional	609	53.7 (12.3)	43.9%	To identify pathways through which objective health affects psychological distress and to clarify how personal characteristics are shaped by objective health and determine psychological distress	Structural equation modelling (SEM)	• Impact of objective health and functional status on psychological distress was fully mediated by subjective health and personal characteristics • Influence of objective health was mediated by successively by functional status and personal characteristics; successively by functional status and subjective health; exclusively by personal characteristics and; exclusively by subjective health	The model explained 32% of variance of psychological distress
Mayo 2015 Canada	Stroke	Cross-sectional	678	67.3 (14.8)	45%	To empirically test a biopsychosocial conceptual model of HRQL for people recovering from stroke	Structural equation modelling (SEM)	• Less comorbidity, less pain, better memory and more vitality associated with better health perception.	

Eilayyan 2015 Canada	Asthma	Longitudinal	299	62.1 (14.4)	69%	To identify direct and indirect predictors of perceived asthma control among primary care population.	Path model	• Symptom was affected by self-efficacy • Emotional status was affected by symptom and self-efficacy • Physical activity was affected through symptom, emotional status and self-efficacy • Perceived asthma control at baseline was affected by asthma symptom, physical activity, self-efficacy and smoking • Perceived asthma control at follow-up was predicted by asthma symptom, physical activity, self-efficacy and baseline perceived asthma control. • Perceived asthma control was indirectly predicted by emotion status through self-efficacy and physical activity	
Wyrwich 2011 USA	General Anxiety Disorder (GAD)	Longitudinal	1692	40.3 (11.8)	65.1%	To test the application of the Wilson-Cleary model to patient population with generalised anxiety disorder (GAD) using longitudinal clinical trial data.	Path Model	• CGI-S had a strong relationship with HAM-A • HAM-A at week 8 had strong path (β=0.5) to PSQI and moderate effect (β=-0.40) on Q-LES-Q(SF) • Q-LES-Q(SF) had a strong relationship with overall quality of life (β=0.66)	Model explained 56% at baseline and 69% at week 8
Hofer 2005 Austria	Coronary Artery Disease (CAD)	Longitudinal	432	61.8 (10.2)	24.1%	To apply Wilson and Cleary model a priori to patients with CAD in a prospective longitudinal design and to find out whether it is applicable to CAD patients and is stable over time.	Structural Equation Modelling (SEM)	• Physical functioning, anxiety symptoms have effect on overall HRQL • Anxiety predicts poorer HRQL • Depression affects physical functioning and general health perception.	• Final model explains 49% at baseline, 62% one month after and 66% 3

								• The higher the level of anxiety, the more severe the symptoms reported	months after intervention of the variance of overall HRQL
Mathisen 2007 Norway	Heart Surgery	Longitudinal	108	64.2	19%	To investigate the existence of a reciprocal relationship between patients' assessment of quality of life and their appraisal of health.	Structural equation modelling (SEM)	• Baseline overall QoL has a cross lagged effect on three months assessment of general health • The path from general health at six months to QoL at 12 months was significant • The simultaneous effects model demonstrated a bidirectional causal paths at each point observed after baseline	
Baker 2007 UK	Xerostomia	Longitudinal	85	59.8 (11.5)	76.5%	To systematically test Wilson and Cleary conceptual model of the direct and mediated pathways between clinical and non-clinical variables in relation to the oral health-related quality of life (OHRQoL) of patients with xerostomia.	Structural Equation Modelling (SEM)	• More severe clinical signs were associated with worse patient-reported symptoms • More symptoms predicted a greater impact on everyday oral functioning • Worse functioning predicted lower global oral health perceptions • Both biological indicators and functioning predicted subjective well-being	• Function accounted for 96.9% of total effects • 88.2% of total effect on functioning was mediated by symptoms status • Symptoms 9% • Functioning 22% • GOH 24% • Well-being 21%

3.10 Research Question 1: Does empirical evidence show the causal relationship of the dominant concepts as proposed in Wilson and Cleary's model?

Adjacent Linkages and Mediators

Wilson and Cleary (Wilson and Cleary, 1995) hypothesised that there existed direct causal links between biological and physiological factors, symptoms, functional status, general health perceptions and HRQL. Symptoms mediate between physiological factors and functional status, while functional status mediates between symptoms and general health perceptions, and general health perceptions mediates between functional status and overall HRQL. Eleven studies supported the direct causal link proposition between biological and physiological factors and symptoms (Figure 3-2). Markers of biological and physiological variables were found to associate with worse symptoms in the patients with HIV/AIDs, xerostomia, coronary artery disease, Hodgkins lymphoma and generalised anxiety disorder (Wettergren and Bjo, 2004; Sousa and Kwok, 2006; Baker, Pankhurst and Robinson, 2007; Ulvik *et al.*, 2008; Wyrwich *et al.*, 2011). The next level of the model associates symptoms with functioning and mediates between functioning and biological/physiological variables. This has been established in 20 studies (e.g., (Arnold *et al.*, 2005; Halvorsrud *et al.*, 2010; Nokes *et al.*, 2011)). More symptoms predicted a greater impact on everyday functioning, with symptoms status explaining 49% of functional health in HIV/AIDs patients (Sousa and Kwok, 2006). Functional status was found to have direct links to general health perception and mediated between general health perception and symptoms in 16 studies. Worse functioning indicated low perceived health. For example, worse functioning was associated with lower global oral health perception in Hodgkin's lymphoma (Wettergren and Bjo, 2004). More symptoms and less functional health may lead to a perceived decrease in perceived general health. The hypothesised effect of general health perception on overall HRQL was established in 12 studies (Figure 3-2).

3.11 Research Question 2: Does the Wilson and Cleary model strictly follow a linear unidirectional path?

Linkages between non-adjacent concepts

I examined the links between non-adjacent variables to establish whether empirical data show that the model allows non-linear, indirect paths.

Biological and physiological variables were directly associated with functional status, general health perception and overall HRQL in nine, two and three studies respectively (Figure 3-2). For example, Kanters *et al.* (Kanters *et al.*, 2012) showed that enzyme activity, a biological marker, was significantly associated with HRQL in adult Pompe disease. Direct links were established between symptom status and, general health perception and HRQL in nine and seven studies respectively. Furthermore, functional status was associated directly with overall HRQL in seven studies. In coronary artery disease, physical functioning showed high positive significant effect on HRQL (β=0.36) indicating that a reduction in functional health may reduce HRQL(Hofer *et al.*, 2005). The studies assumed non-reciprocal relationships except Mathisen *et al.* (Mathisen *et al.*, 2007) who attempted to model reciprocal relationship between general health perception and HRQL. This did not take into consideration possible effects between other concepts. Hence, the possibilities of bidirectional relationships between the abstract concepts could not be established in this study.

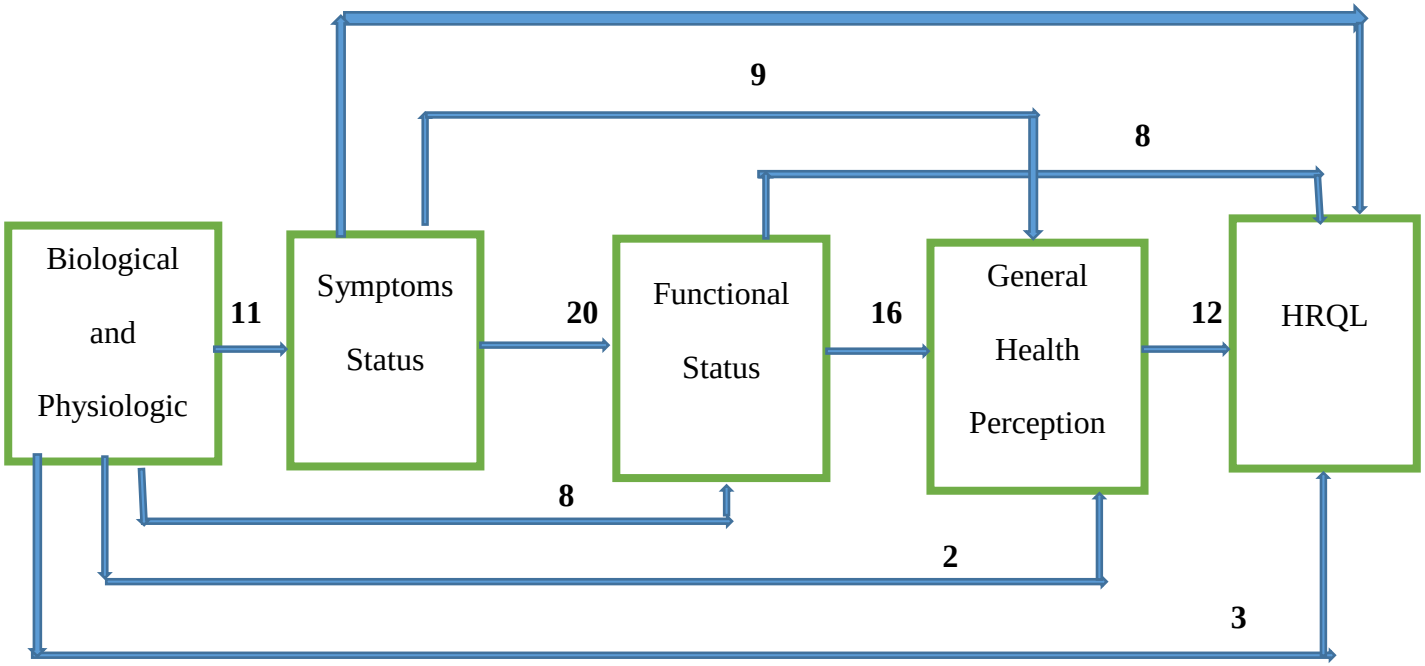


Figure 3-2: Adjacent and non-adjacent linkages of the concepts

Adapted from Wilson and Cleary (1995): Linking Clinical Variables with Health-Related Quality of Life: A Conceptual Model of Patient Outcomes. (JAMA: Journal of the American Medical Association, Page 60). The numbers (7,9, etc) refer to number of studies with significant linkages between concepts (e.g 11 means that eleven studies reported significant relationship between Bio-physiological and symptoms variables and 7 means that seven studies reported direct significant relationship between symptoms and HRQL).

3.12 Research Question 3: What is the relative effect of each variable?

The relative effects of the variables were measured in terms of the magnitude of their influence on HRQL (Figure 3-3). The causal links were labelled 0M, 1M, 2M and 3M to signify the number of mediators between constructs that were bypassed. 0M was a direct link between the concepts with the proposed mediating variable signifying that no mediator was bypassed in the link, 1M was an indirect link with one mediator bypassed, 2M with two mediators bypassed and 3M with three mediators bypassed. 0M, 1M and 2M revealed symptoms status as a consistently important factor that affected HRQL, followed by functional status. In 0M all four concepts: biological and physiological, symptom status, function status and general health perception were compared with respect to the effect of each on the adjacent variable. Clinical factor had the lowest magnitude of effect followed by general health perception, function status and symptoms status in order of increasing magnitude. Clinical factor was however on the same level as functional status when only the immediate mediator was bypassed.

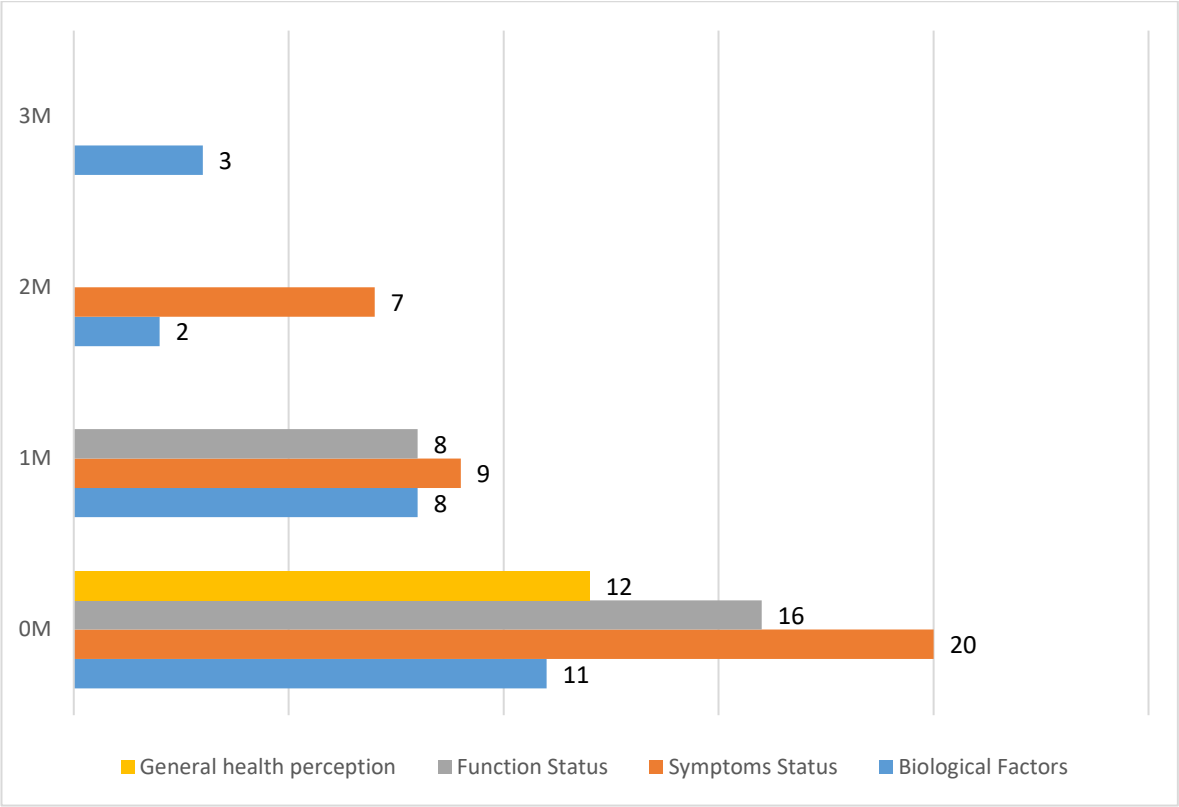


Figure 3-3: Bar chart of observed magnitude of effects

Note: 0M - direct linkage, no mediator between variables, 1M - one mediator between variables bypassed, 2M – two mediators between variables bypassed, 3M – three mediators between variables bypassed. Figures represent number of significant studies.

3.13 Discussion

Summary

The findings of this systematic review support the model of HRQL as proposed by Wilson and Cleary (Wilson and Cleary, 1995) and establish the conceptualised relationships and mediation. Of the articles reviewed, 74% found symptom status to be a significant predictor and critical mediator making it the most important predictor of HRQL by indirect effects through functional status and general health perceptions and by direct effects. More symptoms implied impaired functioning with consequently worse general health perception and lower HRQL. Most of the studies (73%) were of moderate quality; this was because the

quality assessment criteria (Effective Public Health Practice Projects, 2010) gives low ratings to study designs that are not experimental or longitudinal in nature.

Comparison with previous studies

Both symptoms and general health perception were found to account for 38.2% of variance in global HRQL (Krethong *et al.,* 2008) and studies also showed that general health perception alone mediated the relationship between symptom status and HRQL (Arnold *et al.*, 2005; Sousa and Kwok, 2006; Ulvik *et al.*, 2008; Shiu *et al.*, 2014; Mayo *et al.*, 2015). One of the most important symptoms was depression which strongly associated with physical functioning ($\beta = -0.32$) and general health perceptions (Hofer *et al.*, 2005). Two studies found no association between the clinical factors and any of the health constructs in heart failure and diabetes (Heo *et al.*, 2005; Shiu *et al.*, 2014). This may be due to other profound non-clinical factors responsible for impaired HRQL in these populations. The non-adjacent links among the health concepts showed that the model was non-linear, also the effects of the variable were not fully mediated by their proposed mediators. For example, the direct link between symptom status and overall HRQL indicated that both functional status and general health perception did not fully mediate the effects of symptom burden on HRQL.

Possible explanations and implications

The findings of Sullivan *et al.* (Sullivan *et al.*, 2000) in coronary artery disease patients supported the findings of a direct link between biological and physiological variables, and functional status. Further studies of a longitudinal nature will be required to establish possible bidirectional relationships among the concepts and whether the factors exert reciprocal influence on each other. For example, while the symptoms of pain may reduce functioning in patients with sickle cell disease, the inability to function as expected may lead to depression which may further limit functioning and then lower HRQL. This study is the

first to synthesize results of studies on Wilson and Cleary's model and to establish the relative importance of the constructs in determining the quality of life of patients in chronic diseases.

3.14 Limitations

I identified some potential limitations to this study. The systematic review focused on several chronic diseases which have different clinical statuses, prognoses and levels of disability, which restricts the ability to generalise based on the lack of homogeneity of symptom status and functional status of the patients. There is also the potential limitation due to publication bias as only published articles were used in this study. In addition, different instruments were used to measure HRQL in the included studies; while some are generic, some are disease-specific. As there is no instrument that is a "gold standard", researchers often select instruments sensitive to the health state they are investigating (Hawthorne, Richardson and Day, 2001) rather than a general measure of HRQL. Moreover, there are also variations in clinically important differences across groups of patients defined by diseases, conditions, severity level, socio-economic status and nationality (Samsa *et al.*, 1999).

3.15 Conclusion

My findings show that the Wilson and Cleary model demonstrated a good fit and proved useful in identifying relationships among the health constructs, and predictors of HRQL in the studied disease populations. The model explained between 22.9% and 72% of the variance in overall quality of life indicating that, in some cases, the model may require modification to capture factors not specified in the model but that may be important determinants of overall quality of life.

The findings supported the robustness of the Wilson and Cleary model as a conceptual framework to characterise predictors of HRQL in chronic diseases and to aid understanding of the relationship between clinical and psychological outcomes for patients with chronic

illness. Such understanding of specific directions of influence will aid healthcare practitioners and researchers to develop appropriate care protocols that will address psychosocial variables alongside clinical factors in chronic disease management. This study has demonstrated that symptoms are a major determinant of HRQL in patients with chronic disease, thus a clinical approach to reduce symptoms may help improve HRQL. Furthermore, in treating patients with chronic diseases, clinicians and healthcare practitioners should be alert for signs of depression because this study has highlighted depression as a major issue in HRQL.

Further work is needed to examine bidirectional relationships. Studies so far have focused on an assumption of no reciprocal relationship but low health perception or low HRQL might also worsen disease conditions and responses to treatment. Further studies on evaluation of the Wilson and Cleary model should be compared to the findings of this study.

CHAPTER FOUR

METHODOLOGY

4.0 Introduction

There are series of theoretical and methodological decisions to be taken in the course of doing research on quality of life (Streiner, Norman and Cairney, 2015). In health research, quantitative or qualitative methodologies or both can be used (Tonon, 2015, p. 54). Tonon also has suggested that the concepts of perspective play a major role in the process of deciding which method to adopt (Tonon, 2015). This study was approached from the perspective of testing theory in the disease population – those individuals with sickle cell disease - and seeks to understand causal relationships among physiological and psychosocial variables and health-related quality of life constructs. The positivist approach was therefore considered appropriate for the study.

The positivist approach is based on the postulates that objective universal truth exists and assumes that knowledge is obtainable through the means of quantifying concepts and that statistical analysis can be conducted to verify or falsify hypotheses (Denzin and Lincoln, 2011). Quantitative designs are ideal for exploring relationships among variables (Balkin, 2014) as long as variables selected for study are identified as valuable to understand a variety of phenomena relevant to the subject. The claim that quantitative designs represent reductionism has been argued to be “inaccurate” (Balkin, 2014). This is because all quantitative relationships evaluate what is understood by percentage of variance accounted for in the model (measured by square multiple correlation), that is, how much of the variability of the data can be explained by a fitted regression, or the extent to which the equation adequately measure its underlying construct (Byrne, 1998; Kline, 2011). While what is unknown is represented by variance not accounted for in the model. Expressing quantitative findings as relationships therefore allows investigators to address contributing

factors to a phenomenon. Moreover, apart from quantitative studies being less prone to the bias of subjectivity, quality of life studies have been largely based on quantitative methods and are usually categorised as quantitative research (Turato, 2005).

This remaining part of this chapter focuses on the research design, the various instruments used and the statistical protocol.

4.1 Design

This is a non-experimental research study. A cross-sectional, correlational design was employed to examine factors affecting quality of life in persons living with SCD. In a cross-sectional study, data are collected at one point in time. The study was retrospective because respondents were asked to report on events, feelings and behaviour that were past (for example, in the last four weeks) or current.

Data were collected at a point in time from each participant to describe their current level of quality of life, and factors affecting their quality of life. Cross-sectional design was considered appropriate for this study because it enables collection of data on quality of life and possible risk factors at the same time. Additionally, because there was no intervention changes over time was not being investigated.

A cross-sectional design has been described to be best suited to describe the status and /or relationships among phenomena (Polit and Beck, 2008). In addition, cross-sectional surveys are economical in relation to time and resources (Bowling, 2014). Although cross-sectional designs are limited in their ability to provide robust evidence in terms of the direction of cause and effect, Bowling (2014) has argued that the increasing sophistication of statistical techniques can help to minimise this limitation because the generated hypothesis can be tested in experimental or analytic studies. Rothman (1986) also posited that when it comes to analytic abilities, the distinctions between study designs should not be too rigid.

Being a cross-sectional design also informed the correlational approach. A correlational design is useful in examining interrelationships and or associations among variables that cannot be manipulated (Polit and Beck, 2008). This was appropriate because independent variables at the various levels of the Wilson and Cleary model, (biological/physiological function, symptoms, functional status, general health perceptions, age, gender, genotype marital status, socioeconomic status and so on) could not be logistically or ethically manipulated. Also, with a correlational design, hypotheses about associations can be tested and hypotheses generated with respect to possible cause and effect associations between variables (Bowling, 2014).

4.2. Sample and Setting

The setting for this study is Ibadan in southwest Nigeria. Nigeria is the largest and most populous country in sub-Saharan Africa with a population of approximately 185 million people (WHO, 2016) and is the global epicentre of sickle cell disease (Fleming *et al.*, 1979; Aliyu *et al.*, 2008; Modell and Darlison, 2008; Nwogoh *et al.*, 2012). The country is made up of 36 states including the Federal Capital Territory and is organised into six geopolitical zones namely, North-East, North-West, North-Central, South-East, South-West and South-South. The official language is English but there are three major languages, Hausa in the North, Yoruba in the West and Igbo in the East.

This study took place in Ibadan which is situated in the south west part of the country. Ibadan is the largest city in Nigeria and third most populous after Lagos and Kano with a population of over 3 million people and therefore have a large population of people with sickle cell residing in the city. The official language is English while the local language is Yoruba. The map of Nigeria highlighting Ibadan city is shown in Figure 4-1.

Figure 4-1: Map of Nigeria Highlighting Ibadan

Ibadan houses the University College Hospital which is the teaching hospital of the University of Ibadan and Adeoyo Hospital, a general hospital. These are the two major hospitals in Ibadan with haematology clinics where adults with sickle cell disease are referred and treated. These hospitals were therefore selected for data collection for the current study.

The data collection took place in the outpatient units of haematology clinic (where sickle cell patients are attended to) of the two hospitals, the University College Hospital (UCH) and Adeoyo Hospital both in Ibadan, Nigeria.

A convenience sampling designed was used. A convenience sampling, otherwise called availability sampling, is a statistical method of drawing representative data by selecting people because of the ease of access, availability, volunteering or selecting units. In this study, participants were recruited based on their availability at the hospitals where the data were collected. This sampling technique is prompt, uncomplicated, economical and participants were readily approachable to be a part of the sample. The method enabled the researcher in the current study to gather information from the respondents in the easiest

possible manner and without burdens to the participants who were in the hospital on their day of clinic either for treatment or for routine medical check. Participants were recruited at each of the clinics as they arrived the clinic on a clinic day. The inclusion and exclusion criteria are listed below.

Inclusion criteria:

a) individuals diagnosed with sickle cell disease;
b) 18 years of age and older;
c) ability to communicate in English language or the local language (Yoruba);
d) not under intensive care or having any cognitive disability

Exclusion criteria:

a) patients who were below the age of 18 years at the time of the data collection;
b) patients experiencing severe pain crisis and/or on admission, as involving such patients may add to their trauma and pain;
c) patients under intensive care or having any cognitive disability

4.2.1 Procedure

The investigator recruited two students who were studying for a Masters' degree at the University of Ibadan to help as research assistants. These assistants were trained to help in data collection. Part of the training included taking them through the aims of the study, how to explain the study to the participants, the ethical issues involved and the procedure for the data collection.

On a clinic day, the patients were approached after presenting the ethical approval to the nurse on duty. The purpose of the study was explained to the patients present at the clinic jointly both in English and the Yoruba and they were assured that the study was for an

academic purpose. They were informed of their free will to participate and also that they were free to opt out of the study at any time. In addition, a letter briefly explaining the study was provided to eligible participants. The letter was written in equivalent of a junior secondary school student (universal basic education) grade reading level English for easy understanding and also in Yoruba (the local language). Informed consent letters (written in English and Yoruba) were distributed to the participants who showed interest in participating.

These trained assistants along with the researcher responded to participants who asked questions or needed some clarifications before they agreed to participate. Those who did not want to participate were not persuaded. The letter of consent was completed by those who were willing to participate. The questionnaires were then passed to those who gave consent. Further clarification was provided when required by any of the participants to ensure that participants understood and completed the questionnaire as it applied to them. This process continued in both hospitals between 10 January, 2017 and 16 May, 2017 on their different clinic days. Data collection took place in a large spacious enclosed room in each of the hospitals to provide a conducive environment. On average, the questionnaires took about 40 minutes to complete. The participants were also allowed to go with the biros provided for completing the questionnaire. Also, a token for refreshment were given to participants as incentives. It was discovered that in each of the clinics, the sickle cell patients have association and have elected executives led by a president. A meeting of the researcher with the president and the executives helped to disabuse their minds that the study was for commercial or profit-making purpose. This however did not in any way influence any individual, who was not willing, to take part in the study.

4.2.2 Sample size calculation

Structural equation modelling (SEM), is a flexible tool which permits analysis of complex associations, use of various types of data (e.g., categorical, dimensional, censored, count variables), and comparisons across alternative models. However, due to these qualities, developing a general guideline for sample size determination in structural equation modelling is difficult and has been a subject of controversy (MacCallum *et al.*, 1999). While some researchers had their study based on large sample sizes (Boomsma, 1983; Gagne and Hancock, 2006) others have suggested that adequate sample size should be between 100 and 150 (Anderson and Gerbing, 1984, 1988; Tinsley and Tinsley, 1987; Ding, Velicer and Harlow, 1995; Tabachnick, Fidell and Osterlind, 2001; Muthén and Muthén, 2002).

A simulation study has demonstrated that with normally distributed indicator variables and no missing data, a reasonable sample size for a simple CFA model is about 150 (Muthén and Muthén, 2002). There is evidence that simple SEM models could be meaningfully tested even if sample size is quite small (Hoyle and Kenny, 1999; Marsh and Hau, 1999; Iacobucci, 2010). Iacobucci (2010) suggested that a minimum sample size of 50 is appropriate.

There have been various approaches in extant literature as to determining sample size for SEM. One of such method is the 'rule-of-thumb'. According to the proponents of this method, sample size for SEM should be calculated in terms of ratios (Jackson, 2003) depending on the number of variables or model parameters. Different ratios have been suggested which range from 5 or 10 observation per estimated parameter (Bentler and Chou, 1987) for normally distributed data or 10 cases per variable (Nunnally, 1967) to 20 cases per variable (Kline, 2011). This method lacks scientific rigour as they can lead to over- or underestimated sample size requirements (Wolf *et al.*, 2013). Defining sample size as having a linear relationship with the number of factors or indicators implies that the more factors and indicator variables there are, the bigger the sample size. This is not achievable in

practice. A more scientific approach beyond the simplistic single ratio is to identify factors that may affect the size of a sample in SEM. According to MacCallum *et al.* (1999), model characteristics such as level of communality across the variables, sample size and degree of factor determinacy affect both model fit statistics and accuracy of parameter estimates. These factors were not considered in the rule-of-thumb method.

Wolf *et al.*(2013) has demonstrated in a Monte Carlo study that a one-factor, four-indicator model with loading of 0.80 required a sample size of 60 compared to one-factor six-indicator model of the same loading which required less number of sample size, 40. Sample sizes have therefore been shown to be affected by number of latent factors and number of measured variables, power, effect size in SEM (Maccallum, Browne and Sugawara, 1996; Muthén and Muthén, 2002; Wolf *et al.*, 2013).

In a Monte Carlo simulation involving two-factor, 10-variable model, Muthén and Muthén (2002) showed that a sample size of 150 will be adequate in a CFA model without missing value and 175 with missing values. Wolf *et al*. (2013) also using a Monte Carlo simulation observed that increasing the number of factors led to a decrease in sample size when one moves from two factors to a higher number of factors. For example, three was a sharp increase in sample size from one-factor, four-indicator model to a two-factor, four-indicator model, the reverse was the case when a third or fourth factor was added. In the same way, they observed that a model with greater than four indicators required a smaller sample size relative to a model with four indicators. While a one-factor, four-indicator model with loading of 0.8 required a sample size of 60, a corresponding one-factor, six-indicator model of the same loading required a sample size of 40. The decrease in sample size in spite of the increase in number of indicators was attributed to more information available through increase in factor and indicator variables, for use in solving the simultaneous regression equation (Wolf *et al.*, 2013). They further noted that “mediation models with larger effects

tended to achieve adequate statistical power for direct and indirect effects with smaller sample sizes" (Wolf *et al.*, 2013, p. 9) and pointed out that there is broad variability in sample size requirement for latent variable models and that sample size estimates vary greatly from model to model.

For this study, an online calculator (Soper, 2015) that used a priori method to calculate sample size in SEM was used. This calculator uses the number of latent variables, number of indicators, effect size, power and the level of type I error (α). This is supported by findings in literature (MacCallum *et al.*, 1999; Muthén and Muthén, 2002; Iacobucci, 2010; Wolf *et al.*, 2013).

The model for the current study has seven latent variables and 26 measured variables (Table 4-1). Type I error (α =0.05), and power (1-β =0.8) and effect size r=0.3). The calculator yielded n=170 as the required sample size. Scholars agreed that a power of 0.8 is desirable and Cohen suggested that a medium effect of 0.3 is adequate(Cohen, 1988). The sample size for this study was 200 based on the 200 patients that consented, completed and returned the questionnaires. Approximately 1 out of 47 patients declined participation. This translates to about 2.1%, this non-response was considered to have no significant impact on the result of the study.

4.3 Ethics

Necessary documents for conducting the study in Nigeria were submitted to the Ethics Committee of the University of Sunderland who after reviewing the documents gave approval (Appendix 4). The University of Ibadan/University College Hospital (UI/UCH) Ethics Committee (UI/UCH EC) also reviewed the documents and approved the study (Appendix 5). Furthermore, approval was obtained from the Management of Adeoyo Hospital (Appendix 6). Written information on the study were made available to the participants (Appendix 2), the study was also explained verbally to the participants both in

English and/or in the local language. Clarifications were made in response to questions from the participants. No identifiers were placed on the instrument packets as there was no need for follow up and their medical records were not required. All participants were fully informed about the purpose of the study and what was expected should they choose to participate. Each participant completed a consent form (Appendix 3) before they were given the questionnaires (Appendix 1). The consent form clearly stated that participation was completely voluntary and that participants could withdraw from the study without any adverse consequence at any point. The participants were also assured of the confidentiality of the information they supplied.

4.4 Measures

The theoretical construct consists of seven latent factors (see definitions): biological/physiological, symptoms status, functional status, general health perceptions, characteristics of the individual, characteristics of the environment and overall quality of life (Table 4-1). Table 4.1 links the predictors identified in the systematic review of chapter two and the Wislon and Cleary constructs in systematic review of chapter three and the instruments used (see Table 3-2). The seven constructs of the Wilson and Cleary model are listed in column one, column two are the predictors obtained from the review of the studies of sickle cell disease in chapter two and column three are the instruments to measure the variables.

Table 4-1: Latent Factors, Measured Variables and Instruments.

Latent Factor	Variable	Measures
Biological/ physiological	Genotype Comorbidities Disease severity index (DSEI)	Self-report questionnaire
Symptom Status	Pain Emotional wellbeing Depression Anxiety Somatic symptoms Vitality	SF-36 Bodily Pain (BP) subscale, SF-36 Mental Health (MH) subscale The Patient Health Questionnaire (PHQ-9) Generalised Anxiety Disorder (GAD-7) Patient Health Questionnaire (PHQ-15) SF-36 Vitality subscale
Functional Status	Physical functioning Social functioning Emotional functioning Role functioning	SF-36 Physical functioning SF-36 Social functioning SF-36 Role emotional SF-36 Role Physical
General Health Perception	General health Change in health	SF-36 GH subscale SF-36 change in health (HT)
Overall Quality of Life	HRQL Utility score	Single item question* SF6D
Characteristics of the Individual	Age Gender Education Number of children Employment status	Self-report questionnaire
Characteristics of the Environment	Marital status Living situation, Having a confidant Income	Self-report questionnaire

* A single item question to evaluate participants perception of overall quality of life.

4.4.1 Level 1: Biological/physiological

Assessment at this level relates to function of cells, organs and organ systems, they could be diagnoses or laboratory values or factors whose effects on health are mediated by changes in cells, organ or organ system function (Wilson and Cleary, 1995). In this study, these are factors associated with sickle cell disease complications such as genotype, severity, and comorbidities.

Genotype in SCD has been reported to be a predictor of mortality and disease severity or complications (McClish *et al.*, 2005) and of the age of death (Platt *et al.*, 1994). Literature has established that the HbSS genotype was more severe and responsible for frequent pain crisis and debility of the patient compared to the HbSC genotype which exhibited milder complications, for example, Platt *et al.* (1991) reported that hospital utilisation due to pain was 0.8 episode per patient per year in patients with SS genotype compared with 0.4 episode of pain per patient per year in those with SC genotype. Moreover, genotype has been used by researchers to measure disease complications (Lutz *et al.*, 2004).

Several factors have been identified in the literature as indicators of disease severity and could be elicited through self-report. The measures were made up of events in the life of the participants in the last six months such as: visit to emergency department (Aisiku *et al.*, 2009; Ahmed *et al.*, 2016), admission to hospital, blood transfusion, pain episode/experience and other sickle-cell related crisis. Participants were asked to score items on the scale 0 (none) to 4 (more than three times). The sum score was used as a severity index (Carlson *et al.*, 2014). The frequency of emergency department (ED) visits was evaluated by asking for the number of ED visits within the past six months.

Comorbidity expresses the significant concurrent diseases in addition to the chronic condition and known to associate with survival and hospitalisation (Khan, 1998; Beddhu *et al.*, 2000; Wu *et al.*, 2005; Elmariah *et al.*, 2014; McClish *et al.*, 2016). The number of comorbidities reported by patients have been used as a measure of biological and physiological variables, in several studies and illnesses including kidney transplant, end-stage renal disease (ESRD), HIV/AIDS (Kempen, Jelicic and Ormel, 1997; Sullivan *et al.*, 2000; Saban *et al.*, 2007b; Paukert *et al.*, 2010; Schulz *et al.*, 2012; Yang *et al.*, 2015). Also, there is a consensus among researchers that self-reports of comorbidity tend to be accurate, and are therefore a reliable and valid representation of actual comorbidity (Van Den Bos,

1995; Kriegsman *et al.*, 1996; Penninx *et al.*, 1996; Bayliss, Ellis and Steiner, 2005). SCD patients are a vulnerable, chronically ill population with a high prevalence of comorbidities. Eleven comorbidities were specified in this thesis related to SCD and participants were asked to indicate which of these they had. Participants were also asked to mention any other diseases they had that were not listed. The comorbidities were scored for individual respondents (1-12). This was re-coded as 0, 1-2, and 3 or more.

4.4.2 Level II: Symptom Status

Symptoms are an important factor in health-illness experience (Sidani, 2010) and for effective patient care management (Sousa, Tann and Kwok, 2006). Symptoms are viewed as markers for the progression of a disease (Lorenz *et al.*, 2006) and are triggers of beneficial or detrimental behaviour in the individual which often signal a change in health status necessitating healthcare seeking (Sousa, Tann and Kwok, 2006). Wilson and Cleary (1995) defined symptoms as "a patient's perception of an abnormal physical, emotional, or cognitive state" (Pg 61) and stated that depression or any other psychological factor may be regarded as a biological and physiological variable, as symptom status variable or as a functioning status variable. This study identified pain, fatigue, anxiety, depression and somatic symptoms as measures of symptoms status in SCD (Platt *et al.*, 1991; Sogutlu *et al.*, 2011; Treadwell *et al.*, 2015). Pain is a major symptom experienced by SCD patients often referred to as a crisis; such episodes of excruciating musculoskeletal pain are the principal cause of morbidity among SCD patients (Platt *et al.*, 1991). Pain rate (episodes per year) is also a measure of clinical severity (Platt *et al.*, 1991). Some studies have shown that pain intensity in SCD is influenced by psychosocial factors (Anie, Steptoe and Bevan, 2002; Levenson *et al.*, 2008; Sogutlu *et al.*, 2011). The bodily pain subscale of the SF-36 was used to measure this symptom. High somatic symptoms were found to predict increased health care utilisation in primary healthcare and general population (Mewes *et al.*, 2008; Hanel *et*

al., 2009) and in SCD (Sogutlu *et al.*, 2011). Anxiety, depression and somatic symptoms were measured respectively using GAD-7, PHQ-9, and PHQ-15 (Spitzer *et al.*, 1999, 2000; Kroenke and Spitzer, 2002; Kroenke, Spitzer and Williams, 2002).

4.4.3 Level III Functional status

Functional status is a patient's subjective perception of his ability to perform physical functions. Four major domains of functioning commonly measured and generally agreed as the minimum include the physical functioning, role functioning, social functioning and psychological functioning (Ware Jr *et al.*, 1981; Ware, 1987; Cleary, Greenfield and McNeil, 1991; Wilson and Cleary, 1995). In self-report measures of functional status, major dimensions including mobility, self-care and performance of usual activities were assessed (Ware Jr and Sherbourne, 1992; Aaronson *et al.*, 1993; Schulz *et al.*, 2012). This study used four dimensions from the SF-36 to measure functional status. They are the Physical Functioning (PF), the Role Physical (RP), the Social Functioning (SF) and the Role Emotional (RE) subscales of the SF-36.

4.4.4 Level IV General Health Perception

General Health Perception (GHP) is a subjective rating that integrates the other health concepts already mentioned in the model (Wilson and Cleary, 1995). GHP has been observed to be among the best predictors of utilisation of medical, mental and general health services as well as mortality (Wells *et al.*, 1986; Connelly *et al.*, 1989; Idler and Kasl, 1991). This study used the General Health (GH) and Health change or transition (HT) subscales of SF-36 to measure GHP. The GH represents the persons evaluation of his /her health and the HT is a measure of perception of change in health in a space of a year.

4.4.5 Level V: Overall Quality of Life

Overall quality of life is the overall satisfaction or happiness with life as a whole defined as a summary measure of quality of life, life satisfaction or happiness(Wilson and Cleary, 1995). This could be assessed through a single global question asking how the individual is satisfied with life in general (Ferrans *et al.*, 2005). This study used a global measure with the question, "Looking at all parts of my life – physical, emotional, social, spiritual and financial in the last two weeks, the quality of my life has been?". Possible scores range from 0 very bad to 10, excellent; a higher score indicates better HRQL. The single global quality of life measure has been used extensively in literature as a subjective assessment of overall health (Heo *et al.*, 2005; Ulvik *et al.*, 2008; Carlson *et al.*, 2014). Voruganti *et al.*(1998) in a study of schizophrenia asked the patients to appraise their quality of life on a single-item global quality of life measure. They reported that patients' self-reports were highly consistent over the past four weeks and therefore concluded that self-report measures are potentially useful tools in clinical outcomes studies. Gough *et al.*(1983) showed that a single item linear analogue self-assessment which indicated the patients' global feeling of well-being showed excellent psychometric properties therefore a single item asking a direct question such as 'how would you rate your health life today?' is a valid and reliable indicator of quality of life of patients.

4.4.6 Individual Characteristics

Additionally, Wilson and Cleary model conceptualises the characteristics of the individual and of the environment as having impact on each of the five levels. Individual characteristics are defined to include symptom amplification, personality/motivation, and value/preferences. Consistent with literature, patients' sociodemographic status, which included age, gender, educational status and having children (Arnold *et al.*, 2005; Heo *et al.*, 2005; Phaladze *et al.*, 2005; Carlson *et al.*, 2014; Wan *et al.*, 2016) were used as indicators.

4.4.7 Environmental Characteristics

Environmental characteristics were made up of patients' psychological and social economic supports. These were measured in this study by variables such as: living situation, having a confidant, marital status and income (Heo *et al.*, 2005; Moi and Nilsen, 2012; Shiu *et al.*, 2014; Brunault *et al.*, 2015). Having a confidant was a yes or no; marital status was re-coded into three categories to reflect current situation, they are single, married and others (separated, divorcees, widows/widowers). In the same vein, living situation was categorised into 'living alone' and 'living with people' (living with siblings, spouse, children, friends or other relatives).

4.4.8 Utility measures

Utility measures had its origin in health economics and constitute an important subgroup of generic measures used in cost effectiveness studies (Drummond *et al.*, 2015) and medical decision-making analyses (Naglie *et al.*, 1997). Utility measures can be used to calculate quality adjusted life years (QALYs), which is useful in economic valuations (cost-utility analysis) and valuable because they incorporate the gained life years and quality of life years to guide decision making (van Litsenburg Raphaële *et al.*, 2013). QALY also provides an indication of the benefits gained from a variety of medical procedures in terms of quality of life and survival of the patient (Gutteling *et al.*, 2007). A utility measure attempts to express the overall effect of a disease upon the patient in a single continuous scale that ranges from 0-1 where 0 indicates dead and 1, perfect health. Utilities are value-based HRQL indicating patient-preferences for a certain health state which lies between 0 (death) and 1 (perfect health). Such a preference-based method is useful for: assessing the burden of a chronic condition that affects quality of life (Bramlett, Bothe and Franic, 2006); comparison of different therapies in comparative effectiveness research, making decisions about overall health impact (Hays *et al.*, 2014) and cost-effectiveness analysis (Drummond *et al.*, 2015).

Additionally, policy makers found information on utility score useful to guide in making informed decisions based on cost utility analysis(van Litsenburg Raphaële *et al.*, 2013).

Utilities are obtained by direct methods which could be by the method of Time Trade-Off (TTO) or Standard Gamble (SG). In SG patients are asked to choose between life with the health state (living with a chronic disease), and life without the health state but with consequences that carry a risk of immediate death, while in TTO, the consequence may be a reduction in total life time. However, direct measure of utilities are not always feasible in terms of cost, time, personnel and other socio-economic issues. Researchers have therefore developed algorithms to derive utilities from instruments such as the SF-36 (Brazier *et al.*, 1998; Nichol, Sengupta and Globe, 2001; Brazier, Roberts and Deverill, 2002; Lobo, Gross and Matthees, 2004; Kharroubi *et al.*, 2007). Derived utilities have been found to be valid and reliable. The SF-6D was such a derivation that enables data collected with the SF-36 to be transformed into a measure of utility score (Brazier *et al.*, 1998, 2012; Brazier, Roberts and Deverill, 2002; Kharroubi *et al.*, 2007).

4.5 Instruments

In selecting instruments to use for data collection, attention was paid to their psychometric properties, common use in different population including SCD, brevity, ease of scoring and use in the Nigerian population. Five instruments were combined into one and used to collect data from the participants. The instruments were: (a) the Personal information/sociodemographic questionnaire, (b) the SF-36 health survey (c) the Patient Health Questionnaire, PHQ-15 for somatic symptoms, (d) PHQ-9 for depression and (e) Generalised Anxiety, GAD-7 for anxiety.

4.5.1 The Sociodemographic Questionnaire

The questionnaire contains information on the demographic and social characteristics of the patients such as age, marital status, living situation, employment, income, genotype and education, comorbidities and other measures of disease severity such as genotype, frequency of pain, use of emergency department and frequency of admission to hospital. This instrument was used to elicit information which was grouped into physiological, characteristics of the individual and characteristics of the environmental in line with Wilson and Cleary constructs as follows:

- Biological and physiological variables consisted of genotype, comorbidities and measures of disease severity.
- Characteristics of the individual: age, gender, number of children and marital status
- Characteristics of the environment: education, employment status, living situation, having a confidant, income
- A single item question to measure overall quality of life.

4.5.2 The GAD-7 Anxiety

Generalised Anxiety Disorder (GAD) has been reported as one of the most common mental disorders in outpatients (Spitzer *et al.*, 2006). (GAD-7) measure is a 7-item scale developed for screening generalised anxiety disorder in line with the *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition (DSM-IV) (American Psychiatric Association, APA, 2000) diagnoses. The items reflect most of the DSM-IV symptom criteria for generalised anxiety disorder and has been used in screening other forms of anxiety disorder (Spitzer *et al.*, 2006). Respondents were asked to rate their experience in the last two weeks with respect to how they were bothered by these symptoms. Rating options were ‘not at all’, ‘several

days', 'more than half the days', 'nearly every day'. The ratings were allocated scores of 0,1,2,3 respectively. The GAD-7 total score ranges from 0 to 21. Cut points of 5, 10, and 15 were interpreted as representing mild, moderate and severe level of anxiety (Kroenke *et al.*, 2010). In other words, 0-4 = minimal anxiety, 5-9=mild anxiety, 10-14 = moderate anxiety and ≥15 = severe anxiety.

The instrument has good internal, and test-retest reliability as well as convergent, construct and criterion validity (Spitzer *et al.,* 2006). The measure has also been found to have good sensitivity and specificity as a screener for panic, social anxiety and post-traumatic stress disorder (Spitzer *et al.*, 2000; Löwe *et al.*, 2008; Kroenke *et al.*, 2010). GAD-7 has been used to measure anxiety in an SCD population in Brazil (Mastandréa *et al.*, 2015) and the USA (Treadwell *et al.*, 2015).

4.5.3 The PHQ-9 Depression

The Patient Health Questionnaire (PHQ) is a self-administered version of the Primary Evaluation and Mental Disorders (PRIME-ED). The PHQ-9 is a subscale of the PHQ designed to assess depression in patients and focuses on the 9-diagnostic criteria for the DSM-IV major depressive disorders. The instrument has been established to be reliable and valid instrument for screening depressive disorder according to the DSM-IV diagnoses in primary care (Kroenke, Spitzer and Williams, 2001).

Patients were asked to rate how often they have been bothered by each of the depressive symptoms in the last two weeks. Experiences were rated from 0, 'not at all' to 3, 'nearly every day'. The total scores range from 0 to 27. Depression symptoms level of severity were categorised based on scores cut points of 5,10 and 15. Thus the symptom for depression was assumed to be minimal for score < 5, mild = 5-9, moderate = 10-14, and severe, ≥15 (Kroenke *et al.*, 2010).

The psychometric properties of PHQ-9 have been well documented (Kroenke *et al.,* 2010). In a systematic review of 38 studies involving 16 case-finding measures, in over 32,000 patients, PHQ-9 was shown to be equal or superior to other measures of depression (Williams *et al.*, 2002; Henkel *et al.*, 2004; Löwe *et al.*, 2004). The PHQ-9 performed similarly across age, sex (Klapow *et al.*, 2002; Löwe *et al.*, 2004) and racial ethnic groups (Löwe *et al.*, 2004; Chen *et al.*, 2006) and found sensitive to change (Löwe *et al.*, 2004; Williams *et al.*, 2007). PHQ-9 also serves as a dual-purpose instrument for making diagnoses and measuring severity of depressive disorder, the operating characteristics compared favourably with nine other case-finding instruments for depression in primary care, and takes less time to complete (Kroenke *et al.,* 2010).

The PHQ-9 is reputed to be the most commonly used depression measure in the UK National Health Service (Kendrick *et al.*, 2009) and has been tested for validity and reliability in many languages and disease populations such as HIV/AIDs, diabetes, systemic sclerosis (Kroenke, Spitzer and Williams, 2001; Monahan *et al.*, 2009; Milette *et al.*, 2010) and in sickle cell (Mastandréa *et al.*, 2015; Treadwell *et al.*, 2015; Lucchesi *et al.*, 2016; Ola, Yates and Dyson, 2016). A study has also established the validity of the instrument in a Nigerian population (Adewuya, Ola and Afolabi, 2006). The study was conducted among university students to evaluate the psychometric properties of PHQ-9 in a Nigerian population and yielded high reliability (Cronbach alpha, 0.85) with excellent specificity and sensitivity (Adewuya, Ola and Afolabi, 2006).The PHQ-9 was chosen for this work because of its brevity, good psychometric properties, wide use in clinical practice and research, validation in Nigeria, prior use in an SCD population and ease of scoring.

Items left blank (missing data) were filled with the means of the completed items provided missing items were less than 20% otherwise the item is treated as completely missing for the

individual (Kroenke *et al.*, 2010). This approach was considered to have a lower risk of missing persons with depression, anxiety or somatisation (Kroenke *et al.*, 2010).

4.5.4 The PHQ-15 Somatic Symptoms

The Patient Health Questionnaire (PHQ-15) is a subscale of the Patient Health Questionnaire (Kroenke, Spitzer and Williams, 2002) designed as a continuous measure of somatic symptoms burden in patients over the last four weeks. The PHQ-15 screens for 15 somatic symptoms (e.g. headaches, back pain, dizziness) that account for more than 90% of the physical complaints reported in outpatient settings (apart from self-limited upper respiratory symptoms such as cough, nasal symptoms, and sore throat) (Kroenke, Spitzer and Williams, 2002; Kocalevent, Hinz and Brähler, 2013). Patients were asked to rate how much they have been bothered during the past month on a three-point Likert scale that ranges from "0" (not bothered at all) to "2" (bothered a lot) scale. The total raw score of the instrument ranges from 0 to 30 and is categorised as, 'minimal somatic symptoms, 0-4'; 'mild somatic symptoms, 5-9'; 'moderate somatic symptoms, 10-14'; and severe somatic symptoms, ≥15'. (Kroenke *et al.*, 2010). The instrument has been reported to be sensitive to change both in longitudinal studies and large randomised trials where depression is a primary(Andrews *et al.*, 2008; Dimsdale, Creed and Disorders, 2009) outcome measure or a secondary(Kroenke *et al.*, 2010) outcomes measure. PHQ-15 has been recommended as an excellent measure of somatic symptom burden and potential somatisation (Kroenke, 2006, 2007) because of the association between scores on the PHQ-15 and functional impairment, disability and health cost use (Kroenke *et al.*, 2010). In addition, items on PHQ-15 were found to overlap better with other validated instruments for measuring somatisation than any other two measuring instruments do with one another while total self-reported PHQ-15 somatic symptom score has been reported to be highly associated with clinic-rated somatoform disorder symptom counts (Kroenke, Spitzer and Swindle, 1998; Kroenke *et al.*, 2010).

In scoring the instrument, attention was paid to items left unanswered. A prorated score was obtained by multiplying the total score of answered question by 15 and dividing by the number of answered items and rounded to the nearest whole number as specified in the manual. For instance, if 12 questions are answered and the scores add up to 20, the prorated score will be 20*15/12 = 25. This is acceptable provided the items left unanswered are not more than 20% (Kroenke *et al.*, 2010**).**

The validity and reliability of the instrument has been established in over 40 studies, and in different health care settings (Kroenke *et al.*, 2010), as a measure of somatic symptoms in primary care, research and general population (Kocalevent, Hinz and Brähler, 2013). Moreover, the reliability and validity of PHQ-15 in SCD has been established (Sogutlu *et al.*, 2011; McClish *et al.*, 2017).

4.5.6 The Medical Outcomes Study SF-36 Health Survey Questionnaire

The Medical Outcomes Study short form 36 (SF-36v1) health survey is a generic multidimensional measure derived from the original 245 RAND MOS questionnaire and designed to measure various component of HRQL (Ware Jr, 1995) for self-administration by persons of 14 years of age or older (Ware Jr and Sherbourne, 1992).

The instrument cannot be summed up as a single instrument but is made up of eight subscales from 35 of the 36 items, each subscale represents a health dimension. They are Physical Functioning (PF), Role Physical (RP), Role Emotional (RE), Bodily Pain (BP), Vitality (VT), Mental Health (MH), General Health (GH), and Social Function (SF) and the one item on health transition or changes in health. All the eight subscales are independent of each other. Table 3-2 summarises the basic element of SF 36 and the meaning of low and high scores presented by the instrument.

Table 4-2: The Contents of the SF 36

Health concepts/ Domain	Number of items	Meaning of low scores	Meaning of high scores
Physical Functioning (PF)	10	Limited a lot in performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health
Role Emotional (RP)	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Bodily Pain (BP)	2	Very severe and extremely limiting pain	No pain or limitations due to pain
General health (GH)	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality (VT)	4	Feels tired and worn out all the time	Feels full of pep and energy all the time
Social Functioning (SF)	2	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role Emotional (RE)	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Mental Health (MH)	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy and calm all of the time
Reported health transition (HT)	1	Believes general health is much worse now than one year ago	Believes general health is much better now than one year ago

Source: Ware et al. (1999) pp 3:5)

Component analysis showed that the instrument measures two distinct constructs of the HRQL, the physical health dimension referred to as the Physical Component Summary (PCS) or 'physical health', and the psychological or mental health dimension referred to as the Mental Component Summary (MCS) or 'mental health' (McHorney, Ware Jr and Raczek, 1993). Exploratory factor analysi has been used to determine the factor structure of the instrument in 10 different populations (Ware and Gandek, 1998). Heo *et al.*(2005) suggested that using SF-36 had advantages above the sickness impact profile (SIP) because of its more robust validity and test-retest reliability.

The instrument uses a four-week recall, to measure the different dimensions of HRQL. One of the items assesses overall well-being. Subjects are asked to rate their health on a 5-point Likert scale from excellent =1, to poor=5 with lower scores indicating better health.

The SF-36 is a common quality of life measurement and is one of the most widely used general HRQL measures, and has been reported in over 1000 publications (Ware Jr, 2000). The instrument has been validated across a wide variety of age, race, disease populations including many chronic diseases (Ware Jr and Sherbourne, 1992) and as outcomes of clinical trials and with different population.

The instrument is very popular for evaluating HRQL (Lins and Carvalho, 2016). The instrument has been used to measure various aspect of HRQL in diabetes, cancer, HIV/IDs, SCD with acceptable psychometric properties (Bullinger, 1995; Phaladze *et al.*, 2005; Asnani, Lipps and Reid, 2007, 2009; Dampier *et al.*, 2011; Shiu *et al.*, 2014). The SF-36 is well preferred because of its brevity, ease of use, and applicability across a range of health states and cultures (Garratt *et al.*, 1993; Gandek *et al.*, 1998). The validity and reliability of the instrument has been established (Ware Jr and Sherbourne, 1992)., The SF-36 is the most frequent measure used to study quality of life in SCD (Asnani, Lipps and Reid, 2007, 2009). SF-36 has been translated and adapted in more than 40 countries, including Nigeria (Mbada *et al.*, 2015).

The instrument has also been translated to Yoruba and tested in the Nigerian population. Based on the protocol of the International Quality of Life Assessment (IQOLA) Project, Mbada *et al.*(2015) conducted a study that translated and adapted the instrument into Yoruba. The translated version was tested in a population of 1087 participants made up of 95.8% native Yoruba speakers. They established satisfactory psychometric properties, a concurrent validity score of between 0.749 and 0.902 for the scales and domains, convergent validity score of between 0.421 to 0.907 and discriminant validity was also found satisfactory except

for item ‘1’. They reported a reliability score of between 0.636 and 0.843 for scales and range of 0.783 to 0.851 for domains that the Yoruba SF-36 showed excellent psychometric properties comparable to the original American and other versions and indicated that the Yoruba version is a valid tool to assess HRQL among the Yoruba population. Asnani, Lipps and Reid,(2009) have established psychometric properties of the instrument in the SCD population. They reported acceptable degree of internal consistency, reliability and discriminant validity in the Jamaican SCD population.

The instrument was coded on a scale of 0-100 as recommended in the manual (Ware and Kosinski, 2001) and transformed so that higher values reflect better quality of health. Each dimension (subscale) was obtained by adding all the items in the subscale and dividing by the number of items. For example, the physical functioning (PF) subscale was obtained by adding all the 10 items PF01 – PF10 and dividing by 10.

Norm-based scoring has been introduced by the developer to facilitate comparison and interpretation (www.qualitymetric.com). The norm-based scoring was based on the USA 1988 general population each scale was scored to have mean 50 and standard deviation, 10. This implies that all scores above 50 were interpreted as having a more positive response set to whatever the domain measures. A scoring software license was obtained from Quality Metric Inc. (Appendix 8) to score the data and to facilitate the comparison of the HRQL scores of Nigerians with SCD with the norm-based value.

In treating missing values for the instrument, The designer of the instrument recommended that missing data could be substituted with the mean value of valid responses up to 50% of items in the subscale (Ware *et al.*, 2000). If any respondent has more than 50% of the items missing in a subscale, the subscale score for the individual was considered missing. The developers of the scale however hinted at a more sophisticated method of handling the missing values. In this study, a more robust method of treating missing value, the full

information maximum likelihood (FIML) or simply called maximum likelihood imputation technique, was used to reduce bias due to mean values. This method produces unbiased estimates of parameters as well as good estimates of the standard errors (see 3.8.2). In a comparison of methods for dealing with missing items in SF-36, A study reported that multiple imputation and full information maximum likelihood appeared superior to the personal mean score in terms of accuracy and precision (Peyre, Leplège and Coste, 2011). The IBM SPSS AMOS 25 maximum likelihood imputation was used, the pattern analysis showed that no items has more than 20% missing value. The before and after imputation characteristics of the data is shown in Table 3-3. The table shows that no bias was introduced by the imputation whereas more power has been made available through the larger sample size.

Table 4-3: Comparison of Items of SF-36 Before and After Imputation of Missing Values

	Before imputation			After imputation			Test Statistic		
Items	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean diff. (Absolute)**	**p-value**	**Equal Variance test**
PF1	194	38.920	38.838	200	39.00	38.227	0.080	0.984	0.412
PF2	190	62.368	38.036	200	61.75	37.836	0.618	0.872	0.470
PF3	190	53.684	38.656	200	53.50	38.342	0.184	0.962	0.454
PF4	190	51.842	39.296	200	52.00	39.098	0.158	0.968	0.471
PF5	187	63.102	38.479	200	63.00	37.923	0.102	0.979	0.419
PF6	190	55.526	36.493	200	55.75	36.208	0.224	0.952	0.456
PF7	170	55.588	36.259	200	55.5	35.370	0.088	0.981	0.377
PF8	171	60.234	37.148	200	60.75	37.113	0.516	0.894	0.496
PF9	169	68.935	38.142	200	70.25	37.207	1.315	0.738	0.367
PF10	176	74.716	39.640	200	73.25	39.110	1.466	0.719	0.426
RP1	191	59.162	49.283	200	60.00	49.113	0.836	0.866	0.480
RP2	188	53.723	49.994	200	53.50	50.003	0.223	0.965	0.499
RP3	188	45.745	49.952	200	46.00	49.965	0.255	0.960	0.499
RP4	191	56.021	49.767	200	55.50	49.821	0.521	0.918	0.494
RE1	190	60.00	49.119	200	60.00	49.113	0.000	1.000	0.499
RE2	187	59.358	49.248	200	60.00	49.113	0.642	0.898	0.484
RE3	191	64.398	48.008	200	64.50	47.971	0.102	0.983	0.495
BP1	192	72.083	22.415	200	72.20	22.308	0.117	0.954	0.470
BP2	190	67.50	29.317	200	67.37	29.034	0.126	0.966	0.465
SF1	188	68.351	30.955	200	68.62	30.593	0.274	0.930	0.435
SF2	185	59.865	30.629	200	59.75	30.571	0.115	0.971	0.459
VT1	175	62.171	31.548	200	61.50	31.122	0.671	0.836	0.425
VT2	197	64.586	29.092	200	64.60	29.035	0.014	0.996	0.488
VT3	191	65.655	30.253	200	65.20	30.687	0.455	0.883	0.422
VT4	196	60.816	23.693	200	60.90	23.494	0.084	0.972	0.452
GH1	190	64.211	27.132	200	64.88	27.005	0.664	0.809	0.473
GH2	196	51.020	37.791	200	50.50	35.881	0.520	0.888	0.233
GH3	197	65.228	34.112	200	65.50	34.048	0.272	0.937	0.489
GH4	196	80.740	29.562	200	80.38	29.642	0.365	0.902	0.485
GH5	195	74.359	31.134	200	74.38	30.842	0.016	0.996	0.447
MH1	186	64.086	30.922	200	62.70	31.170	1.386	0.661	0.457
MH2	197	72.893	33.047	200	72.40	33.283	0.493	0.882	0.460
MH3	195	74.154	26.877	200	74.00	26.900	0.154	0.955	0.496
MH4	193	67.565	31.865	200	67.50	31.856	0.065	0.984	0.498
MH5	193	80.622	24.144	200	80.20	24.309	0.422	0.863	0.462
HT	185	89.730	20.587	200	89.88	20.221	0.145	0.995	0.333

4.5.7 Derived Utility measure (SF-6D)

The SF-6D is a six-dimensional health classification (Brazier *et al.*, 1998) derived from the SF-36 which estimated utility or preference-based measures from SF-36 score (Brazier *et al.*, 2012). SF-6D was developed in the UK general population from 11 questions of the SF-36. The questions were extracted from the six health dimensions of physical function, role limitations, social functioning, pain, mental health and vitality. SF-6D ranges from 0.30 to 1.0 (full health). The derived measure of utility has been used in many studies to obtain utility scores for patients in general and disease populations (Thein *et al.*, 2005; Walters and Brazier, 2005; Sullivan and Ghushchyan, 2006; Wyld *et al.*, 2012). A license was obtained from the University of Sheffield for the scoring algorithm.

4.6 Analysis of instruments

Though the psychometric properties of these instruments have been established in different studies, populations and countries, researchers have suggested that investigators should not rely on published reliability estimates because alpha is a property obtained from a specific sample of the population being tested (Streiner, 2003; Tavakol and Dennick, 2011). These instruments were therefore examined for validity and reliability in the study population as required in quality of life measurements (Bowling, 1991; Fitzpatrick, 2000).

The reliability, measured by Cronbach alpha (Cronbach, 1951), was for all the scales above the recommended 0.70. The means and standard deviations (SD) of scores were also calculated.

The mean and standard deviation of each item of the SF-36 instruments were computed. The ceiling and the floor effects were also examined, and the reliability was obtained for each domain or subscale. These were all found acceptable. Further psychometric properties beyond the Cronbach alpha were examined for the SF-36. To establish item validity, the correlations between items and the hypothesised scale (item internal consistency) was

expected to be at least 0.40 (Streiner, Norman and Cairney, 2015) and the correlation between each item and its hypothesised scale (corrected for overlap) should be higher than the correlation between that item and the other scales (item discriminant validity). A scaling success rate was tallied for each item whenever it correlated higher with its hypothesised scale than with all the other scales (Prieto, Alonso & Ferrer, 1997). Construct validity was based on sociodemographic variables (Jenkinson, Coulter and Wright, 1993; Prieto *et al.*, 1997). It has been hypothesised that HRQL will be inversely associated with patients' age, with lower socioeconomic level and relatively worse HRQL results for female patients (Hemingway *et al.*, 1997). Percentages were obtained for patients with worst possible scores (floor effect) and best possible score (ceiling effect).

According to the developers of the SF-36, the 35 items were expected to produce an 8-facror structure representing the domains of the instruments (Ware Jr and Sherbourne, 1992; Ware and Gandek, 1998) . Factor analysis was therefore carried out to determine the structure of SF-36 in the Nigerian population of SCD patients whether it conformed to the expected 8-factor structure Principal component analysis followed with varimax rotation was conducted on the 35 items. A factor was assumed relevant if its eigenvalue is greater than one.

4.7 Structural Equation Modelling (SEM)

Structural equation modelling (SEM) is a statistical technique that encompasses factor analysis, path analysis and regression which has been established as an ideal method to test *a priori* hypothesis concerning relationships among latent (theoretical constructs) and measured (observed) variables (Schumacker and Lomax, 2004; Kline, 2011; Mayo *et al.*, 2015). A powerful tool that allows researchers to test simultaneously the underlying relationship between several variables within the framework of a model, SEM allows for confirmatory testing of complex relationships (Byrne, 2001) as well as confirming factor structure of an instrument (Tomarken and Waller, 2005). Some advantages of SEM

according to Chan *et al.*(2007) include the ability of constructs in SEM to perform both as predictor and as criterion construct and also enable a set of measured variables to represent a latent theoretical construct more realistically than a single variable. SEM procedures may be used to compute reliability of both measurement instruments and estimated latent constructs. In addition, SEM enables evaluation of the general compatibility (i.e., the goodness of fit) of the model as well as the strength of relationship among constructs and useful to compare competing theoretical models. The technique has the capacity for assessing and modifying theoretical models (Anderson and Gerbing, 1988) and because it is covariance-based, provide better coefficient estimates and more accurate model analyses (Bollen, 1989).

SEM is made up of two distinct models or sub-models. The first part is the measurement model, in which relationships of the observed indicators to their hypothesised constructs are specified and the constructs are allowed to freely correlate with each other, the second part is the structural model which specifies the causal pathways of the constructs as they relate to one another based on theory (Anderson and Gerbing, 1982; Jöreskog and Sörbom, 1984). Researchers often use the measurement model to examine the extent of interrelationships and the presence or absence of correlation among the latent constructs. SEM has been widely used in HRQL models due to its capability to test such complex models which sets *a priori* hypothesised relationships among multiple correlated variables (Musil, Jones and Warner, 1998; Kline, 2011), researchers are increasingly using it in HRQL studies. This is because SEM allows simultaneous investigation of a set of measurement paths and a structural path proposed by HRQL models. Researchers have used SEM to evaluate the goodness of fit of HRQL model to better understand the relationships of the physiological and psychosocial factors to each other and to HRQL in many disease conditions including epilepsy (Bishop *et al.*, 2002), HIV/AIDs (Sousa and Kwok, 2006), diabetes (Shiu *et al.*, 2014), heart failure (Mayo *et al.*, 2015), Coronary artery disease (Hofer *et al.*, 2005).

The use of SEM has been predicted to increase in research as a means of confirming measurement structures of instruments and to assess appropriateness of theoretical constructs. The ability of SEM to compare a hypothesised model's covariance with that of observed data allows a more 'causal' explanation of findings (Hofer *et al.*, 2005) and is also suitable for investigating mediator effects (Baron and Kenny, 1986; Holmbeck, 1997; Cole and Maxwell, 2003). SEM has been rated better than standard regression models because of its theory-driven approach and the evidences that the resulting prediction equation more accurately represent the true causes of variation in the dependent variable (Anderson and Gerbing, 1988; Hofer *et al.*, 2005). The basic steps for SEM analysis are briefly discussed as follows:

4.7.1 Specification

The generally recommended approach to model specification is the two-phase approach (Anderson and Gerbing, 1988; Mueller and Hancock, 2008) with the measurement and structural models specified separately. This method ensures assessment and earlier detection of possible misspecification error in the measurement which could be addressed before the assessment of the hypothesised causal relationships (Mueller and Hancock, 2008). In this study the measurement model and the structural model were constructed following the theoretical framework of Wilson and Cleary (1995). A multiple-indicator approach (Kline, 2011) was employed so that at least two observed variables were used to measure a construct except the overall QOL which has one indicator variable. Kline (2011) has suggested that scores from multiple indicators measuring the same constructs should be positively correlated. This was ensured by reversing the score of some indicators before analysis in SEM such that all indicators that measure the same construct are in the same direction. For example, since the SF-36 was scored such that high score indicated better health (Ware *et al.*, 2000; Ware, 2007), the BP and MH were reversed so that higher scores indicated worse

health to ensure that for example, bodily pain did not correlate negatively with depression as they were in the same cluster that measures symptoms status. In the initial step, the measurement model stage, the indicators were loaded on the latent constructs and the constructs were allowed to freely intercorrelate. No indicator was allowed to load on more than one latent construct (McDonald and Ho, 2002). In the second part, the latent variables were connected as posited by Wilson and Cleary (1995) to form the structural path of the model. The relationship between the latent variable or between a single predictor and a latent variable were specified as path coefficients or regression coefficients (Hofer *et al.*, 2005; Mueller and Hancock, 2008).

4.7.2 Identification

Identification is an important issue in SEM as it relates to whether there is a unique set of parameters consistent with the data. A structural model has three possible state of identification (Byrne, 2001); under-identified, just-identified and overidentified. An under-identified model has insufficient information to estimate the parameters because the number of parameters to be estimated is more that the data points. A just-identified model has the number of parameters equal to the number of data points which returns a zero degree of freedom, such model is not scientifically useful because the model to be tested cannot be rejected (Chan *et al.*, 2007). The over-identified model has more data points than the number of parameters to be estimated returning a positive degree of freedom to obtain a determinant solution that can lead to rejecting or confirming the hypothesised model (Chan *et al.*, 2007). A simple method for establishing identifiability is to subtract the number of parameters to be estimated form the number of data points. The number of data points is obtained from the formula $s(s+1)$ where s is the number of indicator variables. The number of parameters is based on the sum of the number of regression coefficients, variances and covariances. A

sufficient condition for a parameters of measurement model to be identified required that each latent variable should have at least two indicators (Kline, 2011).

4.7.3 Estimation

The estimation stage of SEM centres on the evaluation of the fit between the hypothesised model and the observed data, and the interpretation of parameter estimates

Parameter estimation

Two commonly used methods for parameter estimation in SEM are the ML (maximum likelihood) and the WLS (weighted least squares). The ML was used in this study because it has been the predominant method (Anderson and Gerbing, 1988) and the most widely used fitting function for SEM (Schermelleh-Engel, Moosbrugger and Müller, 2003). In addition, most available softwares use ML as the default estimator. For a correctly specified model and adequate sample size, the ML produces parameter estimates that are asymptotically unbiased, consistent and efficient (Schermelleh-Engel, Moosbrugger and Müller, 2003). Moreover, the ML allows for a statistical test of overall model fit for overidentified models, in addition, the ML estimates are scale invariant (Bollen, 1989) which means that the values of the fit function do not depend on whether correlation or covariance matrices are analysed, and whether original or transformed data are analysed. Though the ML assumes multivariate normality of data which could be a limitation, research has however shown that ML is robust against violation of the normality assumption (Browne, 1984; Chou and Bentler, 1995; McDonald and Ho, 2002; Muthén and Muthén, 2002). Simulation studies have further shown that under conditions of severe non-normality, ML parameter estimates are still consistent though not necessarily efficient (Schermelleh-Engel, Moosbrugger and Müller, 2003).

4.7.4 Model fit

Model fit in SEM is evaluated by examining various statistics. The purpose is to determine whether the results provide empirical evidence that the model fits the data (Aroian and Norris, 2005). The inferential Chi-square (χ^2) likelihood ratio statistic is used to assess the magnitude of the discrepancy between the sample and fitted matrices. A non-significant Chi-square is expected to confirm model fit. A significant Chi-square indicates a poor fit. However, χ^2 is sensitive to sample size as it increases with increase in sample size (Gerbing and Anderson, 1985) which makes χ^2 always significant with large samples and thus return poor fit to SEM models leading to a rejection of the model even though the model may be well-fitted to the data. Because of this sensitivity, a modified test is the χ^2 divided by its degree of freedom (df). If χ^2/df does not exceed 3.0 the model should be considered a good fit to the data (Schermelleh-Engel, Moosbrugger and Müller, 2003). Researchers have also recommended additional indices to assess the fit of the model. These descriptive fit indices have also been accepted in literature as confirmatory tests. These fit indices have been broadly categorised into three classes (Mueller and Hancock, 2008) as absolute, parsimonious and incremental or comparative indices (Schermelleh-Engel, Moosbrugger and Müller, 2003; Schumacker, Lomax and Group, 2010).

Absolute fit indices include the global chi-square (χ^2) test (already mentioned above as inferential statistic), the root mean square error of approximation (RMSEA) and the standardised root mean residual (SRMR) assess the overall discrepancy between the observed and the expected covariance matrices. The RMSEA (Steiger, 1990) is a measure of discrepancy between the observed and model implied covariance matrices per degree of freedom. Browne and Cudeck (1993) has suggested that RMSEA values between 0.05 and 0.08 indicate an adequate fit. The SRMR (Hu and Bentler, 1998) is a measure of the average

of the fitted residuals and ranges from 0.00 to 1.00, SRMR value less than 0.05 represents an adequate fit (Schermelleh-Engel, Moosbrugger and Müller, 2003).

Parsimonious indices in evaluating overall discrepancy between observed and implied covariance matrices take into account the model's complexity, they include the Parsimony goodness of fit index (PGFI), parsimony normed fit index (PNFI), the Akaike information criterion (AIC) to compare fit across non-nested models and the expected cross validation index (ECVI).

Incremental or comparison indices focus on model comparisons, they evaluate absolute or parsimonious fit relative to a baseline model (a model that specifies no relationship among measured variables), they include the comparative fit index (CFI) the normed fit index (NFI) and the non-normed fit index (NNFI), the goodness of fit index (GFI) and the adjusted goodness of fit (AGFI). The CFI (Bentler, 1990) which is the most popularly used in this group, provides a measure of complete covariation in the data. CFI value greater than 0.95 indicates acceptable fit to the data.

Most commonly used indices in current publications and their threshold for making statements on the model being evaluated are stated on Table 4-4.

Table 4-4: Fit Indices and Threshhold Values

Fit Index	Good fit	Acceptable fit
χ^2	$0 \leq \chi^2 \leq 2df$	$2df \leq \chi^2 \leq 3df$
p value	$0.05 < p \leq 1.00$	$0.05 \leq p \leq 0.10$
χ^2 / df	$0 \leq \chi^2/df \leq 2$	$2 < \chi^2/df \leq 3$
RMSEA	$0 \leq RMSEA \leq 0.05$	$.05 < RMSEA \leq 0.08$
P value for test of close fit (RMSEA < 0.05) Confidence interval (CI)	$0.10 < p \leq 1.00$ Close to RMSEA, left boundary of CI = .00	$.05 \leq p \leq 0.10$ Close to RMSEA
SRMR	$0 \leq SRMR \leq 0.05$	$.05 < SRMR \leq .10$
NFI	$.95 \leq NFI \leq 1.00$	$.90 \leq NFI < .95$
NNFI	$.97 \leq NNFI \leq 1.00$	$.95 \leq NNFI < .97$
CFI	$97 \leq CFI \leq 1.00$	$.95 \leq CFI < .97$
GFI	$95 \leq GFI \leq 1.00$	$.90 \leq GFI < .95$
AGFI	$90 \leq AGFI \leq 1.00$, Close to GFI	$.85 \leq AGFI < .90$, Close to GFI
AIC	Smaller than AIC for comparison model	
CAIC	Smaller than CAIC for comparison model	
ECVI	Smaller than ECVI for comparison model	

Source: 'Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures', *Methods of psychological research online*, 8(2) (Schermelleh-Engel, Moosbrugger and Müller, 2003, p. 52).

4.7.5 Modification

Model modification, where necessary, was expected to be in line with theory such that inferences will be based on established theory and not on data variability.

4.8 Data management

Two computer statistical packages were used in this study. They are the Statistical Package for the Social Sciences (SPSS) version 24 (IBM SPSSv24) and the Analysis of Moment Structures (AMOS) version 25 (IBM SPSS AMOS 25, 2018).

4.8.1 Data Screening procedures

Screening procedures were performed on the raw data to ensure that they were suitable for analysis in SEM. Some of the problems that arise in SEM stem from the violation of its assumptions. SEM assumes among others, multivariate normality, positive definiteness, homoscedasticity and acceptable psychometric properties of instruments (Schumacker,

Lomax and Group, 2010; Kline, 2011). The presence of multicollinearity, outliers and missing data could render data unfit for use in SEM. Data were screened as outlined below to check and ensure the fitness of data for SEM analysis.

Multivariate normality. According to Kline (2011), assumption of multivariate normality implies that all individual univariate distributions are normal, the joint distribution of any pair of variable is normal, all bivariate scatter plots are normal and the distribution of residuals is homoscedastic. He argued that instances of multivariate normality can be detected by examining the univariate distributions. Detecting non-normality in variables can be accomplished by inspecting the skewness (the degree of symmetry around the mean) and kurtosis (the degree of peakedness or flatness of the distribution). Studies suggested that the absolute value of the skew index and kurtosis index should not exceed 3 and 10 respectively (Kline, 2011). DeCarlo (1997) however argued that the lack of univariate skewness and kurtosis are necessary but not sufficient conditions for multivariate skewness, kurtosis and normality, thus the Mardia's multivariate skewness and kurtosis coefficient (Mardia, 1970) was employed to inspect the multivariate property of the data.

Multicollinearity. A collinearity diagnostic check was conducted. Three methods were used to check for multicollinearity in the predictors.

1. Correlation matrix: the presence of multicollinearity is suspected between two predictor variables if the coefficient of correlation between them is almost unity or the squared multiple correlation, $R^2 > 0.90$.

2. Tolerance and the variance inflation factor (VIF): the rule is that tolerance statistic should not be less than 0.1 and the VIF should not be greater than 10 (Kline, 2011).

3. Eigenvalues: an eigenvalue close to zero with a corresponding large condition will indicate the presence of multicollinearity.

Homoscedasticity. To confirm homoscedasticity, the variances of predictor variables were examined. The ratio of the largest variance to the smallest variance was expected not to be greater than 10 otherwise the assumption was considered violated.

Outliers. A linear regression on the predictor variables was performed. The Mahalonobis distance (D) statistic was used to check for the presence of outliers. In a large, normally distributed sample, D^2 follows a central chi-square (χ^2) distribution statistic with the number of variables as degrees of freedom.

Positive definiteness: This was examined through the determinant of the correlation matrix which was expected to be greater than zero.

Sample size: Sufficiency of sample size was examined through the Kaiser-Meyer-Olkin KMO test of sample size adequacy (Williams, Onsman and Brown, 2010). A KMO greater than 0.5 could confirm the adequacy of the sample size.

4.8.2 Missing Data

Missing data is a common occurrence in research. Problems that emanate from using inappropriate methods to deal with missing data include bias in parameter estimates (Jones, 1996), standard errors and test statistics (Glasser, 1964; Little and Rubin, 1987) and inefficient use of the data (Afifi and Elashoff, 1966). Many statistical methods have been recommended to deal with missing data to avoid biased conclusion on the result of analysis. Missing patterns have been categorised in literature to be missing completely at random (MCAR), or missing at random (MAR) Data are said to be MCAR if given two variables X,Y, the probability that data are missing on Y does not depend on X or Y while data are MAR if the probability that the data are missing on Y does not depend on Y but may depend on the value of X holding X constant (Rubin, 1976; Kline, 2011). This implies that in MAR,

missingness depends on things observed but not on things that are not observed (Allison, 2003). Invariably, if data is MCAR, they are also MAR.

In SEM, conventional methods such as the pairwise deletion and the listwise deletion have been reported inappropriate under the assumption of MAR because they produce biased estimates and are also not amenable to estimating standard errors (SEs) or testing hypotheses. The mean imputation technique which involves substituting missing cases with the overall sample mean also yields biased estimates of parameters (Little and Rubin, 1987). Furthermore, the conditional mean imputation method, estimated by regressing variable with missing data on other variables in the data set for cases with complete data, was reported to have a "general tendency" to produce underestimates of variances and overestimate of correlations (Little and Rubin, 1987).

In view of the weaknesses of these highlighted methods, a maximum likelihood (ML) approach was used in this study. Researchers have recognised the ML method as the most widely used method for estimating SEM under the assumption of multivariate normality and has been shown to produce estimates that are consistent (estimates converge in probability to the true parameter value as the sample size increases, i.e. bias shrinks to zero with increasing sample size), asymptotically efficient (sampling variance of estimate is as small or smaller than that of any other estimator, and improves with increasing sample size), and asymptotically normal(Arbuckle, 1996) and can handle missing data under the weaker assumption of MAR as well as under variety of distributional assumptions (Allison, 2003). Under conditions of missing data, there are three major methods of ML estimators of parameters; they are one, the method of factoring of the likelihood (Marini, Olsen and Rubin, 1980), two, the EM (Expectation-Maximisation) algorithm (McLachlan and Krishnan, no date; Dempster, Laird and Rubin, 1977) and three, the direct ML otherwise called the full information ML (FIML) ((Allison, 1987; Muthén, Kaplan and Hollis, 1987). Comparing

these three approaches Allison (2003) reported that direct ML overcomes the weakness of EM algorithm, Arbuckle (1996) also proposed the use of direct ML for general missing data patterns and implemented same in AMOS. In addition, Duncan, Duncan and Li (1998) suggested that direct ML appears to be the best method for handling missing data in SEM. The multiple imputation (MI) technique was also considered in the search for the best means of handling missing data in SEM. Though the MI has statistical properties similar to the optimality of direct ML and can be used in almost any situation, the method lacks the ability to produce determinate results and overestimates the correlation coefficient (Allison, 2003). Also, the parameters estimates are less efficient and the standard error estimates are considered too low because additional variability are not accounted for. Moreover, the need to obtain combined estimates for the various imputations has introduced computational problems which currently can only be handled by the "MINIALIZE" procedure in SAS unlike the direct ML which is available in most statistical packages. Schafer and Olsen (1998) further suggested that the direct ML may be more efficient than the MI because they do not rely on simulation. In view of the robustness of direct ML in handling missing data in SEM including its ability to produce reliable estimates even when multivariate normality assumptions are violated(Allison, 2003), and the recommendation of its use to structural equation modelers (Allison, 1987), the ML approach was employed in handling missing data in this study.

4.9. Psychometric properties of the instruments

The psychometric properties of the SF-36 are displayed on Table 4-5. The reliabilities were acceptable ranging from 0.70 to 0.87. the item internal consistency and the item-discriminant validity were appropriate. The scaling test recorded 100% in all the domains except the GH domain where GH05 '*my health is excellent*' correlated higher with MH (r = 0.68) compared with its hypothesised scale (r = 0.58). The ceiling (the proportion of patients with best possible scores) was high for RP and RE domains 30 and 42.5 respectively. Both domains

also recorded high floor (proportion of patients with worst possible score) 22.5 and 20 respectively.

Table 4-5: Test of Reliability and Scaling Parameters of SF-36 in the Sample.

Scale	No of items	Reliability Cronbach (α)	item internal consistency [a]	Item discriminant validity [b]	Ceiling / floor [c]	Success / totals [d]	Scaling success (%)
PF	10	0.866	0.422 - 0.783	0.00-0.37	5.0 / 2.5	80/80	100
RP	4	0.771	0.731 - 0.796	0.17-0.51	30 / 22.5	32/32	100
RE	3	0.731	0.796 - 0.817	0.09-0.62	42.5 / 20	24/24	100
SF	2	0.774	0.9-0.906	0.15-0.47	18.0 / 1.0	16/16	100
BP	2	0.702	0.873-0.883	0.08-0.50	17.5 / 0.0	16/16	100
VT	4	0.715	0.688 - 0.805	0.02-0.51	1.5 / 0.0	32/32	100
MH	5	0.712	0.529 - 0.819	0.08-0.49	6.0 / 0.0	40/40	100
GH	5	0.716	0.575 - 0.775	0.07-0.68	5.0 / 0.0	39/40	98

Note: [a] Correlation between items and hypothesised scale [b] Correlation between items and other scales [c] Proportion of patients with best possible score (ceiling) and worst possible score (floor) [d] Number of hypothesised correlation higher /total number of correlations. PF=Physical Functioning, RP=Role Physical, RE=Role Emotional, SF=Social Functioning, BP=Bodily Pain, VT=Vitality, MH=Mental Health, GH=General Health.

The reliabilities of the measures of anxiety, depression and somatic symptoms are shown in Table 4-6. The measures showed acceptable reliabilities which ranged between 0.80 and 0.90.

Table 4-6: Reliability of the Measures of Anxiety, Depression and Somatic Symptoms.

Measure	Range	Mean	SD	Reliability
Genarlised Anxiety Disorder (GAD-7)	0-16	3.86	3.91	0.802
Patient Health Questionnaire for depression (PHQ-9)	0-25	5.14	4.70	0.824
Patient Health Questionnaire for somatic symptoms (PHQ-15)	0-30	7.475	6.48	0.902

4.10 Statistical analysis

Both descriptive and inferential statistical analyses were performed on the data in line with the specific objectives and research questions of this study. The P- value was set at 0.05 to be able to make specific statements on statistical properties of results.

4.10.1 Descriptive statistics

The sample characteristics of the population used proportion and percentages to summarise qualitative variables and result presented in frequency tables. Appropriate measures of central tendency were used to summarise and present quantitative variables. These were calculated using SPSS version 24 (IBM SPSS 24).

4.10.2 Inferential statistics

Data were analysed in line with the specific objectives of the study. Statistical tools used included t-test, chi-square and correlations. The student independent t-test was used to measure differences between two groups while the one-way analysis of variance (ANOVA) was used where there were more than two groups. The Turkey's HSD post-hoc test was performed for pairwise comparison of groups among groups. For the second objective, the relationship among biophysiological variables, symptoms status, functional status, general health perceptions and overall quality of life were investigated. Factors that associated with HRQL were also investigated. Correlations for continuous and Chi-square (χ^2) statistic for discrete variables were used to investigate hypothesised relationships.

Hierarchical regression modelling was used to test predictors. Hierarchical regression was preferred to simple linear or stepwise regression because this study is based on a theoretical model that signifies order of relationship hence groups of variables were entered into the regression model based on the Wilson and Cleary model of health-related quality of life.

4.10.3 Structural equation modelling

Structural equation modelling is a powerful statistical tool that allows for the simultaneous testing of complex interrelationships between variables specified within *a priori* models (Kline, 2011), and currently regarded as the best technique for assessing and modifying theoretical models (Baker, 2007). SEM has been described as "the preeminent multivariate method of data analysis" (Hershberger, 2003, pp. 43–44; Mueller and Hancock, 2008). The technique is a confirmatory method (Jöreskog, 1978; Bentler, 1985) which allows researchers to assess and modify theoretical models (Anderson and Gerbing, 1988). Also SEM is useful to express complicated variable relationships through hierarchical or non-hierarchical, recursive or non-recursive structural equations, and to present a more complete picture of the entire model (Hanushek and Jackson, no date; Bullock, Harlow and Mulaik, 1994). The step by step application of SEM to the data is detailed as follows.

Model specification

An exploratory factor analysis was first carried out on the data. The analysis yielded a 7-factor model with 59.11% cumulative percentage of variance explained. The determinant of the correlation matrix was greater than zero satisfying the condition of positive definiteness. The Kaiser-Meyer-Olkin (KMO) test (Williams, Onsman and Brown, 2010) returned by SPSS was 0.75 confirming that the sample size of 200 was adequate to run the 7-factor model.

A two-step procedure recommended by Anderson and Gerbing (1988) was implemented. The model building procedure was viewed as the analysis of two distinct models; measurement and structural (Anderson and Gerbing, 1982, 1988). The initial step was to develop models to represent each of the constructs. A confirmatory factor analysis (CFA) was carried out on each of the model separately, individual measured variables for each construct were allowed to load on a single factor or latent construct it was hypothesised to

measure. For example, the scales of role emotional (RE), social function (SF), physical functioning (PF) and role physical (RP) were allowed to load on the latent construct, function status (FS). This was to ensure that indicator variables reflect the latent construct they were hypothesised to measure. Next, a first-order CFA was implemented to assess the adequacy of the measurement model of the latent variables. This process allowed all the constructs to intercorrelate freely with each other. Applying the second step of Anderson and Gerbing, the structural model was specified as hypothesised by Wilson and Cleary (1995). Relationship among the dependent and independent latent variables were estimated. Fit indices (see Table 4-4) were examined. All analyses were conducted with the Analysis of Moment Structures (AMOS) software version 25 (IBM AMOS 25).

Model identification

The identification property of the model was checked based on the counting rule which requires the model's degree of freedom $df_M > 0$ based on the difference between number of free parameters and observations (Kline, 2011). A $df_M < 0$ means that the model is unidentified and is unusable, a $df_M = 0$ implies the model is just identified and one cannot test any hypothesis since degree of freedom is zero while a $df_M > 0$ implies an overidentified model and suitable for statistical test.

In the current study, number of distinct single moments = 153

Number of parameters to be estimated = 50.

Degree of freedom, $df_M = 153 - 50 = 103$. As this is greater than zero, the model is overidentified.

Evaluation of model assumptions

The assumptions of the model include that of linearity of relationship, normality of distribution, independence/homogeneity of variances, homoscedasticity and multicollinearity. They were examined as follows:

Normality. The distribution properties of the variables were examined by checking the skewness and kurtosis of each variable to establish the deviation or otherwise of such variable from normality. Skewness and kurtosis close to zero implies symmetrical and mesokurtic distribution. The rule of thumb for interpreting kurtosis and skewness in a large sample is that the absolute value of kurtosis greater than 10 may indicate problem and greater than 20 evidence a very serious problem while variable with absolute skewness greater than 3.0 may be considered extremely skewed (Kline, 2011). Table 4-7 shows that none of the variables have a value of skewness greater than 3.0 and none of the kurtosis was greater than 10. Hence, the univariate normality assumption was not violated.

Multicollinearity. Multicollinearity is the problem of high correlations between two independent variables in the model, this disturbance may affect SEM procedure and make statistical inference about the data unreliable (http://www.statisticssolutions.com/multicollinearity/). To check for multicollinearity, collinearity diagnostics was carried out in SPSS (See Table 4-7. The values of variance inflation factor (VIF) and tolerance were examined. Multicollinearity is indicated if tolerance is less than 0.01 and if VIF is greater than 10. Table 4-7 shows that VIF ranged from 1.11 to 3.14 while tolerance ranged from 0.318 to 0.898. Thus, the assumptions of absence of multicollinearity was not violated by the data for the current study.

Table 4-7: Skewness and Kurtosis and Collinearity Diagnostics

	N = 200 Minimum	N = 200 Maximum	Skewness		Kurtosis		Collinearity Statistics	
	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error	Tolerance	VIF
Gender	1	2	-.348	.172	-1.898	.342	.772	1.296
Age	1.00	3.00	1.601	.172	1.476	.342	.589	1.697
Marital status	1.00	3.00	1.728	.172	2.106	.342	.548	1.826
N. children	1.00	3.00	2.157	.172	3.916	.342	.500	2.000
Level of Education	1.00	3.00	-.417	.172	-.687	.342	.699	1.431
Employment status	1	3	.916	.172	-.897	.342	.542	1.847
Living situation	1	2	-2.887	.172	6.399	.342	.783	1.277
Confidant	1	2	-2.032	.172	2.149	.342	.833	1.201
Genotype	1	2	1.975	.172	1.921	.342	.857	1.167
N. Comorbidities	.00	2.00	1.315	.172	.568	.342	.520	1.921
HT	25.00	100.00	-2.010	.172	3.077	.342	.661	1.513
PF	.00	100.00	-.320	.172	-.496	.342	.672	1.487
RP	.00	100.00	-.129	.172	-1.440	.342	.365	2.739
RE	.00	100.00	-.449	.172	-1.274	.342	.383	2.608
SF	.00	100.00	-.317	.172	-1.041	.342	.496	2.018
GH	5.00	100.00	-.579	.172	-.464	.342	.528	1.894
PHQ9	.00	25.00	1.062	.172	.927	.342	.339	2.952
GAD7	.00	16.00	.992	.172	.150	.342	.318	3.144
PHQ15	.00	26.00	1.168	.172	1.266	.342		
Overall Qol	1	7	-.781	.172	.146	.342	.776	1.289
BPR	.00	80.00	.289	.172	-.936	.342	.549	1.821
MHR	.00	92.00	.629	.172	-.380	.342	.517	1.936
Income status	1.00	2.00	1.819	.172	1.321	.342	.549	1.823
VTR	.00	95.00	.551	.172	.180	.342	.898	1.114
DSEI							.710	1.408

Notes: PF=Physical Functioning; RP=Role Physical; RE=Role Emotional; SF= Social Functioning; GH=General Health; HT= Health Transition; PHQ9=Patient Health Questionaire-9; GAD7=Generalised anxiety Disorde-7; PHQ15=Patient Health Questionnaire-15; BPR=reversed score of Bodily Pain; MHR=reversed score of Mental; VTR= reveserd score of Vitality; Health; DSEI=Disease sveverity index.

Homoscedasticity. The possible presence of homoscedasticity was checked by using the principle of relative variance, that is comparing the variances of all the variables entered to detect if there is any variance that is 10 times the other. A relative variance greater than 10 is ill-scaled. SEM procedure is iterative (initial estimates are derived by the computer and then modified through subsequent cycles of iteration). The analysis of a covariance that is ill-scaled will be problematic. No variance was 10 times greater than the variance of any

other variable hence the assumption of absence of homoscedasticity was satisfied (See Table 3-8).

Outliers. Both univariate and multivariate outliers were assessed both by graphical and statistical methods. Data were inspected to ensure they were accurately entered. Kline (2011) opined that there is no single definition of an extreme outlier. Univariate outliers could be detected by examining the frequency distribution of the z-score. Absolute value of Z greater than 3 standard deviations from the mean ($|Z| \leq 3.29$, $p < 0.001$) may indicate an outlier (Kline 2011). This rule of thumb was applied, the boxplots were also examined. Extreme outliers were observed in 10 cases from 3 variables namely number of children, 7 cases, PHQ-9, 1 case and PHQ-15, 3 cases. The boxplot of each variable was also examined. A transformation was applied to correct for the outliers (see Table 3-8.).

A method based on the Mahalanobis distance (D) was computed to evaluate possible presence of multivariate outliers. The Mahalanobis distance is the distance of a case from the centroid of all cases where the centroid is calculated as the intersection of the mean of the variables being assessed. The Mahalanobis distance squared (D^2) is distributed as chi-square (χ^2) statistic with degree of freedom equal to the number of variables. A value of D^2 with a low p-value ($P < 0.001$) indicates multivariate outliers. The SPSS returned a Mahalanobis distance value of 57.544, the Chi-square value was obtained using Microsoft Excel. None of the variables had a $p < 0.001$, the assumption of absence of multivariate outliers was therefore satisfied.

Table 4-8: Skewness, Kurtosis and Collinearity Diagnostics after Transformation

	Before transformation				After transformation		
	Skewness		Kurtosis		Skewness	Kurtosis	Variance statistic
Variable (N = 200)	Statistic	Std. Error	Statistic	Std. Error			
Gender	-.348	.172	-1.898	.342	-.348	.172	.244
Age	1.601	.172	1.476	.342	1.24	-.113	.248
Marital status	1.728	.172	2.106	.342	1.402	.394	.113
N. children	2.157	.172	3.916	.342	1.64	.793	.172
Level of Education	-.417	.172	-.687	.342	-.417	-.687	
Employment status	.916	.172	-.897	.342	.916	.897	.677
Living situation	-2.887	.172	6.399	.342	-2.887	6.399	.082
Confidant	-2.032	.172	2.149	.342	-2.032	2.149	.125
Genotype	1.975	.172	1.921	.342	1.975	1.921	.128
N. Comorbidities	1.315	.172	.568	.342	.997	-.616	.149
HT	-2.010	.172	3.077	.342	-1.443	.391	.434
PF	-.320	.172	-.496	.342	-.320	-.496	.253
RP	-.129	.172	-1.440	.342	-.743	-.912	.568
RE	-.449	.172	-1.274	.342	.041	-1.711	.177
SF	-.317	.172	-1.041	.342	-.317	-1.041	.304
GH	-.579	.172	-.464	.342	.041	-1.121	.337
PHQ9	1.062	.172	.927	.342	-.316	-.924	.767
GAD7	.992	.172	.150	.342	.390	-.967	.171
PHQ15	1.168	.172	1.266	.342	-.072	-.271	.350
Overall Qol	-.781	.172	.146	.342	-.205	-1.006	.498
BPR	.289	.172	-.936	.342	.289	-.936	.802
MHR	.629	.172	-.380	.342	.198	-.180	.420
Income status	1.819	.172	1.321	.342	.874	-.901	.297
VTR	.551	.172	.180	.342	.551	.180	.688
DSEI					.130	-.146	.363

Notes: PF=Physical Functioning; RP=Role Physical; RE=Role Emotional; SF= Social Functioning; GH=General Health; HT= Health Transition; PHQ9=Patient Health Questionaire-9; GAD7=Generalised anxiety Disorde-7; PHQ15=Patient Health Questionnaire-15; BPR=reversed score of Bodily Pain; MHR=reversed score of Mental; VTR= reveserd score of Vitality; Health; DSEI=Disease sveverity index.

Linearity assumption. Figure 4-2 below shows that most of the variables are linearly related with one another.

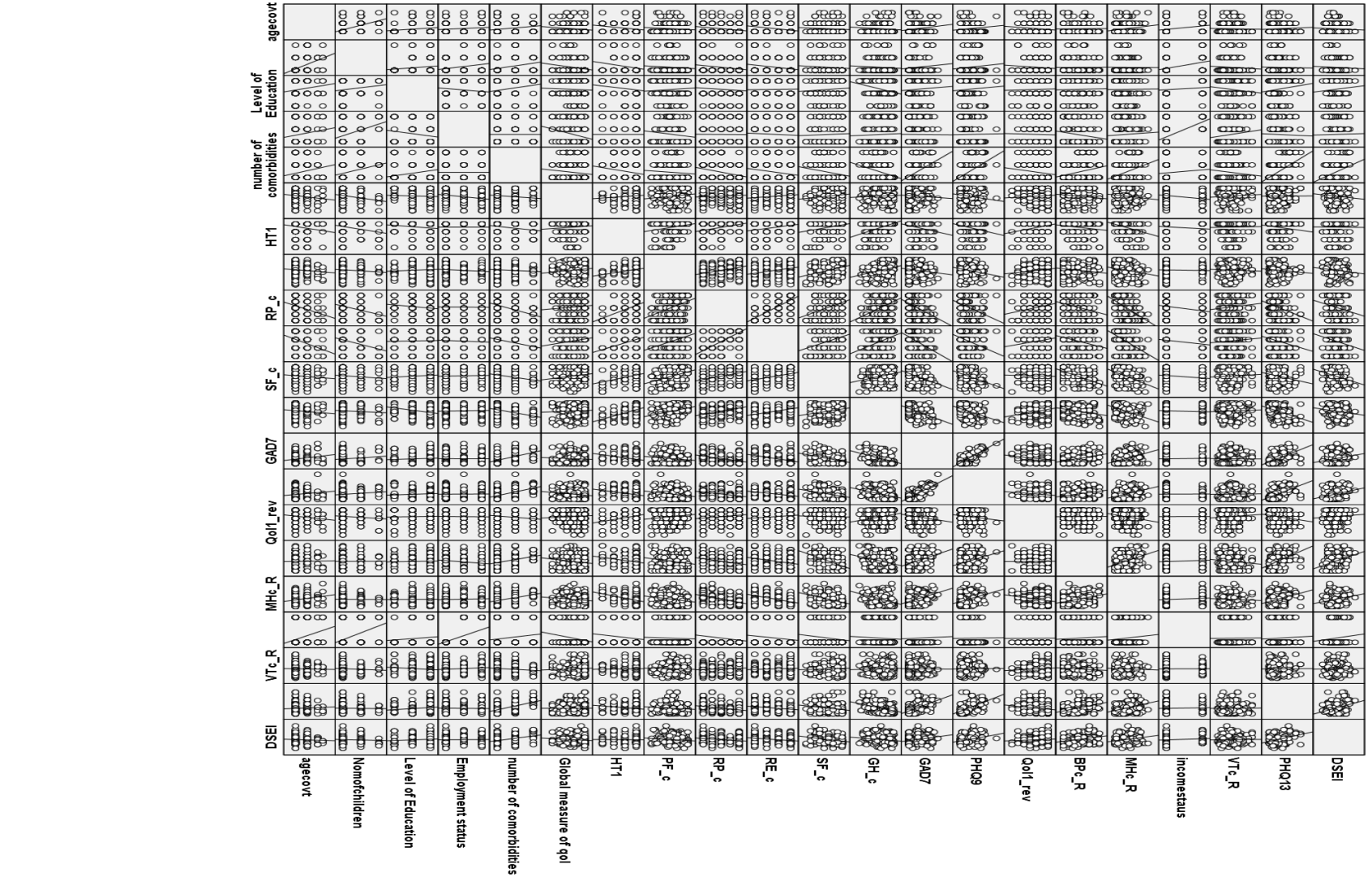


Figure 4-2: Linearity Test

Model Estimation

SEM with maximum likelihood (ML) estimation was implemented in AMOS 25 (IBM SPSS AMOS 25) to estimate the parameters of the model. The main *a priori* hypotheses were that bio-physiological factors would predict symptoms status which in turn would predict functional status and functional status would predict general health perception which in turn would predict overall quality of life. Additionally, both characteristics of the individual and characteristics of the environment would predict symptom status, functional status, general health perception and overall quality of life. AMOS provides estimates for the total effects, made up of both the direct effects (a path direct from one variable to another e.g. symptoms status → functional status) and the indirect effects (a path mediated through other variables e.g. symptom status → general health perceptions via functional status). Mediation was investigated using the bootstrap method.

SEM Bootstrapping

The bootstrap framework has been recommended as the best approach to test both direct and indirect effects in mediation models (MacKinnon *et al.*, 2002; Shrout and Bolger, 2002; Baker, 2007) even when sample sizes are small to moderate, 20-80 (Tibshirani and Efron, 1993). The presence of mediation was therefore assessed by testing the significance of the indirect effects using bias-corrected bootstrap confidence intervals.

Following Strout and Bolger techniques (Shrout and Bolger, 2002), 2000 bootstrap sampling was created (resampled from the original dataset) in order to derive less biased standard errors and 95% confidence interval (95% CI) bootstrap percentiles. The bias corrected 95% CI (BC95%CI) is reported. These have been shown to be more accurate even with small sample sizes (Tibshirani, 1984; Tibshirani and Efron, 1993).

Model Fit

The adequacy of the fit of the model was assessed by the Chi-square test statistic, together with the chi-square divided by its degree of freedom, the comparative fit index (CFI), the root-mean-square error of approximation (RMSEA) with 90% confidence interval (90% CI) and the standardised root mean residual (SRMR). Statements of the fitness of the model were based on the recommended threshold values of these indices (see Table 3.4).

4.11 The Pratt Index

The Pratt relative index was used to create the hierarchy of importance of the predictors. Several indices have been proposed for determining relative importance of predictor variables in regression models. Such indices include the Beta coefficients β, t-values, partial correlation and relative Pratt index. Pedhazur (1982) and Darlington (1990) has argued that beta weights and partial correlations lack proportionality and additive properties and hence should not be used to determine relative importance but recommended the use of partial correlations.

Pratt relative index because of its good additive properties and simplicity in interpretation has been shown to have advantage over the semi-partial correlation and has been recommended as the better index to use in determining relative importance and ordering of variables (Thomas, Hughes and Zumbo, 1998).

The relative Pratt index (Pratt, 1987) d_j in a regression equation is determined by the proportion of the variance in the criterion variable Y accounted for by X_j (a predictor variable). The value is computed from the product of the sample correlation and beta coefficient of a variable X_j from the standardized regression equation of the form:

$$Y = \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_j X_j + \beta_p X_p$$

The relative Pratt index d_j is obtained as

$d_j = \beta * | r | / R^2$.

d_j is the proportion of variance R^2 in the criterion variable accounted for by the predictor variable X_j. The relative Pratt index of the predictors sum up to one.

CHAPTER FIVE

RESULTS

5.0 Introduction

This chapter presents the findings of the study. The results are presented in line with the specific objectives and research questions of the study.

5.1 Characteristics of the sample

The socio-demographic characteristics of the participants are displayed in Table 5-1(a). Participants were made up of 41.5% male and 58.5% female. Seventy-three percent (73%) of participants were between 18 and 30 years of age and only 5 (2.5%) were above 50 years of age. About 3 out of 4 (75.5%) of the participants had never been married, 20.5% were married and 4% were either divorced, separated or widowed. Eighty-one percent (81%) had no child, 13% had one child while the remaining 6% had 5 (2.5%) and 7 (3.5%) children respectively. The HbSS genotype was found in 85% of the participants compared to 15% HbSC, there was no Hb thalassemia in the study population. The educational profile of the sample population was high with only 9.5% having below secondary education, while 48% had secondary education and 42.2% had tertiary education. However, only 36% indicated that they had full time or part time employment, and few, 16.5% were earning above the national minimum wage, 20% were earning below the minimum wage while 63.5% did not report having any income. Majority of the participants, 91%, were either living with relatives or friends. Most of the participants reported that they have confidants (85.5%). Most of the participants 87.5% were from the states in the south west, 7% from North central, 3% from south-south, 1.5% from south East and 1 % were non-Nigerians. The participants were distributed along religious groups with 52.5% Christians, 47% Muslims and 0.5% traditional worshippers.

Table 5-1: Characteristics of Study Participants

Demographic Variables	**All (N=200)** **n (percent)**	**Male (N = 83)** **n (percent)**	**Female (N= 117)** **n (percent)**
Age (Years)			
18-30	146 (73%)	56 (67.5%)	90 (76.9%)
31-40	41 (20.5%)	22 (26.5%)	19 (16.2%)
41-50	8 (4%)	4 (4.8%)	4 (3.4%)
Above 50	5 (2.5%)	1(1.2%)	4 (3.4%)
Genotype			
HbSS	170 (85%)	71(85.5%)	99 (84.6%)
HbSC	30 (15%)	12 (14.5%)	18 (15.4%)
Marital Status			
Never Married	151 (75.5%)	66 (79.5%)	85 (72.6%)
Married	41 (20.5%)	13 (15.7%)	28 (23.9%)
Others (separated, divorced, widowed)	8 (4%)	4 (4.8%)	4 (3.4%)
Education			
Primary	19 (9.5%)	3(3.6%)	16 (13.7%)
Secondary	97 (48.5%)	43 (51.8%)	54 (46.2%)
Post-secondary	84 (42%)	37 (44.6%)	47 (40.2%)
Employment status			
Not employed	127 (63.5%)	57 (68.7%)	70 (59.8%)
Part-time employment	30 (15%)	12 (14.5%)	18 (15.4%)
Full employment	43 (21.5%)	14 (16.9%)	29 (24.8%)
Income level			
No income	127 (63.5%)	57 (68.7%)	70 (59.8%)
Below minimum wage	40 (20%)	16 (19.3%)	24 (20.5%)
≥ Minimum wage	33 (16.5%)	10 (12%)	23 (19.7%)
Have Children			
No	182 (81%)	70 (84.3%)	92 (78.6%)
Yes	38 (17%)	13 (15.7%)	25 (21.4%)
Number of children			
0	162 (81%)	70 (84.3%)	92 (78.6%)
1-2	31 (15.5%)	10 (12.1%)	21 (17.9%)
≥ 3	7 (3.5%)	3 (3.6%)	4 (3.4%)
Living situation			
Living alone	18 (9%)	6 (7.2%)	12 (10.3%)
Living with others	182 (91%)	77 (92.8%)	105 (89.7%)
Have confidants			
No	29 (14.5%)	15 (18.1%)	14 (12%)
Yes	171 (84.5%)	68 (81.9%)	103 (88%)
Religion			
Christianity	105 (52.5%)	38 (45.8%)	67 (57.3%)
Islam	94 (47%)	45 (54.8%)	49 (41.9%)
Traditional	1 (0.5%)		1 (0.95)
Comorbidity			
No	135 (67.5%)	55 (66.3%)	80 (68.4%)
Yes	65 (32.5%)	28 (33.7%)	37 (31.6%)

One out of three participants (32.5%) indicated that they have been diagnosed to have comorbidities, the number of comorbidities ranged from 0 to 5 in the sample; the most prevalent comorbidity in the sample was leg ulcers (12.5%) followed by priapism (8.5%) and high blood pressure (8%). Other identified comorbidities were mostly pain-related, rheumatism, chest pain and back pain (See Table 5-2).

Table 5-2: Comorbidity by Type

Comorbid disease	Frequency	Percent
Asthma	8	4%
Arthritis	11	5.5%
Diabetes	6	3%
Epilepsy	3	1.5%
Heart disease	3	1.5%
High blood pressure	16	8%
Leg ulcers	25	12.5%
Lung disease	9	4.5%
Pneumonia	13	6.5%
Priapism	17	8.5%
Stroke	3	1.5%
Others	5	2.5%

5.1.1 Healthcare resources utilisation

In the 6 months preceding the data collection, 12.5% of the participants had visited emergency department 3 or more times, 15.5% twice, 55% once and 17% not at all. Eighty-five percent (85%) had been admitted into hospital at least once in the last six months while 97% reported experiencing pain at least once in the last six months, 35% had pain episode 3 or more times in the last six months. Also, 87% had SCD-related health issues at least once in the last six months and about 20% had blood transfusion more than once (see Table 5-3).

Table 5-3: Disease Severity/Healthcare Resources Utilisation in Adults with Sickle Cell Disease

	All (N=200) n (percent)	**Male (N = 83) n (percent)**	**Female (N= 117) n (percent)**
In the last 6 months:			
1. Visited emergency dept			
None	34 (17%)	18 (21.7%)	16 (13.7%)
Once	110 (55%)	38 (45.8%)	72 (61.5%)
Twice	31 (15.5%)	14 (16.9%)	17 (14.5%)
3 times	13 (6.5%)	10 (12%)	3 (2.6%)
More than 3 times	12 (6%)	3 (3.6%)	9 (7.7%)
2. Admitted to hospital			
None	30 (15%)	15 (18.1%)	15 (12.8%)
Once	98 (49%)	44 (53%)	54 (46.2%)
Twice	34 (17%)	13 (15.7%)	21 (17.9%)
3 times	19 (9.5%)	4 (4.8%)	15 (12.8%)
More than 3 times	19 (9.5%)	7 (8.4%)	12 (10.3%)
3. Have pain episodes			
None	6 (3%)	4 (4.8%)	2 (1.7%)
Once	50 (25%)	20 (24.1%)	30 (25.6%)
Twice	59 (29.5%)	30 (36.1%)	29 (24.8%)
3 times	35 (17.5%)	16 (19.3%)	19 (16.2%)
More than 3 times	50 (25%)	13 (15.7%)	37 (31.6%)
4. Have other SCD-related crisis	26 (13%)	11 (13.3%)	15 (12.8%)
None	101 (50.5%)	42 (50.6%)	59 (50.4%)
Once	30 (15%)	14 (16.9%)	16 (13.7%)
Twice	20 (10%)	7 (8.4%)	13 (11.1%)
3 times	23 (11.5%)	9 (10.8%)	14 (12%)
More than 3 times			
5. Have blood transfusion	34 (17%)	13 (15.7%)	21 (17.9%)
None	105 (52.5%)	49 (59%)	56 (47.9%)
Once	42 (21%)	14 (16.9%)	28 (23.9%)
Twice	15 (7.5%)	6 (7.2%)	9 (7.7%)
3 times	4 (2%)	1 (1.2%)	3 (2.6%)
More than 3 times			

5.1.2 Psychosocial status of study participants

Table 5-4 reveals that a significant number 131 (66.5%) of the participants indicated minimal or no anxiety (GAD7 < 5), 22.5% had mild anxiety, 11.5% had moderate anxiety and one person, reported severe anxiety. Signs of depression were found in 42.5% of the participants (PHQ9 ≥ 5); 23.5% was mild, 13.5% moderate and 5.5% were moderately severe or severe while 115 (57.5%) reported minimal or no depression. Forty percent of the participants indicated minimal or no somatic symptoms, 30.5% had low somatic symptoms, 16%

medium and 13.5% had high somatic symptoms, 19 (70.4%) of the 27 people with somatic symptoms were women.

Table 5-4: Level of Anxiety, Depression and Somatic Symptoms in Adults with Sickle Cell

	All (N=200)	**Male (N = 83)**	**Female (N= 117)**
	n (percent)	**n (percent)**	**n (percent)**
Anxiety (GAD-7)			
None/minimal anxiety	131 (65.5%)	59 (71.1%)	72 (61.5%)
Mild anxiety	45 (22.5%)	14 (16.9%)	31 (26.5%)
Moderate anxiety	23 (11.5%)	10 (12%)	13 (11.1%)
Severe anxiety	1 (0.5%)	-	1 (0.9%)
Depression (PHQ-9)			
None/minimal depression	115 (57.5%)	50 (60.2%)	65 (55.6%)
Mild depression	47 (23.5%)	20 (24.1%)	27 (23.1%)
Moderate depression	27 (13.5%)	10 (12%)	17 (14.5%)
Moderately severe depression	10 (5%)	3 (3.6%)	7 (6%)
Severe depression	1 (0.5%)	-	1 (0.9%)
Somatic symptoms (PHQ-15)			
None/minimal somatic	80 (40%)	44 (53%)	36 (30.8%)
symptoms	61 (30.5%)	21 (25.3%)	40 (34.2%)
Low somatic symptoms	32 (16%)	10 (12%)	22 (18.8%)
Medium somatic symptoms	27 (13.5%)	8 (9.6%)	19 (16.2%)
High somatic symptoms			

From Table 5-5, the mean age of participants was 27.9 (SD = 6.95). Although female participants appeared slightly older there was no statistical difference in age between genders ($p > 0.05$).

The means and standard deviations of the SF-36 domains in the SCD population are also displayed in Table 5-5. Higher scores represented better health. The best score was in Mental Health (above 70) while the worst scores were in the Role Physical and Physical Functioning (below 60). All the other domains; Bodily Pain, Vitality, General Health Role Emotional and Social Functioning had means scores between 60 and 70.

Table 5-5: Means and Standard Deviations of SF-36 and other Measure Instruments in the Sample.

	All Mean (SD)	**Male Mean (SD)**	**Female Mean (SD)**	**T-test**	**P value**
Age	27.88 (6.95)	28.40 (6.85)	27.51 (7.03)	0.892	0.374
SF-36 domains					
Physical Functioning (PF)	58.48 (25.14)	62.59 (23.55)	55.56 (25.92)	1.96	0.051
Bodily Pain (BP)	69.79 (22.39)	76.69 (19.23)	64.89 (23.24)	3.79	0.000
Vitality (VT)	63.05) 20.73)	64.28 (20.66)	62.18 (20.83)	0.70	0.462
General Health (GH)	67.13 (23.51)	63.61 (22.19)	69.62 (24.20	1.79	0.075
Role Physical (RP)	53.75 (38.40)	54.52 (36.03)	53.21 (40.14)	0.24	0.812
Role Emotional (RE)	61.5 (38.41)	64.26 (35.61)	59.54 (40.31)	0.85	0.394
Social Functioning (SF)	64.19 (27.59)	69.43 (26.28)	60.47 (27.99)	2.29	0.023
Mental Health (MH)	71.36 (20.85)	70.99 (19.32)	71.62 (21.95)	0.21	0.832
Physical Health Component Summary (PCS)	67.66 (13.18)	69.63 (12.82)	66.26 (13.27)	1.79	0.075
Mental Health Component Summary (MCS)	68.77 (15.91)	69.30 (15.08)	68.40 (16.52)	0.39	0.697
Health Transition (HT)	89.88 (20.22)	89.16 (19.98)	90.38 (20.4)	0.42	0.673
Others					
Global measure of QOL	5.44 (1.42)	5.55 (1.27)	5.36 (1.52)	0.96	0.339
Anxiety (GAD-7)	3.86 (3.91)	3.47 (3.92)	4.14 (3.89)	1.189	0.236
Depression (PHQ-9)	5.14 (4.70)	4.48 (4.35)	5.61 (4.89)	1.677	0.095
Somatic symptoms (PHQ-15)	7.48 (6.48)	5.88 (6.13)	8.61 (6.51)	2.989	0.003
Body Mass Index (BMI)	19.25(3.86)	18.81 (3.67)	19.56 (3.98)	1.1382	0.169
No of comorbidities	0.40 (0.63)	0.42 (0.65)	0.39 (0.63)	0.312	0.755
Disease Severity Index (DSEI)	7.97 (3.41)	7.52 (3.01)	8.29 (3.64)	1.587	0.114
Emergency dept visit	1.30 (1.02)	1.30 (1.05)	1.29 (1.00)	0.072	0.943
Admitted to hospital	1.495 (1.15)	1.33 (1.09)	1.62 (1.17	1.771	0.078
Frequency of pain	2.37 (1.19)	2.17 (1.11)	2.50 (1.23)	1.978	0.005
SCD-related crisis	1.57 (1.18)	1.53 (1.16)	1.59 (1.21)	0.350	0.727
Blood transfusion	1.25 (0.83)	1.19 (0.83)	1.29 (0.94)	0.761	0.448

The summary scores, Physical Component Scores (PCS) and Mental Health Scores (MCS) had means between 65 and 70 with no statistical significance difference between males and females. The mean global measure of quality of life was 5.44 (SD = 1.42).

The mean anxiety score was 3.86 (SD=3.91), depression 5.14 (SD=4.70) and somatic symptoms (PHQ15) was 7.48 (SD=6.48). Females reported worse anxiety, depression and somatic symptoms, these differences however were not significant except in somatic symptoms ($p< 0.05$). The female participants reported significantly higher frequency of pain than the male participants ($p < 0.05$).

The results of the study with respect to the objectives are outlined below.

5.2 Objective one.

To Describe the HRQL profile of adult living with sickle cell disease

5.2.1 Research Question 1:

What is the profile of Health-related quality of life in adults with sickle cell disease in the study area?

Norm-based scores of SF-36 in the study population

The norm-based scores of SF-36 were also compared with the conventional percentile score. (Table 5-6). The norm-based scores facilitated comparison with other populations based on 1988 US general population with mean 50, and standard deviation, 10 (Ware *et al.*, 2000; Ware, 2007). One subscale, Physical Functioning was below 40, three subscales; Social Functioning, Role Physical and Role Emotional were between 40 and 45. Furthermore, three subscales; General Health, Bodily pain and Mental health were between 45 and 50. The norm-based scores confirmed that the HRQL of SCD patients in Nigeria was significantly reduced compared to the norms in all the domains (all $p < 0.01$) except in vitality which was similar to the scores in the general population (mean = 50.96, SD=9.93, $p = 0.176$).

Table 5-6: Quality ofLlife Domain Scores of SF-36 in Adults with Sickle Cell Disease: Norm-based Scores versus Conventional Scores.

	Conventional score*		**Norm-based score****	
Scale	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
Physical Functioning (PF)	58.475	25.14	38.62	10.98
Role Physical (RP)	53.750	38.40	41.88	11.36
Role Emotional (RE)	61.50	38.41	44.01	11.63
Social Functioning (SF)	64.188	27.59	41.33	12.33
Bodily Pain (BP)	69.788	22.39	47.58	9.50
Vitality (VT)	63.05	20.73	50.96	9.93
Mental Health (MH)	71.36	20.85	48.07	11.58
General Health (GH)	67.125	23.51	47.48	11.66
Physical Component Summary (PCS)	67.66	13.18	42.61	8.07
Mental Component Summary (MCS)	68.77	15.91	48.25	10.07

* Score based on the 0-100 transformation

**Score based on US 1988 general population with mean 50 and SD 10.

Comparison of Southwest SCD patients and other reference groups on SF-36 Measure

Table 5-7 shows the comparison of the result in the current study with the hypertensive patients group in Southwest Nigeria. Sickle cell disease patients reported better health score in Physical Function, and Role Emotional, similar scores in Role Physical and Mental Health and lower scores in Social Functioning, Bodily Pain and Vitality than hypertensive patients in southwest Nigeria.

Table 5-7: Comparison of SF-36 HRQL Domains Scores between SCD Patients and Hypertension Patients in Southwest Nigeria.

SF-36 domains	**Hypertensive patients Southwest Nigeria[1] (N = 265)**		**SCD Southwest Nigeria N =200)**		**P**
	Mean	SD	Mean	SD	
Physical Functioning (PF)	33.53	29.65	58.48	25.14	0.000
Role Physical (RP)	54.66	40.36	53.75	38.40	0.806
Role Emotional (RE)	51.14	40.58	61.5	38.41	0.006
Social Functioning (SF)	75.19	22.97	64.19	27.59	0.000
Bodily Pain (BP)	76.28	30.17	69.79	22.39	0.000
Vitality (VT)	79.85	14.57	63.05	20.73	0.000
Mental Health (MH)	70.65	17.87	71.36	20.85	0.693
General Health (GH)	n/a	n/a	67.13	23.51	

Source: [1]Ogunlana et al., 2009

Sociodemographic variables and Health-related quality of life

The profile of HRQL in adults with SCD with respect to sociodemographic variables are displayed in Table 5-8

Age: Younger participants reported better health in 4 of the 8 domains of the SF-36 measure of HRQL namely, Role Physical, Role Emotional, General Health and Mental Health as well as in the mental health summary. Similar scores were reported in other domains by the different age groups.

Gender: Poorer health-related quality of life was observed for women in Bodily pain ($t = 3.806$, $p < 0.01$) and Social functioning ($t = 2.112$, $p < 0.05$). Though women recorded lower net scores in the other domains, they were not significant.

Marital Status: The result was similar for the group in all the domains except in Role Emotional where those never married reported better health ($p < 0.05$) than those married, separated, divorced or widowed

Education: Participants with higher education reported worse quality of life in Role Physical and General Health, no differences were observed in other domains of SF-36.

Employment: Participants in full-employment or part-time employment reported higher net scores in five domains which included Role physical, Social functioning, Bodily Pain, General Health and Vitality along with PCS and MCS but no statistical difference.

Living situation: In the Social Functioning domain, adults with SCD living with others reported better health ($p < 0.01$), while the HRQL appeared similar between those living alone and those living with others in the other domains. People living with others also reported better health in the mental health component summary score ($p < 0.01$).

Confidants: Participants who reported having confidants had better health scores in General Health and Mental health while the scores are similar in other domains of the SF-36.

Table 5-8: The Sociodemographic Profile of HRQL in Adults with Sickle Cell Disease

Variables	N	PF Mean ± SD	RP Mean ± SD	RE Mean ± SD	SF Mean ± SD	BP Mean ± SD	VT Mean ± SD	GH Mean ± SD	MH Mean ± SD	PCS Mean ± SD	MCS Mean ± SD
Age											
18-30	146	59.35±26.29	60.27±36.75	68.95±36.23	66.10±27.23	70.53±22.86	62.57±21.63	69.66±23.17	73.78±20.42	68.49±13.0	71.03±15.9
Above 30	54	56.11±21.79	36.11±37.51	41.36±37.16	59.03±28.15	67.78±21.13	64.35±18.20	60.28±23.28	54.81±20.77	0	6
T-test, P		0.81, 0.42	4.11, 0.00	4.75, 0.00	1.62, 0.11	0.77, 0.44	0.54, 0.59	2.54, 0.012	2.74, 0.013	65.42±13.5	62.66±14.1
Cohen's d		0.1	0.7	0.8	0.3	0.1	0.1	0.4	0.4	2	8
(ES)										1.47, 0.14	3.39, 0.00
										0.2	0.5
Gender											
Male	83	62.59±23.55	54.52±36.03	64.26±35.61	69.43±26.28	76.69±19.23	64.28±20.66	63.61±22.19	70.99±19.32	69.63±12.8	69.30±15.0
Female	117	55.56±25.92	53.21±40.14	59.54±40.31	60.47±27.99	64.89±23.24	62.18±20.83	69.62±24.20	71.62±21.95	2	8
T-test (T), P		1.96, 0.051	0.24, 0.812	0.85, 0.394	2.29, 0.023	3.79, 0.000	0.70, 0.462	1.79, 0.075	0.21, 0.832	66.26±13.2	68.40±16.5
Cohen's d		0.3	0.3	0.1	0.3	0.6	0.1	0.3	0.03	7	2
(ES)										1.79, 0.075	0.39, 0.697
										0.3	0.1
Marital Status	151	60.07±25.35	57.28±38.69	65.34±37.49	65.73±27.48	69.32±23.38	61.92±21.5	67.12±24.35	71.50±21.10	68.21±13.4	69.29±16.3
Never	41	54.87±24.76	43.90±37.82	49.59±40.91	58.54±28.29	71.10±19.68	64.88±18.52	67.56±21.00	72.88±17.94	4	6
married	8	46.87±20.34	37.5±23.15	50.00±30.86	64.06±25.39	71.88±17.41	75.00±11.95	65.00±22.04	61.00±28.98	68.17±12.7	67.25±13.7
Married		1.58, 0.208	2.75, 0.066	3.15, 0.045	1.09, 0.336	0.14, 0.872	1.73, 0.181	0.04, 0.961	1.10, 0.335	7	9
Others										64.85±10.3	66.74±16.6
Anova (F), P										5	3
										0.57, 0.565	0.33, 0.718
Num of child.	162	59.26±25.04	57.25±37.97	65.23±37.59	65.35±27.38	69.68±22.40	62.81±21.09	67.41±23.56	71.33±21.48	68.16±13.1	69.39±16.1
0	31	56.77±27.25	45.55±35.92	51.61±36.35	59.68±28.08	71.29±24.09	65.16±20.23	69.19±21.68	71.10±19.59	4	7
1-2	7	47.86±16.55	17.86±37.40	19.05±37.80	57.14±31.34	65.71±14.91	59.29±15.12	51.43±27.95	73.14±10.76	67.22±13.2	66.86±14.9
≥ 3		0.77, 0.463	5.02, 0.007	6.40, 0.002	0.79, 0.457	0.19, 0.830	0.29, 0.752	1.70, 0.185	0.03, 0.972	5	3
Anova (F), P										57.94±11.7	62.92±13.9
										0	5
										2.06, 0.130	0.82, 0.443

Notes: PF – Physical Functioning; RP – Role Emotional; SF- Social Functioning; BP- Bodily Pain; VT- Vitality; GH- General Health; MH- Mental Health; PCS – Physical Health Component Summary Score; MCS – Mental Health Summary Score

Table 5-8 cont: The Sociodemographic Profile of HRQL in Adults with Sickle Cell Disease

Variables		PF Mean ± SD	RP Mean ± SD	RE Mean ± SD	SF Mean ± SD	BP Mean ± SD	VT Mean ± SD	GH Mean ± SD	MH Mean ± SD	PCS Mean ± SD	MCS Mean ± SD
Employment											
Full-Time	43	53.49±18.24	56.98±38.70	60.47±42.57	68.02±26.91	77.15±22.58	63.60±22.07	69.30±24.77	70.98±20.71	68.90±10.83	69.32±16.15
Part-time	30	57.67±23.03	42.50±39.47	52.22±40.76	58.75±32.36	67.83±21.01	64.33±19.60	65.50±24.01	66.67±26.08	66.64±13.01	64.97±18.88
Not employed	127	60.35±27.44	55.32±37.88	64.04±36.27	64.17±26.60	67.76±22.28	62.56±20.67	66.77±23.10	72.60±19.50	67.48±13.98	69.49±15.06
Anova (F), P		1.22, 0.298	1.55, 0.214	1.17, 0.312	0.998, 0.37	3.02, 0.051	0.11, 0.898	0.27, 0.765	0.99, 0.373	0.29, 0.749	1.01, 0.365
Living situation											
Alone	18	54.44±26.17	54.17±38.59	50.00±44.65	44.44±23.18	65.56±17.83	61.39±19.69	67.50±19.87	62.44±22.88	68.62±11.21	59.43±15.22
With others	182	58.87±25.08	53.71±38.49	62.64±37.68	66.14±27.27	70.21±22.79	63.21±20.88	67.09±23.89	72.24±20.50	67.57±13.38	69.70±15.71
T-test (T), P		0.72, 0.477	0.05, 0.962	1.33, 0.184	3.26, 0.001	0.84, 0.402	0.36, 0.723	0.07, 0.944	1.91, 0.057	0.32, 0.747	2.65, 0.009
Cohen's d (ES)		0.2	0.0	0.3	0.8	0.2	0.1	0.0	0.5	0.1	0.7
Confidants											
Yes	171	59.24±25.14	54.82±38.194	62.18±38.08	65.42±27.135	68.86±22.037	63.45±20.376	68.83±22.32	72.75±20.136	67.88±13.00	69.67±15.85
No	29	53.97±25.16	7.41±39.72	57.47±40.72	6.90±29.62	5.26±24.09	0.69±23.02	57.07±27.95	3.17±23.41	66.38±14.36	63.49±15.47
T-test (T), P		0.84, 0.297	0.86, 0.338	0.42, 0.543	0.48, 0.124	0.64, 0.155	0.66, 0.509	2.52, 0.012	2.31, 0.022	0.57, 0.573	1.95, 0.053
Cohen's d (ES)		0.2	0.2	0.1	0.3	0.3	0.1	0.5	0.5	0.1	0.4

Notes: PF – Physical Functioning; RP – Role Emotional; SF- Social Functioning; BP- Bodily Pain; VT- Vitality; GH- General Health; MH- Mental Health; PCS – Physical Health Component Summary Score; MCS – Mental Health Summary Score.Effects sizes were calculated using a website calculator www.psychometrica.de/effect_size.htm assessed 17/05/2018

Clinical and Psychosocial variables and Health-related quality of life

Table 5-9 displays the profile of HRQL in adults with SCD with respect to the clinical and psychosocial variables.

Genotype: There was no significant difference between the genotypes though net scores were higher in participants with the HbSC genotype in all the domains apart from Bodily Pain.

Comorbidity: Participants who reported to have a comorbid disease expressed worse scores in 6 HRQL domains; Role physical, Role Emotional Social Functioning, Bodily Pain, General Health, Mental Health (all $p < 0.01$) and in the Physical health Component Summary scores and the Mental Health component Summary scores ($p < 0.01$)

Anxiety: Twelve percent of the participants had high symptoms of anxiety (GAD7 ≥10). They expressed worse ($p < 0.01$) health in 7 of the 8 HRQL domains and the summary scores PCS and MCS. Only in Physical Functioning was the score similar.

Depression: Moderate to severe symptoms of depression (PHQ9 ≥ 10) was reported in 19% of the participants. High depressive symptoms reduced the HRQL in 7 of the domains of HRQL and towards low HRQL in Physical Functioning (P=0.055)

Somatic Symptoms: High somatic symptoms (PHQ15 ≥15) was reported in 13.5% of the patients. Participants with somatic symptoms reported worse health in all the HRQL domains, the summary scores PCS and MCS except physical Functioning and Role Emotional.

Healthcare Utilisation: Utilisation of healthcare facilities also reflected a deteriorating quality of life; high emergency department utilizers had lower quality of life in Functioning, General Health and Mental Health. In addition, high rate of hospital admission associated with worse quality of life in Role Physical, Role Emotional, Social Functioning, Bodily Pain,

General Health, Mental Health and the summary scores but similar in Physical Functioning and Vitality ($p > 0.05$).

Table 5-9: Clinical and Psychosocial Profile of HRQL in Adults with Sickle Cell Disease.

Variables	N	PF Mean ± SD	RP Mean ± SD	RE Mean ± SD	SF Mean ± SD	BP Mean ± SD	VT Mean ± SD	GH Mean ± SD	MH Mean ± SD	PCS Mean ± SD	MCS Mean ± SD
Genotype											
SS	170	57.32±24.85	52.94±37.77	61.37±38.61	63.31±28.04	70.90±21.92	62.24±21.35	67.00±24.14	70.92±21.55	67.48±13.01	68.40±16.54
SC	30	65.00±26.23	58.33±42.21	62.22±37.89	69.17±24.73	63.5±24.31	67.67±16.33	67.83±19.90	73.87±16.43	68.70±14.29	70.86±11.72
T-test (T), P		1.55, 0.123	0.71, 0.480	0.11, 0.911	1.07, 0.285	1.68, 0.095	1.32, 0.187	0.18, 0.858	0.71, 0.476	0.47, 0.640	0.78, 0.437
Comorbidity											
No	135	59.74±25.67	62.59±36.63	68.89±37.37	68.43±27.27	73.50±21.82	64.89±22.30	72.89±22.10	76.18±19.95	69.86±12.61	72.47±15.25
Yes	65	55.85±23.99	35.38±35.60	46.15±36.18	55.38±26.33	62.08±21.72	59.23±16.54	55.15±21.92	61.35±19.19	63.09±13.26	61.10±14.54
T-test (T), P		1.03, 0.306	4.96, 0.000	4.07, 0.000	3.20, 0.00	3.47, 0.001	1.82, 0.071	5.33, 0.000	4.98, 0.000	3.5, 0.001	5.01, 0.000
Anxiety											
Low	176	59.46±25.67	56.68±37.91	64.29±37.88	66.83±27.15	71.34±22.30	64.38±20.82	68.52±22.47	73.14±20.62	68.67±12.93	70.37±15.60
High	24	51.25±19.90	32.29±35.72	41.67±37.11	44.79±22.99	58.44±19.97	53.33±17.55	49.58±24.04	58.33±18.00	60.22±12.89	57.03±13.24
T-test (T), P		1.51, 0.134	2.98, 0.003	2.74, 0.007	3.79, 0.000	2.69, 0.008	2.48, 0.014	4.04, 0.000	3.35, 0.001	3.01, 0.003	4.00, 0.000
Depression											
Low	162	60.12±25.51	56.64±37.67	64.61±37.09	69.98±26.61	71.59±21.98	65.59±20.74	69.78±22.49	73.60±20.77	68.87±13.08	70.97±15.37
High	38	51.45±22.51	41.45±39.54	48.25±41.51	48.03±26.08	62.11±22.78	52.24±17.07	55.79±24.70	61.79±18.57	62.52±12.50	59.41±14.91
T-test (T), P		1.92, 0.055	2.22, 0.026	2.39, 0.018	4.18, 0.000	2.38, 0.018	3.68, 0.000	3.39, 0.001	3.22, 0.002	2.72, 0.007	4.19, 0.000
Somatic symptoms											
Low	173	59.71±25.68	57.37±37.45	63.20±38.39	67.05±26.93	72.73±21.43	65.09±20.58	70.49±21.72	74.17±19.84	69.27±12.66	70.59±15.41
High	27	50.56±20.02	30.56±36.91	50.62±37.41	45.83±25.00	50.93±19.24	50.00±16.87	45.56±23.47	53.33±18.23	57.35±11.95	57.11±14.27
T-test (T), P		1.77, 0.078	3.47, 0.000	1.56, 0.114	3.84, 0.000	4.98, 0.000	3.62, 0.000	5.49, 0.000	5.13, 0.000	4.59, 0.000	4.27, 0.000
Emergency Dept											
Utilisation	175	59.14±25.45	55.43±42.00	63.43±38.27	66.21±27.67	70.70±22.16	63.17±20.90	68.43±23.25	73.30±20.33	68.03±13.21	70.13±15.93
Low	25	53.80±22.79	42.00±37.31	48.00±37.37	50.00±22.82	63.40±23.38	62.20±19.90	58.00±23.76	57.76±19.67	65.09±12.91	59.28±12.30
High		0.99, 0.324	1.64, 0.102	1.89, 0.06	2.80, 0.006	1.53, 0.128	0.22, 0.827	2.09, 0.038	3.59, 0.000	1.04, 0.299	3.27, 0.001
T-test (T), P											
Hosp											
Admission	162	59.35±25.07	57.87±37.12	65.23±37.224	66.36±27.91	72.84±22.295	63.67±21.62	69.04±23.12	74.17±20.16	68.76±12.78	70.67±15.70
Low	38	54.74±25.44	36.18±39.29	5.61±39.84	54.93±24.41	6.78±17.88	60.39±16.41	58.95±23.71	59.37±16.70	62.99±13.98	60.69±14.33
High		1.02, 0.310	3.21, 0.002	2.89, 0.004	2.32, 0.021	4.14, 0.000	0.88, 0.382	2.41, 0.017	4.09, 0.000	2.46, 0.015	3.58, 0.000
T-test (T), P											

Notes: PF – Physical Functioning; RP – Role Emotional; SF- Social Functioning; BP- Bodily Pain; VT- Vitality; GH- General Health; MH- Mental Health; PCS – Physical Health Component Summary Score; MCS – Mental Health Summary Score

Clinical, psychosocial land HRQL profile in the study population

Table 5-10 presents the impact of the comorbid diseases on HRQL of adults with SCD. Sickle cell patients who also had arthritis reported limitations in Role Physical, Role Emotional, Bodily Pain, Mental Health and Mental Health Summary compared to those who did not have arthritis. Participants who had asthma reported similar health status with those who did not have asthma. Participants with diabetes had worse General Health compared with those who did not have diabetes. Epilepsy was associated with worse mental Health in the population. Patients who had hypertension had worse scores in Role Physical, Bodily Pain, Vitality, General Health, Mental health and in both the Physical and Mental health Summary scores. Leg ulcers was associated with reduced quality of life in all the domains including the summary scores except in vitality where the health status appeared similar. Participants who had pneumonia reported worse scores in Physical Functioning, Social Functioning, Bodily Pain, Vitality, General health, Mental Health and the Summary scores. Priapism was responsible for worse Mental Health and Mental Component Summary Score. Stroke associated with reduced Physical Functioning.

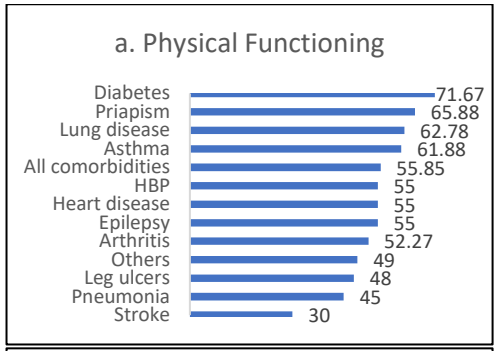
Figure 5-1 (a – j) show the HRQL profile of the participants with respect to reported comorbid diseases. Participants with leg ulcers reported the lowest mean quality of life scores in role physical, role emotional and bodily pain and consistently low in other HRQL domains. In addition, participants with epilepsy, pneumonia, arthritis, high blood pressure and stroke reported low scores in most of the HRQL domains. Participants with epilepsy reported lowest scores in social functioning and mental health.

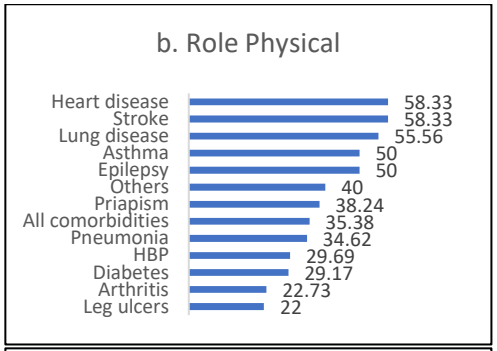
Table 5-10: Comorbid Diseases and HRQL Domains in the Study Population.

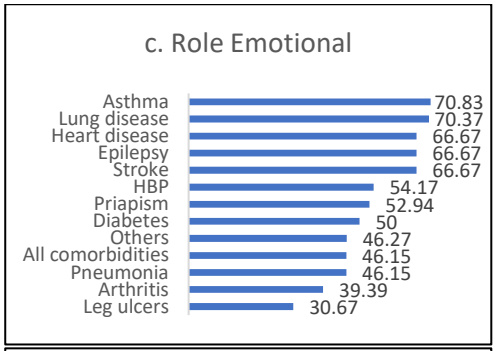
Disease		N	PF	RP	RE	SF	BP	VT	GH	MH	PCS	MCS
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Arthritis	No	189	58.84±25.65	55.56±38.45	62.79±38.70	65.08±27.67	70.58±22.59	63.28±21.06	67.51±24.00	2.32±20.905	68.01±13.3	69.44±16.0
	Yes	11	52.27±12.92	22.73±20.78	39.39±25.03	48.86±21.98	56.14±12.96	59.09±14.11	60.45±11.06	.91±11.18	4	8
			0.84, 0.401	2.80, 0.006	1.98, 0.049	1.91, 0.058	2.10, 0.037	0.65, 0.516	0.97, 0.334	2.74, 0.007	61.61±8.39	57.30±4.42
											1.57, 0.118	2.36, 0.034
Asthma	No	192	58.33±25.52	53.91±38.60	61.11±38.79	64.39±27.625	70.04±22.396	62.94±21.046	67.53±23.575	71.77±20.9	67.73±13.2	68.88±16.0
	Yes	8	61.88±13.87	50.00±35.36	70.83±27.82	9.38±28.15	3.75±22.95	5.63±11.48	7.50±21.04	2	265.97±13.	466.24±12.
			0.39, 0.697	0.28, 0.779	0.70, 0.484	0.50, 0.616	0.78, 0.438	0.36, 0.721	1.18, 0.238	61.50±17.2	03	96
										3	0.37, 0.713	0.46, 0.647
										1.37, 0.173		
Diabetes	No	194	58.07±25.31	54.51±38.54	61.86±38.39	64.11±27.90	69.83±22.67	63.17±20.76	68.07±22.92	71.71±20.9	67.76±13.2	69.01±15.9
	Yes	6	71.67±14.72	29.17±24.58	50.00±40.82	66.67±15.14	68.33±10.57	59.17±21.31	36.67±24.01	1	764.28±10.	4
			1.31, 0.193	1.60, 0.112	0.74, 0.458	0.22, 0.824	0.16, 0.872	0.47, 0.642	3.30, 0.001	60.00±16.2	35	61.12±13.7
										0	0.64, 0.524	7
										1.36, 0.176		1.20, 0.232
Epilepsy	No	197	58.53±25.33	53.81±38.69	61.42±38.69	64.59±27.60	69.82±22.56	63.07±20.89	67.08±23.68	71.72±20.8	67.62±13.2	68.98±15.9
	Yes	3	55.00±0.00	50.00±0.00	66.67±0.00	37.50±0.00	67.50±0.00	61.68±2.89	70.00±5.00	1	8	455.46±0.5
			0.24, 0.810	0.17, 0.865	0.23, 0.815	1.70, 0.091	0.18, 0.859	0.12, 0.908	0.21, 0.832	48.00±0.00	70.36±1.01	2
										1.97, 0.05	0.36, 0.722	1.46, 0.145
Hyperten	No	184	58.78±25.44	55.84±38.36	62.14±38.77	64.88±28.18	71.02±22.27	64.35±20.87	69.35±22.76	73.15±20.3	68.43±13.0	69.76±15.8
sion	Yes	16	55.00±21.83	29.69±30.58	54.17±34.16	56.25±18.26	55.63±19.14	48.13±11.53	41.56±15.99	0	8	4
			0.58, 0.566	2.65, 0.009	0.80, 0.427	1.20, 0.231	2.68, 0.008	3.07, 0.002	4.78, 0.000	50.75±15.7	58.83±11.2	57.48±12.2
										8	4	4
										4.30, 0.000	2.84, 0.005	3.02, 0.003
Heart	No	197	58.53±25.29	53.68±38.50	61.42±38.55	64.59±27.57	69.99±22.47	62.99±20.82	67.18±23.38	71.49±20.8	67.70±13.2	68.86±15.9
disease	Yes	3	55.00±15.00	58.33±38.19	66.67±33.33	37.50±12.50	56.67±11.27	66.67±16.07	63.33±37.53	6	0	7
			0.24,0.810	0.21, 0.836	0.23, 0.815	1.70, 0.091	1.02, 0.308	0.30, 0.762	0.28, 0.779	62.67±22.0	65.26±13.9	62.91±11.5
										3	1	8
										.073, 0.468	0.32, 0.752	0.64, 0.522
Leg	No	175	59.97±24.37	58.29±36.98	65.91±37.13	66.71±26.52	72.51±21.27	63.37±21.06	68.37±23.10	73.44±19.9	68.88±12.4	70.42±15.3
ulcers	Yes	25	48.00±28.36	22.00±33.32	30.67±33.22	45.50±28.98	50.70±21.04	60.80±18.52	58.40±25.03	6	8	2
			2.25, 0.026	4.64, 0.000	4.49, 0.000	3.52, 0.001	4.80, 0.000	0.58, 0.563	2.00, 0.047	56.80±21.5	59.11±14.9	57.25±15.4
										4	9	4
										3.86, 0.000	3.57, 0.000	4.01, 0.000

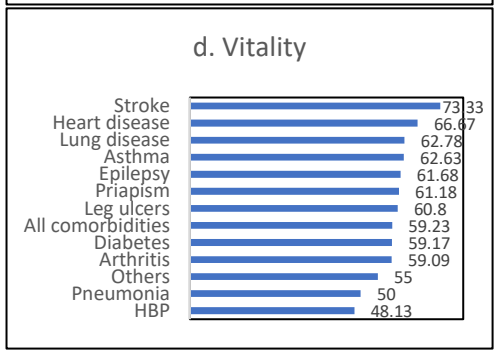
Lung disease	No	191	58.27±25.57	53.66±38.56	61.08±38.59	64.40±27.60	69.92±22.70	63.06±21.09	67.43±23.37	71.75±20.88	67.64±13.29	68.92±16.00
	Yes	9	62.78±13.250	55.56±37.03	70.37±35.14	59.72±28.49	66.94±14.99	62.78±11.49	60.56±27.09	63.11±19.47	68.15±11.22	65.68±14.17
			.52, 0.601	0.14, 0.886	0.71, 0.480	0.50, 0.620	0.39, 0.698	0.04, 0.968	0.86, 0.392	1.22, 0.225	0.11, 0.909	0.60, 0.552
Pneumonia	No	187	59.41±25.21	55.08±38.29	62.57±38.66	65.71±27.64	71.03±22.30	63.96±20.86	68.96±22.56	72.56±20.49	68.47±12.96	69.63±15.88
	Yes	13	45.00±20.62	34.62±36.14	46.15±32.03	42.31±14.91	51.92±15.28	50.00±13.69	40.77±21.78	53.85±18.66	55.94±10.91	56.38±10.40
			2.01, 0.045	1.87, 0.063	1.49, 0.137	3.01, 0.003	3.04, 0.003	2.37, 0.019	4.37, 0.000	3.20, 0.002	3.40, 0.001	2.96, 0.003
Priapism	No	183	57.79±25.60	55.19±38.70	62.30±39.29	64.48±27.96	70.11±22.27	63.22±21.19	67.54±24.26	72.48±21.06	67.55±13.29	69.50±16.18
	Yes		65.88±18.56	38.24±32.01	52.94±26.51	61.03±23.75	66.32±24.03	61.18±15.26	62.65±12.64	59.29±13.95	68.82±12.24	60.92±9.83
			1.27, 0.205	1.75, 0.082	0.96, 0.338	0.49, 0.623	0.67, 0.506	0.39, 0.698	0.80, 0.413	2.53, 0.012	0.38, 0.706	2.15, 0.033
Stroke	No	197	58.91±24.84	53.68±38.50	61.42±38.55	64.28±27.61	69.59±22.39	62.89±20.82	67.34±23.25	71.11±20.87	67.83±13.08	68.58±15.90
	Yes	3	30±34.64	58.33±38.19	66.67±33.3	58.33±31.46	82.50±22.22	73.33±10.41	53.33±41.63	88.00±12.00	56.23±17.90	81.26±12.45
			.99, 0.048	0.21, 0.836	0.23, 0.8153	0.37, 0.712	0.99, 0.323	0.87, 0.388	1.02, 0.307	1.40, 0.164	81.52, 0.131	1.37, 0.172

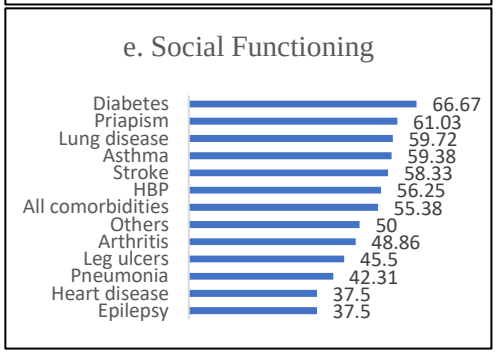
Notes: PF – Physical Functioning; RP – Role Emotional; SF- Social Functioning; BP- Bodily Pain; VT- Vitality; GH- General Health; MH- Mental Health; PCS – Physical Health Component Summary Score; MCS – Mental Health Summary Score

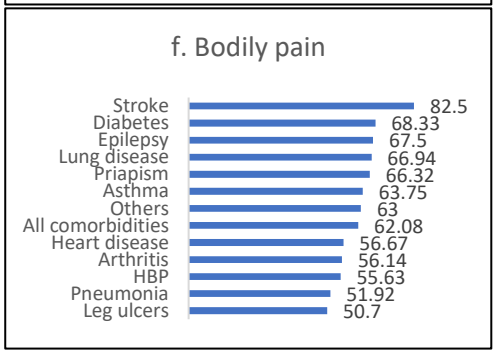

a. Physical Functioning
Diabetes 71.67
Priapism 65.88
Lung disease 62.78
Asthma 61.88
All comorbidities 55.85
HBP 55
Heart disease 55
Epilepsy 55
Arthritis 52.27
Others 49
Leg ulcers 48
Pneumonia 45
Stroke 30


b. Role Physical
Heart disease 58.33
Stroke 58.33
Lung disease 55.56
Asthma 50
Epilepsy 50
Others 40
Priapism 38.24
All comorbidities 35.38
Pneumonia 34.62
HBP 29.69
Diabetes 29.17
Arthritis 22.73
Leg ulcers 22


c. Role Emotional
Asthma 70.83
Lung disease 70.37
Heart disease 66.67
Epilepsy 66.67
Stroke 66.67
HBP 54.17
Priapism 52.94
Diabetes 50
Others 46.27
All comorbidities 46.15
Pneumonia 46.15
Arthritis 39.39
Leg ulcers 30.67


d. Vitality
Stroke 73.33
Heart disease 66.67
Lung disease 62.78
Asthma 62.63
Epilepsy 61.68
Priapism 61.18
Leg ulcers 60.8
All comorbidities 59.23
Diabetes 59.17
Arthritis 59.09
Others 55
Pneumonia 50
HBP 48.13


e. Social Functioning
Diabetes 66.67
Priapism 61.03
Lung disease 59.72
Asthma 59.38
Stroke 58.33
HBP 56.25
All comorbidities 55.38
Others 50
Arthritis 48.86
Leg ulcers 45.5
Pneumonia 42.31
Heart disease 37.5
Epilepsy 37.5


f. Bodily pain
Stroke 82.5
Diabetes 68.33
Epilepsy 67.5
Lung disease 66.94
Priapism 66.32
Asthma 63.75
Others 63
All comorbidities 62.08
Heart disease 56.67
Arthritis 56.14
HBP 55.63
Pneumonia 51.92
Leg ulcers 50.7

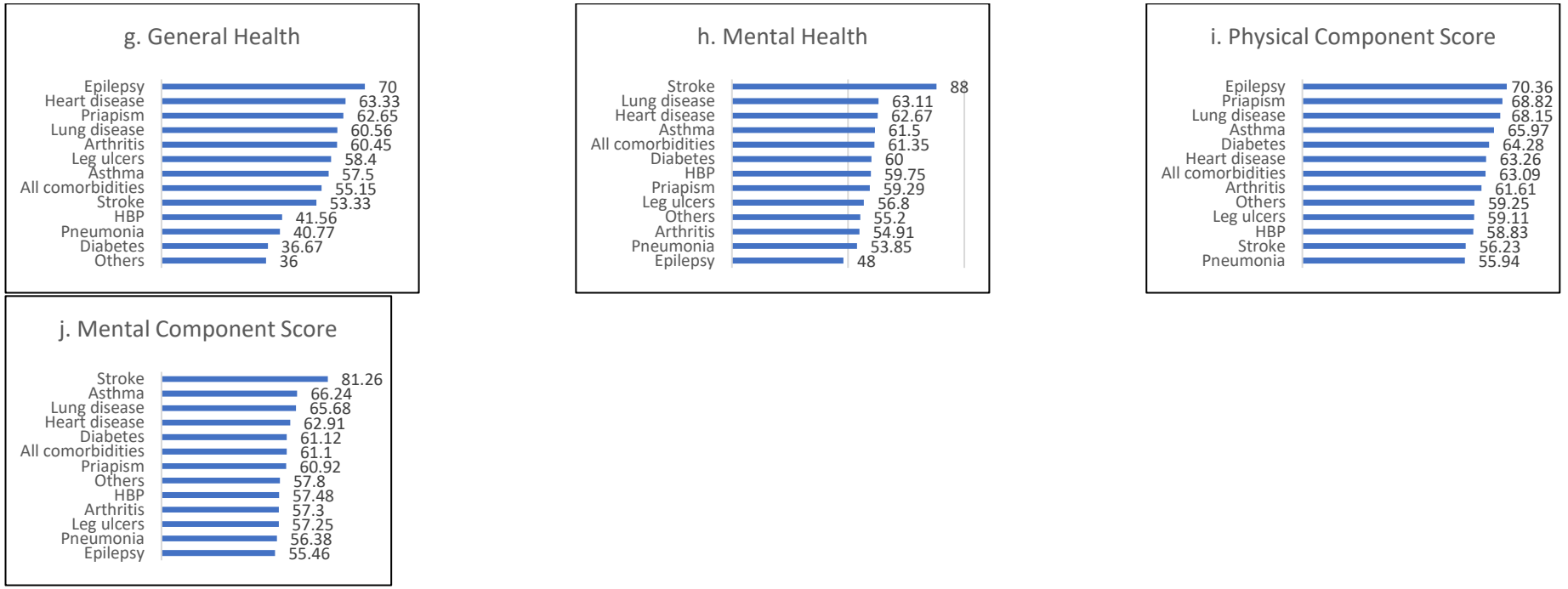


Figure 5-1: Profile of Domains Related to Disease

Charcteristics of psychsoscial factors in the study population

Participants reported their anxiety, depression and somatic symptoms (Table 5-11). Younger participants showed less anxiety and depression, but similar somatic symptoms compared to those between ages 31 and 50 years (Table 5-11). While depression increases with age from 18 years to 50 years ($F = 5.98$, $P < 0.01$). Participants above 50 years reported less anxiety and depression with similar somatic symptoms compared with those in ages between 31 and 50 years. Participants with comorbidities experience significantly worse anxiety, depression and somatic symptoms compared to those who reported no comorbidities ($P < 0.001$). The worst expression of somatic symptoms was found among those with comorbidities (mean = 11.65, SD=7.81).

Table 5-11: Anxiety, Depression and Somatic Symptoms in the Study Population

	N	GAD-7 Mean ± SD	PHQ-9 Mean ± SD	PHQ-15 Mean ± SD
Age				
18-30	146	3.35±3.64	4.61±4.53	7.04±6.65
31-40	41	5.34±4.03	7.05±4.22	9.37±6.25
41-50	8	7.25±5.37	6.13±8.18	7.75±3.99
Above 50	5	1.20±1.79	3.4±2.41	4.20±3.27
Anova, P		5.98, 0.001	3.34, 0.020	1.83, 0.142
Gender				
Male	83	3.47±3.92	4.48±4.35	5.88±6.13
Female	117	4.14±3.89	5.61±4.89	8.61±6.51
T-test (T), P		1.19, 0.236	1.68, 0.095	2.99, 0.003
Marital Status				
Never married	151	3.72±3.87	4.87±4.75	7.66±6.71
Married	41	4.20±3.81	5.98±4.77	7.14±6.12
Others (divorced, separated, widowed)	8	4.88±5.33	6.00±2.45	5.75±3.49
Anova (F), P		0.52, 0.595	1.04, 0.356	0.39, 0.676
Number of children				
0	162	3.79±3.91	4.98±4.74	7.43±6.45
1-2	31	3.13±3.10	5.12±4.33	7.87±7.12
≥ 3	7	8.71±4.46	9.00±4.24	6.71±4.57
Anova (F), P		6.27, 0.002	2.50, 0.085	0.11, 0.897
Education				
≤ Primary	19	6.00±4.06	7.84±6.17	10.58±7.21
Secondary	97	2.65±3.26	3.61±3.64	5.07±4.03
Post-secondary	84	4.77±4.15	6.30±4.85	9.55±6.48
Anova (F), P		10.73, 0.000	12.07, 0.000	14.98, 0.000
Employment				
Full-Time	43	3.67±4.03	5.14±4.95	7.33±1.12
Part-time	30	4.23±4.42	5.47±5.13	7.03±1.28
Not employed	127	3.83±3.77	5.06±4.54	6.07±0.54
Anova (F), P		0.19, 0.830	0.09, 0.915	0.31, 0.732
Living situation				
Alone	18	4.94±4.58	8.39±5.77	7.94±5.66
With others	182	3.75±3.84	4.82±4.47	7.43±6.57
T-test (T), P		1.23, 0.219	3.15, 0.002	0.32, 0.748
Confidants				
Yes	171	3.76±3.79	4.94±4.45	7.68±6.72
No	29	4.45±4.62	6.31±5.88	6.28±4.79
T-test (T), P		0.88, 0.383	1.46, 0.147	1.08, 0.282
Genotype				
HbSS	170	3.91±3.93	5.20±4.83	7.45±6.39
HbSC	30	3.60±3.86	4.80±3.93	7.53±7.12
T-test (T), P		0.39, 0.694	0.43, 0.668	0.05, 0.958
Comorbidity				
No	135	2.44±2.86	3.59±3.59	5.46±4.55
Yes	65	6.82±4.16	8.37±5.09	11.66±7.81
T-test (T), P		8.69, 0.000	7.67, 0.00	7.08, 0.000

5.3 Objective two.

To Characterize predictors of HRQL in adults with sickle cell disease

5.3.1 Research Question 2:

What are the factors that associate with the measures of HRQL?

Table 5-12 shows the correlation of hypothesised predictor variables with the domains of HRQL and the summary scores (PCS and MCS). The direction of relationship with each HRQL domain and significance are stated as follows.

Physical Functioning: The correlations sign of all the variables were as expected however only depression associated significantly with Physical Functioning ($r = 0.22$, $p < 0.05$).

Role Physical: Age, anxiety, depression, somatic symptoms number of comorbidity and diseases severity associated significantly with Role Physical ($p < 0.01$) and they were in the expected direction. Also, number of children associated inversely with Role Physical ($r = -0.20$, $p < 0.01$).

Role Emotional: All the variables associated significantly with Role Emotional and followed the expected direction. The value of r ranged from -0.19 to -0.43. Number of children also associated negatively with Role Emotional ($r = -0.20$, $p < 0.01$). Table 4-7 also shows that marital status associated with role emotional ($p < 0.05$).

Social Functioning: Reduced Social Functioning was associated with increased anxiety, depression, somatic symptoms, number of comorbidities and disease severity ($p < 0.05$), age did not significantly associate with Social functioning ($r = -0.11$, $p > 0.05$). Reduced Social Functioning also associated with the female gender and living alone (Table 5-8).

Table 5-2: Correlations between Health-related Quality of Llife and Hypothesised Determinants in Adult Sickle Cell population

Variables	PF	RP	RE	SF	BP	VT	GH	MH	PCS	MCS
Age	-0.068	-0.281**	-0.305**	-0.106	-0.044	0.030	-0.154*	-0.191**	-0.095	-0.224**
GAD7	-0.128	-0.411**	-0.430**	-0.342**	-0.340**	-0.324**	-0.446**	-0.413**	-0.318**	-0.513**
PHQ9	-0.218**	-0.384**	-0.346**	-0.297**	-0.294**	-0.364**	-0.373**	-0.363**	-0.357**	-0.413**
PHQ15	-0.106	-0.361**	-0.223**	-0.237**	-0.438**	-0.409**	-0.407**	-384**	-0.362**	-0.379**
Comorbidity	-0.078	-0.322**	-0.226**	-0.219**	-0.270**	-0.196**	-0.352**	-0.361**	-0.253**	-0.343**
DSEI	-0.123	-0.206**	-0.192**	-0.226**	-0.280**	-0.169*	-0.154*	-0.210**	-0.205**	-0.241**
N. children	-0.071	-0.204**	-0.213**	-0.088	0.006	0.006	-0.038	0.004	-0.091	-0.084

Notes: PF – Physical Functioning; RP – Role Emotional; SF- Social Functioning; BP- Bodily Pain; VT- Vitality; GH- General Health; MH- Mental Health; PCS – Physical Health Component Summary Score; MCS – Mental Health Summary Score *Correlation significant at 0.05 level (2 tailed); **Correlation significant at 0.01 level (2 tailed).

Bodily Pain: Age did not associate significantly with Bodily Pain ($p > 0.05$), but anxiety, depression, somatic symptoms, number of comorbidities and disease severity associated with bodily pain ($p < 0.01$). In addition, female gender was also associated with worse health of bodily pain ($p < 0.01$).

Vitality: Variables that associated with vitality included anxiety ($r = -0.32$, $p < 0.01$), depression ($r = -0.36$, $p < 0.01$), somatic symptoms ($r = -0.41$, $p < 0.01$), number of comorbidities ($r = -0.20$, $p < 0.01$) and disease severity ($r = -0.17$, $p < 0.05$).

General health: A worse expression of General Health was associated with increasing age, anxiety, depression, somatic symptoms, number of comorbidities and disease severity. The correlation coefficient ranged from $r = -0.15$ to $r = -0.45$. Being without a confidant also contributed to reduced reported general health ($p < 0.05$, see Table 5-8).

Mental Hhealth: Reduced Mental Health was associated with increasing age, anxiety, depression, somatic symptoms, number of comorbidities and disease severity; r ranged from -0.19 to -0.41 (all $p < 0.01$) as well as with being without a confidant ($p < 0.05$).

Physical Component Summary: Low physical health summary score associated with more anxiety, depression, somatic symptoms, number of comorbidities and disease severity.

Mental Component Summary: The mental component summary score associated with age ($r = -0.22$, $p < 0.01$), anxiety ($r = -0.51$, $p < 0.01$), depression ($r = -0.41$, $p < 0.05$), somatic symptoms ($r = -0.38$, $p < 0.01$), number of comorbidity ($r = -0.34$, $p < -0.01$), disease severity ($r = -0.24$, $p < .01$) and living alone ($t = 2.65$, $p < 0.01$; see Table 5-8).

Further analysis was carried out on the variables with significant associations to examine which variables predicted a domain of HRQL. A hierarchical regression was used. Based on the Wilson and Cleary's (1995) model of HRQL, the biological-physiological variables DSEI and number of comorbidities were entered first as possible predictors of the respective

HRQL domain (Block 1), these were followed by psychosocial variables of anxiety, depression and somatic symptoms (Block 2) and finally, the relevant sociodemographic variables were entered (Block 3). The results are displayed on Table 5-13.

The biological-physiological factor, measured by number of comorbidities and disease severity, predicted all the HRQL domains including the Physical Component Summary score and the Mental Component Summary scores except Physical Functioning ($F = 1.7$, $p > 0.05$). The biological-physiological factor accounted for variation in the model ranging from 5.2% to 14.2 %. The number of comorbidities was a significant predictor of all the domains while disease severity predicted Social Functioning, Bodily Pain and MCS. The psychosocial factors; anxiety, depression and somatic symptoms explained additional 3.9% (lowest) in Physical Functioning, and 17.4% (highest) in Social Functioning. Anxiety was a significant predictor of Role Physical, Role Emotional, Social Functioning, General Health, Mental Health, Physical Component Score and Mental Health score. Depression was a significant predictor of Physical Functioning and Vitality while somatic symptoms was a significant predictor of Bodily Pain, Vitality) and General Health. All the signs were negative as expected. The sociodemographic variable, age, was a significant predictor of Role Physical and Role Emotional; the negative direction of prediction implies that each of Role Physical and Role Emotional reduced with advancing age. Gender significantly predicted Bodily Pain with female gender experiencing worse health in Bodily Pain. Having confidant predicted General Health and Mental Health; participants who had confidants experienced better Mental Health and General Health. Living situation was a significant predictor of the Mental Component Summary scores; participants living with others reported better mental health than participants living alone.

Table 5-33: Hierarchical Regression Modelling of Predictors of Health-related Quality of Life

		Physical Functioning						**Role Physical**					
Block	**Variables**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**	**B**	**SE(B)**	***Std. β**	**p**	**R^2**	**F (p)**
1	Constant	2.872	0.337			0.017	1.71	1.823	0.239				
	DSEI	-0.182	0.123	-0.109	0.14		(0.19)	-0.152	0.088	-0.122	0.08	0.117	13.05
	Comorbidity	-0.121	0.193	-0.046	0.53			-0.559	0.137	-0.286	0.000		(< 0.001)
2	Constant	3.123	0.554				2.31	2.631	0.379				
	DSEI	-0.159	0.128	-0.095	0.22		(0.046)	-0.093	0.088	-0.074	0.29		
	Comorbidity	0.099	0.229	0.038	0.67	0.056		-0.149	0.156	-0.076	0.34		10.53
	GAD7	-0.011	0.246	-0.004	0.97			-0..393	0.168	-0.215		0.214	(< 0.001)
											0.021		
	PHQ9	-0.274	0.111	-0.239	0.014			-0.125	0.076	-0.145	0.10		
	PHQ15	0.078	0.153	0.050	0.61			-0.096	0.104	-0.082	0.36		
3	Constant	3.141	0.555					2.752	0.373				
	DSEI	-0.167	0.129					-0.122	0.086	-0.097	0.16		
	Comorbidity	0.134	0.235					0.024	0.162	0.012	0.88		
	GAD7	0.001	0.247					-0.375	0.165	-0.205	0.024		
	PHQ9	-0.271	0.111					-0.112	0.074	-0.130	0.13	0.259	9.58
	PHQ15	0.070	0.153					-0.136	0.103	-0.117	0.19		(< 0.001)
	Age	-0.029	0.062					-0.099	0.046	-0.158	0.033		
	N. children							-0.193	0.134	-0.106	0.15		

Notes: DSEI=Disease Severity Index;GAD7= Geneeralised Anxiety disorder-7; PHQ9=Patient Health Questionnaire-9; PHQ15=Patient Health Questionnaire-15.

Table 5-13 cont.: Hierarchical Regression Modelling of Predictors of Health-related Quality of Life

		Role Emotional						**Social Functioning**					
Block	**Variables**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**	**B**	**SE(B)**	***Std. β**	**p**	**R^2**	**F (p)**
1	Constant	4.949	0.134				7.239	10.033					8.195
	DSEI	-0.094	0.049	-0.137	0.058	0.06	0.001	-0.142		-0.177	0.014	0.077	(< 0.001)
	Comorbidity	-0.198	0.077	-0.186	0.01	8		-0.209		-0.167	0.021		
2	Constant	5.775	0.207					10.666					
	DSEI	-0.096	0.048	-0.141	0.045			-0.133		-0.17	0.023		
	Comorbidity	0.019	0.085	0.018	0.82	0.21	10.55	-0.009		-0.007	0.94	0.151	6.891
	GAD7	-0.404	0.092	-0.406	< 0.001	4	(< 0.001)	-0.308		-0.264	0.006		(< 0.001)
	PHQ9	-0.065	0.041	-0.138	0.12			-0.062		-0.113	0.22		
	PHQ15	0.090	0.057	0.141	0.117			0.040		0.053	0.57		
3	Constant	5.852	0.201					10.245					
	DSEI	-0.116	0.046	-0.170	< 0.013			-0.134		-0.168	0.020		
	Comorbidity	0.131	0.088	0.123	0.136			-0.025		-0.020	0.81		
	GAD7	-0.392	0.089	-0.394	< 0.001	0.27	9.19	-0.315		-0.271	0.004		
	PHQ9	-0.059	0.040	-0.126	0.145	8	(< 0.001)	-0.025		-0.045	0.63		
	PHQ15	0.067	0.056	0.106	0.231			0.042		0.057	0.54	0.197	
	Age	-0.067	0.025	-0.196	0.009			-0.013		-0.032	0.65		5.846
	Nom Child	-0.138	0.082	-0.139	0.094								(< 0.001)
	Marital status	0.043	0.097	0.035	0.66								
	Gender							0.113		-0.116	0.09		
	Living situation							0.300		0.179	0.009		

Notes: DSEI=Disease Severity Index;GAD7= Geneeralised Anxiety disorder-7; PHQ9=Patient Health Questionnaire-9; PHQ15=Patient Health Questionnaire-15.

Table 5-13 cont.: Hierarchical Regression Modelling of Predictors of Health-related Quality of Life

		Bodily Pain						Vitality					
Block	**Variables**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**
1	Constant	3.816	0.284					1.207	0.161				5.413
	DSEI	-0.327	0.104	-0.220	0.002	0.117	13.059 (< 0.001)	-0.099	0.059	-0.122	0.09	0.052	(0.005)
	Comorbidity	-0.477	0.163	-0.205	0.004			-0.204	0.092	-0.160	0.028		
2	Constant	4.257	0.449					1.390	0.249				
	DSEI	-0.197	0.104	-0.132	0.06			-0.014	0.058	-0.018	0.80		
	Comorbidity	0.003	0.185	0.001	0.99	0.217	10.754	0.118	0.103	0.093	0.25	0.199	9.667
	GAD7	-0.287	0.199	-0.133	0.15		(< 0.001)	-0.084	0.110	-0.071	0.45		(< 0.001)
	PHQ9	-0.003	0.090	-0.003	0.97			-0.103	0.050	-0.185	0.039		
	PHQ15	-0.423	0.124	-0.306	0.001			-0.230	0.069	-0.305	0.001		
3	Constant	4.708	0.472					1.374	0.248				
	DSEI	-0.185	0.103	-0.125	0.07			-0.007	0.058	-0.009	0.91		
	Comorbidity	-0.082	0.190	-0.035	0.67		9.051	0.086	0.105	0.068	0.42		8.380
	GAD7	-0.289	0.197	-0.13	0.14	0.248	(< 0.001)	-0.095	0.110	-0.080	0.39	0.207	(< 0.001)
	PHQ9	0.012	0.089	0.012	0.89			-0.107	0.050	-0.191	0.033		
	PHQ15	-0.359	0.124	-0.260	0.004			-0.223	0.069	-0.294	0.001		
	Age	-0.003	0.049	-0.004	0.96			0.037	0.028	0.090	0.19		
	Gender	-0.332	0.118	-0.118	0.006								

Notes: DSEI=Disease Severity Index;GAD7= Geneeralised Anxiety disorder-7; PHQ9=Patient Health Questionnaire-9; PHQ15=Patient Health Questionnaire-15.

Table 5-13 cont.: Hierarchical Regression Modelling of Predictors of Health-related Quality of Life

		General Health						Mental Health					
Block	**Variables**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**
1	Constant	3.172				0.126	14.251	3.470	0.261				16.345
	DSEI	-0.086	0.109	-0.055	0.43		(< 0.001)	-0.157	0.096	-0.113	0.10	0.142	(< 0.001)
	Comorbidity	-0.819	0.170	-0.335	0.000			-0.710	0.149	-0.328	0.000		
2	Constant	4.229	0.464					4.272	0.417				
	DSEI	0.015	0.108	0.010	0.89			-0.087	0.097	-0.063	0.37		
	Comorbidity	-0.247	0.192	-0.101	0.20		12.316	-0.287	0.172	-0.133	0.097	0.223	11.111
	GAD7	-0.565	0.206	-0.248	0.007	0.241	(< 0.001)	-0.416	0.185	-0.206	0.026		(< 0.001)
	PHQ9	-0.075	0.093	-0.070	0.42			-0.080	0.084	-0.084	0.34		
	PHQ15	-0.249	0.128	-0.17	0.053			-0.155	0.115	-0.120	0.18		
3	Constant	3.276	0.572					3.545	0.514				
	DSEI	0.013	0.106	0.009	0.90			-0.095	0.095	-0.069	0.32		
	Comorbidity	-0.251	0.194	-0.103	0.20		10.318	-0.257	0.175	-0.119	0.14		9.352
	GAD7	-0.523	0.203	-0.230	0.011	0.273	(< 0.001)	-0.372	0.183	-0.184	0.043		(< 0.001)
	PHQ9	-0.047	0.092	-0.044	0.61			-0.055	0.083	-0.058	0.51	0.254	
	PHQ15	-0.301	0.127	-0.208	0.019			-0.203	0.114	-0.158	0.078		
	Age	-0.019	0.051	-0.024	0.71			-0.051	0.046	-0.074	0.27		
	Confidant	0.474	0.168	0.178	0.005			0.370	0.151	0.157	0.015		

Notes: DSEI=Disease Severity Index;GAD7= Geneeralised Anxiety disorder-7; PHQ9=Patient Health Questionnaire-9; PHQ15=Patient Health Questionnaire-15.

Table 5-13 cont.: Hierarchical Regression Modelling of Predictors of Health-related Quality of Life

		Physical Component Summary						Mental Component Summary					
Block	**Variables**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**	**B**	**SE(B)**	***Std. β**	**P**	**R^2**	**F (p)**
1	Constant	3.126	0.170				8.895	3.125	0.199				15.933
	DSEI	-0.125	0.062	-0.143	0.047	0.083	(< 0.001)	-0.162	0.073	-0.154		0.139	(< 0.001)
											0.027		
	Comorbidity	-0.289	0.098	-0.211	0.003			-0.492	0.114	-0.298			
											0.000		
2	Constant	3.347	0.272					4.482	0.303				
	DSEI	-0.062	0.063	-0.071	0.32			-0.126	0.070	-0.119	0.07		16.079
	Comorbidity	-0.019	0.112	-0.014	0.87		8.050	-0.077	0.125	-0.047	0.54		(< 0.001)
	GAD7	-0.090	0.121	-0.071	0.46	0.172	(< 0.001)	-0.597	0.134	-0.388	0.000	0.293	
	PHQ9	-0.112	0.055	-0.187	<0.041			-0.072	0.061	-0.099	0.24		
	PHQ15	-0.145	0.075	-0.178	0.054			-0.022	0.084	-0.022	0.79		
3	Constant	3.353	0.273				6.715	3.981	0.400				
	DSEI	-0.065	0.063	-0.075	0.31	0.173	(< 0.001)	-0.140	0.069	-0.133	0.045		
	Comorbidity	-0.007	0.116	-0.005	0.95			-0.023	0.127	-0.014	0.86		
	GAD7	-0.086	0.121	-0.067	0.48			-0.589	0.133	0.382		0.322	13.019
											0.000		(< 0.001)
	PHQ9	-0.111	0.055	-0.185	0.044			-0.038	0.061	-0.052	0.54		
	PHQ15	-0.148	0.075	-0.182	0.051			-0.050	0.083	-0.051	0.55		
	Age	-0.014	0.030	-0.031	0.65			-0.059	0.033	-0.112	0.077		
	Living situation							0.278	0.137	-0.125	0.043		

Notes: DSEI=Disease Severity Index;GAD7= Geneeralised Anxiety disorder-7; PHQ9=Patient Health Questionnaire-9; PHQ15=Patient Health Questionnaire-15.

5.4 Objective three

To Test the Wilson-Cleary HRQL model in the population of adults with sickle cell disease

5.4.1 Research Question 3:

How does the Wilson and Cleary model fit the HRQL data of the study population?

Latent factors and indicator variables

A 2-step procedure recommended by Anderson and Anderson and Gerbing (1988) was implemented. The first step was implemented in two stages. The first stage of the first step was carried out to examine the fit of the indicator variables to the construct they were hypothesised to measure. The results are displayed in Table 5-14 .

Table 5-14: The Fit Indices for Each Factor in the Construct (N=200)

Latent constructs	CMIN (χ^2)	χ^2 / df	SRMR	CFI	RMSEA
Biological-Physiological Factors (BPF)	0.888	0.444	0.02	1.00	0.00
Symptoms Status (SS)	15.163*	3.033	0.05	0.97	0.12
Functional Status (FS)	9.602**	4.801	0.05	0.96	0.10
General Health Perception (GHP)	32.825**	32.825	0.03	1.00	0.40
Characteristics of Individual (COI)	5.656	2.828	0.04	0.98	0.09
Characteristics of the Environment (COE)			0.00	1.00	0.06

Notes: CMIN=chi-square value, χ^2 / df=relative chi-square, SRMR=Standardised Root Mean Square Residual, CFI=Comparative Fit Index, RMSEA=Root Mean Square Error of Approximation, CI=Confidence Interval, df=degree of freedom. *p<0.05, **p<0.01

In determining the fit of the model, the chi-square was considered. A non-significant chi-square where the p-value associated with the chi-square is larger than 0.05 can indicate that the model adequately represents the relations among the variables (Schermelleh-Engel, Moosbrugger and Müller, 2003). However, a weakness of chi-square is its sensitivity to large samples such that in most cases, the chi-square will return significant values. Other fit

indices were thus considered (see Table 4-4). The biological/physiological construct had a non-significant chi-square while other fit indices also indicated good fit. The three indicator variables for this construct were genotype, a measure of disease severity index and number of comorbidities. Apart from genotype ($p > 0.05$) all the variables associated with the construct ($p < 0.01$). Symptom status was measured with five indicators; though the chi-squared was significant ($p < 0.05$), the CFI and SRMR were within acceptable limits. All the five indicators; bodily pain, mental health, anxiety, depression and somatic symptoms associated with the symptoms status construct ($p < 0.01$). All the four indicators of functional status; physical functioning, role emotional, role physical and social functioning associated with the construct ($p < 0.01$) and have acceptable CFI and SRMR but the chi-square was significant and the RMSEA was outside acceptable limit. Three of the four indicators of the characteristics of the individual: age, number of children and marital status associated with the construct ($p < 0.05$) but gender did not ($p > 0.05$). The chi-square was not significant ($p > 0.05$) and all the other fit indices were acceptable except RMSEA which was outside the acceptable limit at 0.096.

The Full Measurement model

The second stage of the first step was implemented to examine the full measurement model. The measurement model is a 7-factor model made up of 22 variables (see Figure 5-2). Table 5.15 displays the measurement model and the modification steps. Model1, was the full 7-factor measurement model with 22 variables.

The model converged within 9 iterations and was admissible. The chi-square (χ^2) was large and significant ($\chi^2_{(189)} = 387.098$, $p < 0.01$). However, the fit indices $\chi^2/DF = 2.048$ (≤ 3), SRMR = 0.076 (≤ 0.08), RMSEA = 0.073 (≤ 0.08) were all within acceptable limits but CFI = 0.83 (≥ 0.9) was outside the acceptable limits.

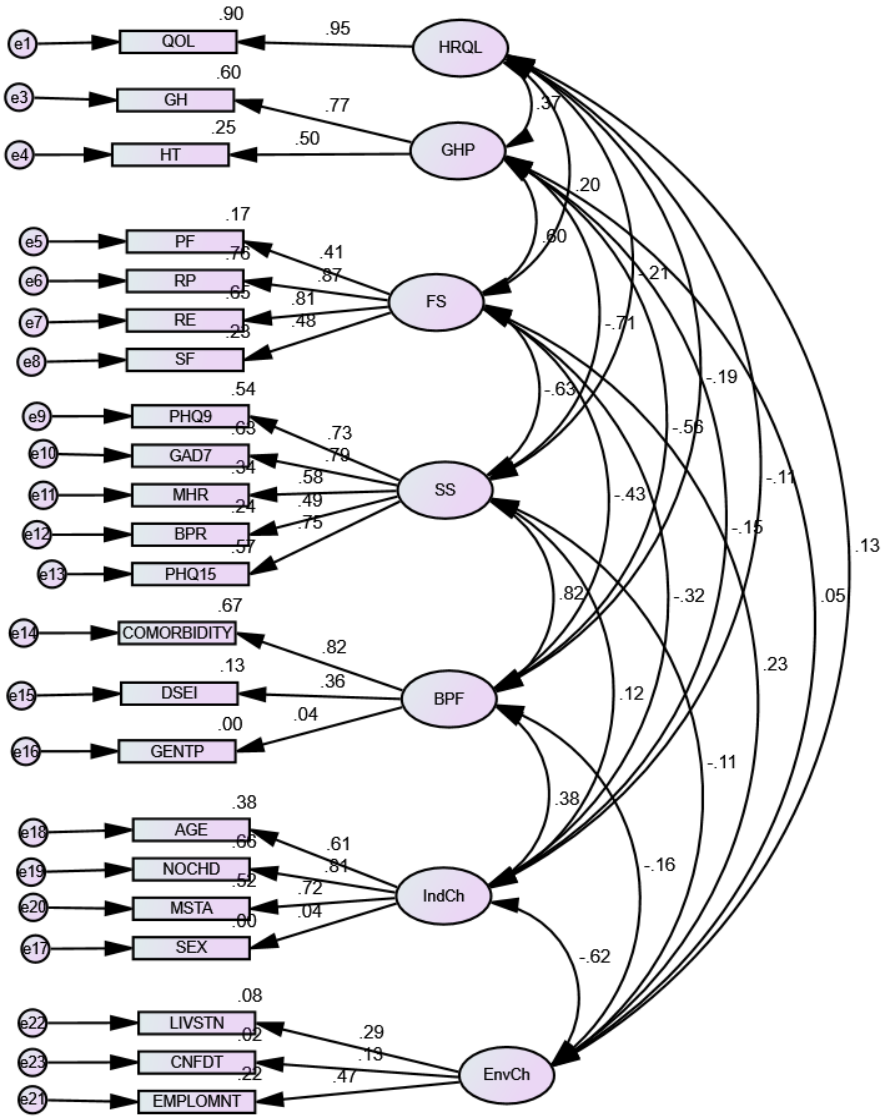


Figure 5-2: The 7-Factor, 22-Variable Basic Model

Notes: PF=Physical Functioning, RP= Role Emotional, SF=Social Functioning, BPR=Bodily Pain reversed, VT=Vitality, GH=General Health, MHR=Mental Health reversed, NOCHD=Number of children, DSEI=Disease severity index, LIVSTN=living situation, CNFDT=confidant, HRQL=Health-related quality of life, BPF=bio-physiological factor, GHP=General health perception, FS=Function status, SS=symptoms status, IndCh=Characteristics of the individual, EnvCh=Charateristics of the environment.

An attempt was made to improve the fit of the model. The modification indices suggested by AMOS were examined in line with theory. A path was constructed to correlate the residual (e8) of Social functioning with the residual (e12) of bodily pain. This correlation

was considered reasonable because bodily pain could limit social functioning and a heightened social activity on the part of the patient could trigger bodily pain. The model containing this additional path was re-tested (Model 2 in Table 5-15). The chi-square difference test showed that the model improved significantly over the original model ($\chi^2_{(1)}$ = 387.098 – 360.109 = 26.99, $p < 0.01$). all the other fit indices also improved. The 90% CI of RMSEA was 0.057-0.078 (acceptable limit: 0.00-0.08). A further effort was attempted to improve the fit; to further reduce the chi-square and improve the CFI which was still outside the acceptable limit. Model 3 was developed by removing the gender variable which contributed almost nothing to the measurement model ($R^2 = 0.002$) or 0.2%. The model was retested. A significant improvement in Model 3 over Model 2 was observed (($\chi^2_{(20)} = 58.00$, $p < 0.01$), all the fit indices also improved. A further attempt was made to improve the model (Model 4) by drawing a path from e8 (Social functioning) to e22(living situation). It was felt reasonable to correlate these residuals because social functioning could be expected to be affected by living situation; participants living with people are more likely to enjoy better social relationship and functioning than participants who leave alone. The chi-square reduced by 10.57 though the change in chi-square was not significant ($p > 0.05$), there were improvements in the other fit parameters (Model 4, Table 5-15).

Model 5 correlated the residual, e15 of Disease severity and the residual, e13 of somatic symptoms. This is also reasonable because somatic symptoms could be aggravated with worsen disease condition. Model 6 modified model 5 by drawing a path to relate the error terms of the Physical functioning and Social functioning, again this was reasonable as both indicators measured function status. Other fit modifications applied included drawing a path to link residuals of living situation and depression as well as linking the residual of Role emotional and anxiety, a path was also drawn to link the residuals of anxiety and depression. Finally, the variables, genotype and confidant were removed as indicator variables because they had no significant contributions to the model, genotype ($R^2 = 0.002$) and having

confidant (R^2 = 0.015). This gave rise to the final model (Figure 4.3). The fit indices were acceptable $\chi 2/df$ = 1.391 (close to 1), SRMR = 0.06 (< 0.08), CFI = 0.957 (> 0.95) and RMSEA = 0.04 (< 0.08), 90% CI for RMSEA = 0.0027-0.060. The measurement model was therefore an acceptable fit.

Table 5-15: Full Measurement Model and Modification Summary

Model	**CMIN (χ^2)**	**DF**	**P**	**χ^2/DF**	**SRMR**	**CFI**	**RMSEA**	**90% CI for RMSEA**	**Difference in χ^2, (p)**
1.Full Model, 7-factor CFA 23 variables	387.098	189	0.00	2.048	0.076	0.831	0.073	0.062-0.083	
2. Path was added from e8(SF) to e12(BP)	360.109	188	0.00	1.915	0.073	0.853	0.068	0.057-0.078	26.99 (0.00)
3. The indicator variable, gender was removed	302.108	168	0.00	1.798	0.069	0.88	0.063	0.052-0.075	58.00 (0.00)
4. Path from e22 (Living situation) to e8(SF)	291.536	167	0.00	1.746	0.068	0.89	0.061	0.049-0.073	10. 57 (0.11)
5. Path from e13 PHQ15) to e15 (DSEI)	280.476	166	0.00	1.690	0.08	0.90	0.059	0.047-0.071	11.06 (0.12)
6. Path e5 (PF) to e8 (SF)	272.172	165	0.00	1.650	0.067	0.91	0.057	0.045-0.069	8.30 (0.36)
7. e22 (living situation) to e9 (PHQ9)	263.170	164	0.00	1.605	0.067	0.91	0.055	0.042-0.067	9.00 (0.26)
8. Path e7(RE) to e10(GAD7)	254.555	163	0.00	1.562	0.067	0.92	0.053	0.040-0.063	8.62 (0.33)
9. Path e9(PHQ9) to e10(GAD7)	246.364	162	0.00	1.521	0.067	0.93	0.051	0.038-0.064	8.2 (0.42)
10. Removed confidant and genotype	169.730	122	0.00	1.391	0.06	0.957	0.044	0.027-0.060	76.63 (0.04)

Notes: CMIN=chi-square value, χ^2 / df=relative chi-square, SRMR=Standardised Root Mean Square Residual, CFI=Comparative Fit Index, RMSEA=Root Mean Square Error of Approximation, CI=Confidence Interval, df=degree of freedom.

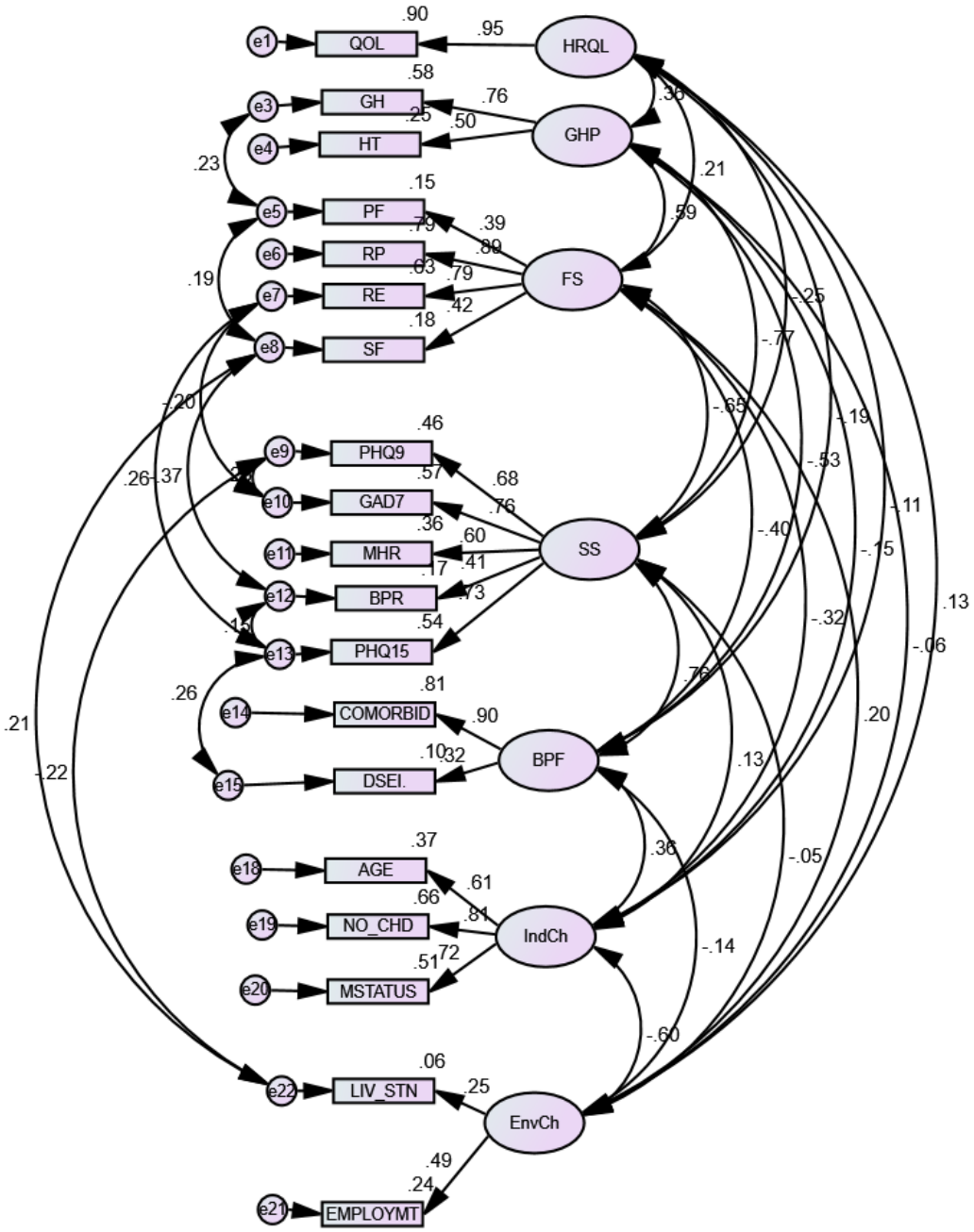


Figure 5-3: The 7-Factor, 19-Variable Measurement Model

χ^2/df = 1.391, SRMR = 0.06; CFI = 0.957, RMSEA = 0.04

Notes: PF=Physical Functioning, RP= Role Emotional, SF=Social Functioning, BPR=Bodily Pain reversed, VT=Vitality, GH=General Health, MHR=Mental Health reversed, NOCHD=Number of children, DSEI=Disease severity index, LIVSTN=living situation, CNFDT=confidant, HRQL=Health-related quality of life, BPF=bio-physiological factor, GHP=General health perception, FS=Function status, SS=symptoms status, IndCh=Characteristics of the individual, EnvCh=Charateristics of the environment.

The correlation matrix of the 19 variables is displayed on Table 5-16. All the composites were significantly correlated with each other ($p < 0.01$) except the characteristic of the environment ($p > 0.05$). The range of correlations were functional status 0.305-0.718, general health perception 0.265-0.390, symptom status 0.340-0.647, biophysiological construct 0.294 and characteristics of the individual 0.444-0.588.

Table 5-16: Correlation Matrix for Variables in the Measurement Model

Constructs	Variables	1	2	3	4	5	6	7	8	9	10	11	12
HRQL	1. QOL	1											
	2. GH	0.254**	1										
GHP	3. HT	0.215**	0.390**	1									
	4. PF	0.124	0.307**	0.160*	1								
FS	5. RE	0.156*	0.333**	0.195**	0.305**	1							
	6. RP	0.185**	0.397**	0.321**	0.347**	0.718**	1						
	7. SF	-0.042	0.244**	0.172*	0.354**	0.353**	0.386**	1					
	8. BPR	0.023	-0.265**	-0.123	-0.168*	-0.261**	-0.313**	-0.487**	1				
	9. GAD7	-0.183**	-0.446**	-0.267**	-0.128	-0.430**	-0.411**	-0.342**	0.340**	1			
SS	10. PHQ9	-0.118	-0.373**	-0.251**	-0.218**	-0.346**	-0.384**	-0.297**	0.294**	0.647**	1		
	11. PHQ15	-0.161*	-0.407**	-0.185*	-0.106	-0.223**	-0.361**	-0.237**	0.438**	0.589**	0.568**	1	
	12. MHR	-0.190**	-0.427**	-0.296**	-0.174*	-0.413**	-0.449**	-0.399**	0.362**	0.416**	0.368**	0.391**	1
	13. Comorbidity	-0.173*	-0.352**	-0.253**	-0.078	-0.226**	-0.322**	-0.219**	0.270**..	0.523**	0.470**	0.526**	0.363**
BPF	14. DSEI	0.072	-0.154*	0.051	-0.123	-0.192**	-0.206**	-0.226**	-0.280**	0.194**	0.241**	0.397**	0.208**
	15. Age	-0.137	-0.154*	-0.210**	-0.068	-0.305**	-0.281**	-0.106	0.044	-0.209**	0.178*	0.095	0.188**
CoI	16. Mar_status	-0.034	-0.004	-0.071	-0.122	-0.163*	-0.131	-0.083	-0.037	0.071	0.135	-0.057	0.029
	17. No_ childr	-0.084	-0.038	-0.183*	-0.071	-0.213**	-0.204**	-0.088	-0.006	0.067	0.082	0.010	0.022
	18. Employment	-0.048	0.020	-0.009	-0.099	-0.106	-0.062	-0.009	-0.120	-0.007	0.008	0.001	0.062
	19. Livingsitu	0.013	-0.005	-0.018	0.051	0.107	-0.005	0.222**	-0.060	-0.081	-0.212**	-0.023	-0.137

**Correlation significant at 0.01 level (2tailed) *Correlation significant at 0.05 level (2 tailed); BPR and MHR are reversed scores of BP and MH respectively so that higher values represented worse scores, they were reversed to have same direction with measured variables of the constructs.

Table5-16 cont: Correlation Matrix for Variables in the Measurement Model

Constructs	Variables	13	14	15	16	17	18	19
	13. Comorbidity	1						
BPF	14. DSEI	0.294**	1					
	15. Age	-0.281**	-0.026	1				
CoI	16. Mar_status	0.165*	-0.009	0.444**	1			
	17. No_ childr	0.289**	-0.015	0.491**	0.588**	1		
	18. Emploment	0.063	0.033	0.092	0.295**	0.233**	1	
COE	19. Livingsitu	-0.060	-0.003	-0.135	-0.193**	-0.071	0.124	1

**Correlation significant at 0.01 level (2tailed) *Correlation significant at 0.05 level (2 tailed); BPR and MHR are reversed scores of BP and MH respectively so that higher values represented worse scores, they were reversed to have same direction with measured variables of the constructs.

5.4.2 Research Question 4:

Are there relationships among the bio-physiological variables, symptoms, functional status, general health perceptions, individual characteristics and the overall quality of life as hypothesized by Wilson and Cleary?

Table 5-17 was obtained from the measurement model. The biological-physiological construct associated positively with the symptom status construct. This was as expected as worse biological conditions were associated with increased symptoms ($p < 0.01$). The association between biological-physiological construct and general health perception was negative indicating that worse disease conditions reduced general health perception. Similarly, worse disease condition was associated with reduced HRQL. An increase in symptoms was associated with reduced functional status, reduced general health perception and reduced HRQL. Better functional status was associated with better general health perception and better HRQL. General health perception was also associated positively with HRQL. The characteristics of the environment and the characteristics of the individual were negatively associated. The characteristics of the individual followed the same direction as biological-physiological and symptom status constructs.

Table 5-17: Intercorrelations among the Constructs of the Wilson and Cleary model

	BPF	**SS**	**FS**	**GHP**	**HRQL**	**COI**	**COE**
BPF	-						
SS	0.764**	-					
FS	-0.396	-0.649**	-				
GHP	-0.533**	-0.769**	0.587**	-			
HRQL	-0.191	-0.251	0.213	0.357**	-		
COI	0.363	0.130	-0.318	-0.152	-0.113	-	
COE	-0.143	-0.050	0.196	-0.064	0.126	-0.605**	-

Notes: BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual.

5.4.3 Research Question 5:

What are the patterns and paths of the relationship of the HRQL determinants?

The second step for conducting structural equation modelling recommended by Anderson and Gerbing, (1988) was implemented here. To test whether the hypothesized structural relationship proposed by Wilson and Cleary (1995) was consistent with observations in the sickle cell disease population. The causal relationship is depicted in Figure 5-4.

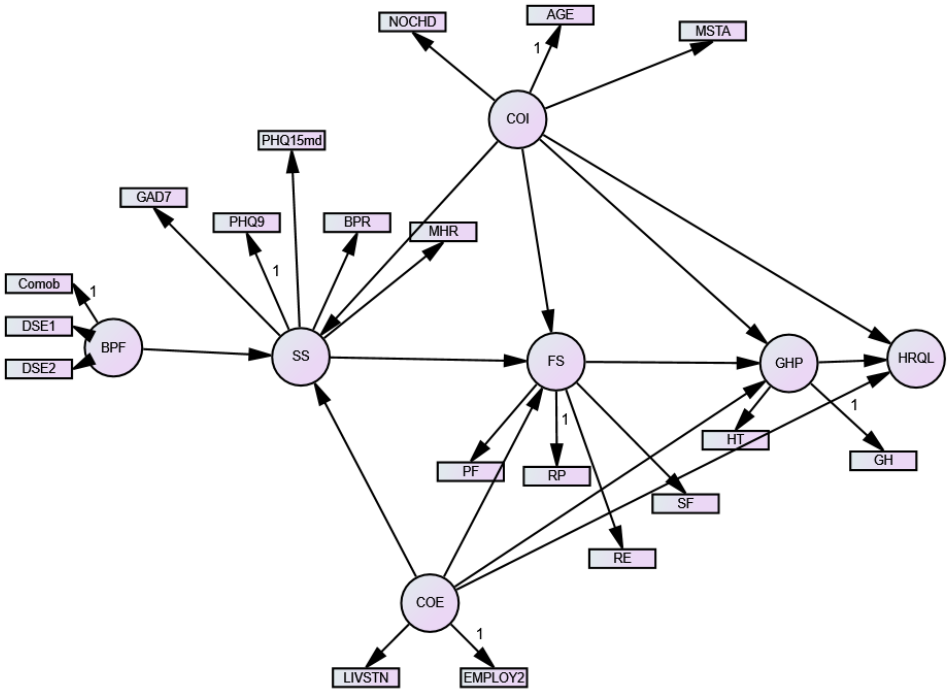


Figure 5-4: The Structural Model

The path coefficients representing the strength of relationship between the concepts were assessed and tested for statistical significance at 5% level of significance. The magnitudes of the path coefficients were also evaluated using the thresholds of 0.10, 0.30 and 0.50 to identify small, moderate and strong effect sizes (Cohen, 1988).

The paths of relationship are shown in figure 5-5. From SEM analysis, it was observed that the Wilson and Cleary model fits well the data of people with sickle cell disease in Southwest Nigeria (χ^2 == 200.760, df=152, p > 0.05, χ^2/df = 1.321, SRMR = 0.06, CFI = 0.959, RMSEA = 0.04 (90% CI = 0.023-0.054), pclose = 0.864).

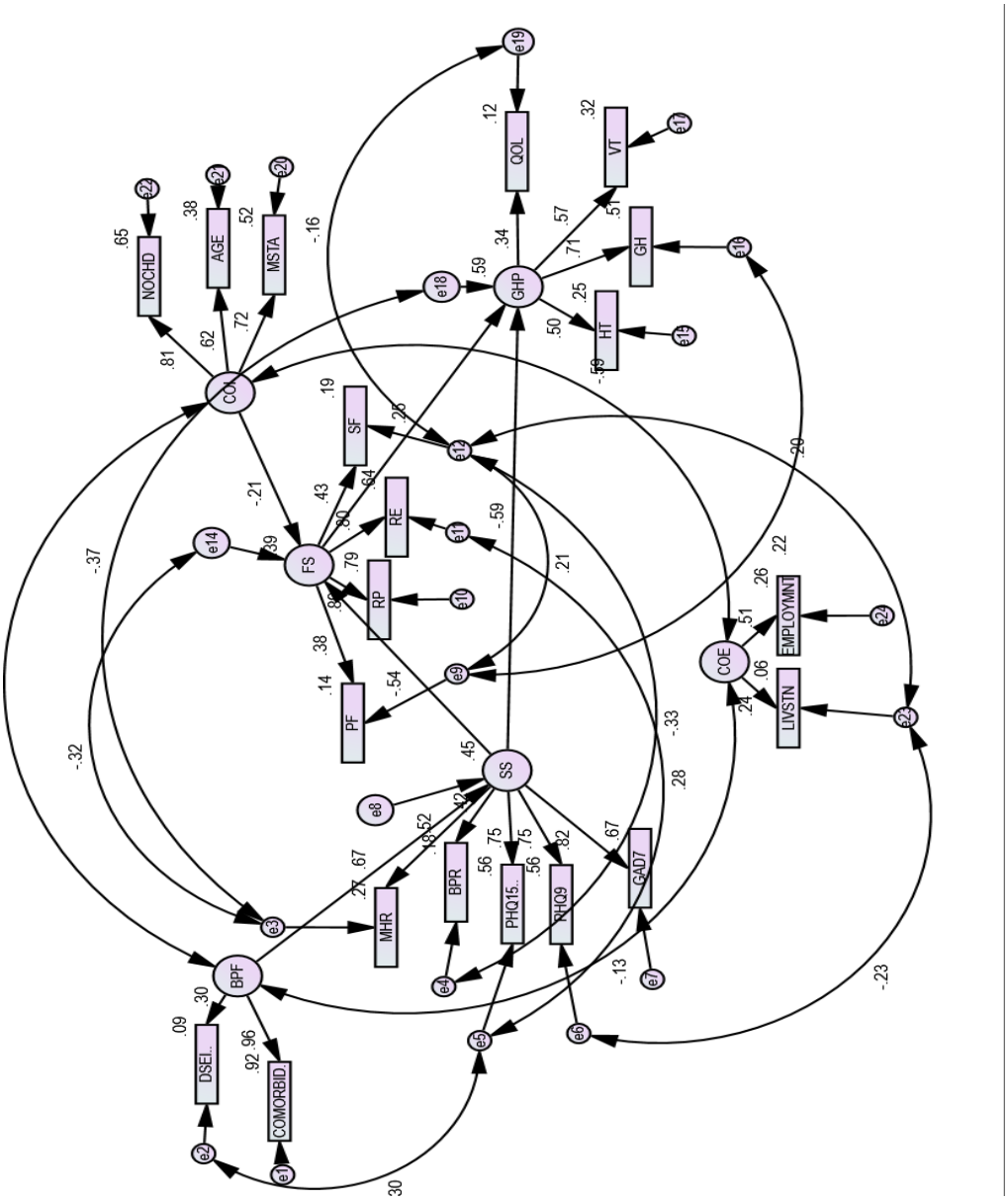


Figure 5-5: Un-standardised Beta (Initial Model)

Notes: PF=Physical Functioning, RP= Role Emotional, SF=Social Functioning, BPR=Bodily Pain reversed, VT=Vitality, GH=General Health, MHR=Mental Health reversed, NOCHD=Number of children, DSEI=Disease severity index, LIVSTN=living situation, CNFDT=confidant, HRQL=Health-related quality of life, BPF=bio-physiological factor, GHP=General health perception, FS=Function status, SS=symptoms status, COI=Characteristics of the individual, COE=Charateristics of the environment.

However, the latent factor, characteristics of the environment (COE) did not show any direct or indirect effect on any of the other latent factors, (Figure 5-5), it was therefore removed to achieve optimal fit and parsimony (Arnold *et al.*, 2005). The model was then re-tested. The model converged in 8 iterations and was admissible (Figure 5-6). A bootstrap procedure was implemented with 2000 bootstraps samples. Nevitt and Hancock (2001) recommended 2000 samples to assure the stability of the standard deviation. Bollen-Sline bootstrap method (Bollen and Stine, 1992) was used to further examine whether the model was correctly specified. According to Bollen and Sline the null hypothesis tests that the model is correct, a Bollen and Sline (B-S) p-value less than 0.05 indicates that the model is not correct. The bootstrap procedure returned a B-S p-value of 0.152, hence it was established that the data used in this study confirmed that the model was correct.

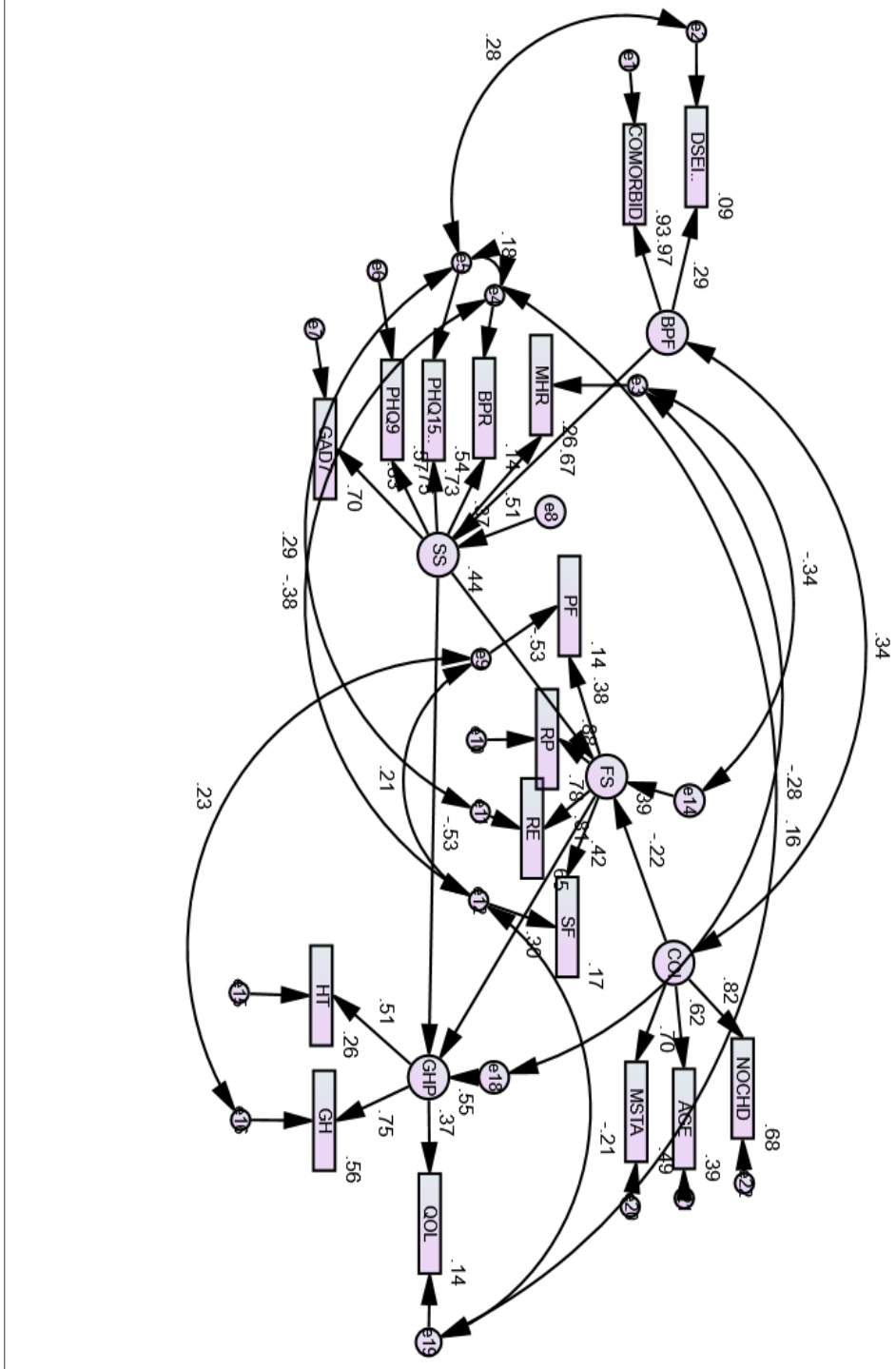


Figure 5-6: Standardised Beta (Final Model)

Fit indices

The fit indices are first presented in Table 5-18. The exact fit test, chi-square was significant ($p < 0.05$), but $\chi^2/df = 1.3$ (close to 1, the closer χ^2/df is to 1 the better the model fit). The SRMR = 0.04 <0.08, and CFI = 0.98. all the fit indices showed good fit of the model to the data. The standardised residual covariances were also examined; only 3.2% had an absolute value greater than 2 thus the model was considered a good fit to the data. The interpretation of the fit indices was guided by the criteria recommended in the overview by Schermelleh-Engel, Moosbrugger and Müller (2003)(Engel *et al.*, 2014), some studies, for example, Höfer *et al.* (2005) used less stringent criteria.

Table 5-18: Model Fit Indices

Fit indices	Criteria	Value	Conclusion
χ^2_{103}(p)	130.392, ($p < 0.05$)	0.035	
χ^2/df	< 3	1.27	Good fit
SRMR	≤ 0.08	0.06	Good fit
CFI	≥ 0.95	0.975	Good fit
RMSEA	≤ 0.08	0.04	Good fit
90% CI for RMSEA	0.00-0.08	0.010 – 0.054	Good fit
PClose	> 0.05	0.884	Good fit
Bollen-Sline (B-S) bootstrap p-value	Reject if $p < 0.05$	0.152	Model was accepted as correct

Notes: SRMR=Standardised Root Mean Square Residual, CFI=Comparative Fit Index, RMSEA=Root Mean Square Eerror of Approximation, CI=Confidence Interval, df=degree of freedom.

Direct Effects

Results of the structural equation modelling of the Wilson and Cleary model are presented in Table 5-19. The path analysis showed that:

1. The Biological factors had a statistically significant direct effect on the symptom status of the participants ($\beta = 0.67$, $p < 0.001$), the direction of influence was as expected indicating that a worsening health condition as a result of the disease was associated with more symptoms of illness in the patients. This path explained 44.3% of the variance in symptom status.

2. Symptoms status affected functional status ($\beta = -0.53$, $p < 0.001$), the negative sign indicated that as symptoms increased, functional health declined in the patient. Symptoms status and the characteristics of the individual explained 38.8% of the variance of functional status.

3. Functional status directly affected general health perceptions ($\beta = 0.30$, $p < 0.001$), the direction of influence is positive as expected which implies that patient who had better functional health had better perception of their health. This path and the direct path from symptoms status explained 54.7% of the variance in general health perception.

4. General health perception directly affected overall quality of life ($\beta = 0.37$, $p < 0.001$), quality of life improved with better perception of health. Fourteen percent of variance in global quality of life was explained by general health perception.

5. Symptoms status had a direct negative effect on general health perception ($\beta = -0.52$, $p < 0.001$); patients with more disease symptoms had a low perception of their general health.

6. Characteristics of the individual (age, marital status and number of children) had a negative effect on functional status ($\beta = -0.22$, $p < 0.001$) of the patient, this was as expected for example functional status declined with increasing age.

Items 1 to 4 satisfied the basic structural model of Wilson and Cleary (1995), Item five also confirm their observation that direct relationship was possible between non-adjacent constructs.

Table 5-19: Direct Effects for the Wilson and Cleary HRQL Model in the SCD Population Sample

Path	Unstandardized B	SE (B)	CR	Standardised β	Explained variance R^2	Total effects Standardised β
BPF → SS	1.180**	0.278	4.250	0.666	0.443	0.666
SS → FS	-0.539**	0.084	-6.438	-0.534	0.388	-0.534
SS → GHP	-0.563**	0.120	-4.679	-0.525	0.547	-0.684
FS → GHP	0.316**	0.114	2.769	0.298	0.547	-0.298
GHP → QOL	0.452**	0.102	4.429	0.374	0.14	0.374
COI → FS	-0.198**	0.067	-2.951	-0.223	0.388	-0.223

*P < 0.05, **p < 0.01, SE = standard error, B = regression coefficient, β = standardised estimate, BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual.

Indirect effects

There were several significant indirect effects between non-adjacent levels of the model. These paths are presented in Table 5-20. The bootstrap bias-corrected confidence intervals are reported in this study as they have been established to be more accurate for testing the significance of indirect effects (MacKinnon *et al.*, 2002; Shrout and Bolger, 2002).

1. The biological-physiological construct had significant indirect effect on functional status through symptom status (β = -0.36, BC95%CI = -0.536 – -0.184, p < 0.01). The negative sign of effect was as expected as patients with worsened biological markers of health and more symptoms had reduced functional health.
2. Biological-physiological construct affected general health perception through symptom status and through functional status (BPF → SS → FS → GHP). The direction of effect was negative in line with expectations and significant (β = -0.46, BC95%CI = -0.661 – -0.265, p < 0.01). Patients who experienced worsening health, more symptoms and reduced functional status had low perception of their general health.
3. Biological-physiological construct affected overall quality of life through symptom status, through functional status and through general health perception (BPF → SS → FS → GHP → QOL). The effect was negative and significant (β = -0.17,

BC95%CI = -0.268 – -0.086, $p < 0.01$). Patients who experienced declining health due to the disease, more symptoms, reduced functional status and low health perception had reduced quality of life.

4. Symptoms status had indirect effect on general health perception through functional status (SS → FS → GHP). The direction of effect was negative ((β = -0.16, BC95%CI = -0.305 – -0.027, $p < 0.05$). Patients who had more symptoms and reduced functional health had low perceptions of their general health.
5. Symptoms status had indirect effect on overall quality of life through function status and through general health perception (SS → FS → GHP → QOL). The direction of effect was negative (β = -0.26, BC95%CI = -0.363 – -0.152, $p < 0.01$). Patients who had more symptoms, reduced functional health and low general health perception had reduced overall quality of life.
6. The indirect effect of functional status on overall quality of life through general health perception (FS → GHP → QOL) was positive, and the bias-corrected 95% confidence interval was significant (β = 0.11, BC95%CI = 0.014 – 0.236, $p < 0.05$). Patients who had better functional health and high general health perception had better overall quality of life.
7. Characteristics of the individual had indirect effect on general health perception through functioning status (COI → FS → GHP). The direction was negative and statistically significant (β = -0.07, BC95%CI = -0.168 – -0.012, $p < 0.05$).
8. Characteristics of the individual had indirect effect on overall quality of life through functioning status through general health perception (COI → FS → GHP → QOL). The direction was negative and statistically significant (β = -0.03, BC95%CI = -0.073 – -0.004, $p < 0.05$).

Table 5-20: Total Iindirect Effects for the Wilson and Cleary HRQL Model in the SCD Population Sample

Path	Unstandardised β	SE (B)[1]	Standardised β	BC 95% CI
BPF → SS → FS	-0.636	0.297	-0.355	-0.536 – -0.184**
BPF → SS → FS → GHP	-0.865	0.381	-0.456	-0.661– -0.265**
BPF → SS → FS → GHP → QOL	-0.391	0.173	-0.170	-0.268 – -0.086**
SS → FS → GHP	-0.170	0.077	-0.159	-0.305 – -0.027*
SS → FS → GHP → QOL	-0.331	0.077	-0.256	-0.363 – -0.152**
FS → GHP → QOL	0.143	0.073	0.111	0.014 – 0.236*
COI → FS → GHP	-0.063	0.036	-0.066	-0.168 – -0.012*
COI → FS → GHP → QOL	-0.028	0.019	-0.025	-0.073 – -0.004*

[1]Notes: Bootstrap standard error*P < 0.05, **p < 0.01 BC95%CI = bias-corrected 95% confidence interval, BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual.

In summary, this study identified six determinants of HRQL in sickle cell disease.

a) One direct determinant, the general health perception which explained 14% (95%BCI: 10% - 26%) of the variance;

b) two indirect determinants through general health perception, functional status and symptom status which explained 55% (95% BCI: 39% - 74%) of the variance;

c) two indirect determinants through functional status namely, symptom status and characteristics of the individual which explained 39% (95%BCI: 24% - 53%); and

d) one indirect determinant through symptoms status namely biological-physiological factor which explained 44% of the variance.

5.5 Objective four.

To Create a hierarchy of importance of the determinants as targets for potential intervention.

5.5.1 Research Question 6:

What is the relative importance of each construct?

Effect size

Effect sizes were obtained from the absolute value of the standardised path coefficients. From Table 5-20, large effect size was observed in the biological-physiological → symptoms status path (β = 0.67), the biological factor did not have any further direct effect on other factors. Symptoms status had direct effect on both functional status and general health perception. These effects were large (SS → FS, β = 0.53; SS→GHP, β = 0.53). The effect of functional status → general health perception path was of medium size (β = 0.3). Also, the effect size of the general health perception → overall quality of life path was medium (β = 0.37). characteristics of the individual only had direct path to functional status and the size was small (β = 0.22). Effect sizes of indirect paths ranged from small in COI→FS→GHP→QOL (β = 0.030 to medium in BPF→SS→SS→GHP (β = 0.46).

Total effect and percentage contribution of constructs

The total effects of the latent factors are displayed on Table 5-21. Symptoms had the highest impact on functional health and general health perception while general health perception had the highest impact on overall quality of life followed by symptom status.

Table 5-21: Total Effects

Factor	BPF	SS	FS	COI	GHP
SS	0.666				
FS	-0.355	-0.534		-0.223	
GHP	-0.456	-0.684	0.298	-0.066	
QOL	-0.17	-0.256	0.111	-0.025	0.374

Notes: BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual., QOL=Quality of Life

Tables 5-22 to 5-24 show the contribution of the latent factors as we move through the HRQL model continuum, from the initial end of the model, the biological function, to the end of the model, the overall quality of life. The Pratt index shows that biological-physiological factor contributed 28.2% of variance explained in functional status, 24.5% of variance explained in general health perception and 11.5% of total variance explained in the overall quality of life. Symptoms status contributed 57.7% to the variance explained in functional health, 53.7% of the variance explained in general health perception and 25.3% of the variance explained in overall quality of life. General health perception contributed 52.9% of the variance explained in the overall quality of life while the characteristics of the individual contributed 14.1% to the variance explained in functional status, 1.6% to variance explained in general health perceptions and less than 1% to variance explained in overall quality of life.

Table 5-22: Contributions to Functional Status

	BPF	SS	COI	R^2	BC 95% CI for R^2
Std Beta	-0.355	-0.534	-0.223		
Correlation	-0.430	-0.584	-0.342	0.39	0.24-0.53
Pratt index %	28.2	57.7	14.1		

Notes: BPF = Biological-physiological, SS = symptoms status, COI = characteristics of the individual.

Table 5-23: Contributions to General Health Perception

	BPF	SS	FS	COI	R^2	BC95%CI for R^2
Std Beta	-0.456	-0.684	0.298	-0.066		
Correlation	-0.478	-0.699	0.604	-0.219	0.55	0.39-0.74
Pratt index %	24.5	53.7	20.2	1.6		

Notes: BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual.

Table 5-24: Contributions to Global quality of life.

	BPF	SS	FS	COI	GHP	R^2	BC95%CI for R^2
Std Beta	-0.170	-0.256	0.111	-0.025	0.374		
Correlation	-0.179	-0.261	0.226	-0.082	0.374	0.14	0.1-0.26
Pratt index %	11.5	25.3	9.5	0.8	52.9		

Notes: BPF = Biological-physiological, SS = symptoms status, FS = functional status, GHP = general health perception, COI = characteristics of the individual.

5.6 Objective five

To Determine the health utility score and its associated factors in people with sickle cell disease

5.6.1 Research Question 7:

What is the health utility score and its determinants in the population?

The mean utility score in the population was 0.65 (SD: 0.12; Range: 0.310-0.965). The utility score was lower for participants who had co-morbidities than participants who did not (see Table 5-23). This difference was statistically significant ($p < 0.01$) with an effect size of 0.63. Women also had lower but not statistically significant utility score. The utility scores between patients with SS and SC genotypes was similar. Participants living alone and participants living with others also reported similar health utilities.

Table 5-25: Group Differences and Effects sizes

	N	Mean	SD	95% CI	P-value	Cohen's d
Gender						
Male	83	0.66	0.11	0.64 – 0.69	0.179	0.17
Female	117	0.64	0.12	0.62 – 0.66		
Marital Status						
Never married	151	0.66	0.12	0.64 – 0.68		0.12
Married	41	0.63	0.09	0.61 – 0.66	0.322	
Others (divorced, separated, widowed)	8	0.61	0.12	0.53 – 0.69		
Education						
≤ Primary	19	0.60	0.12	0.55 – 0.65		
Secondary	97	0.65	0.11	0.63 – 0.67	0.092	0.16
Post-secondary	84	0.66	0.12	0.64 – 0.67		
Employment						
Full-Time	43	0.66	0.11	0.63 – 0.67	0.732	0.06
Part-time	30	0.64	0.10	0.60 – 0.68		
Not employed	127	0.65	0.12	0.63 – 0.70		
Living situation						
Alone	18	0.62	0.08	0.58 – 0.65	0.227	0.30
With others	182	0.65	0.12	0.64 – 0.67		
Confidants						
Yes	171	0.651	0.11	0.60 – 0.70	0.891	0.02
No	29	0.647	0.13	0.63 – 0.67		
Genotype						
HbSS	170	0.651	0.12	0.63 – 0.67	0.894	0.03
HbSC	30	0.648	0.12	0.61 – 0.69		
Co-morbidity						
No	135	0.67	0.12	0.65 – 0.69	0.000	0.63
Yes	65	0.60	0.10	0.58 – 0.63		

The mean utility score for the 65 (32.5%) participants having comorbidities was 0.60 (SD = 0.10). Figure 5-7 shows that participants who had epilepsy, arthritis and leg ulcers reported lower utility scores. The score was below the mean for 8 out of the 11 comorbid diseases. Participants having epilepsy as comorbid condition reported the minimum quality of life.

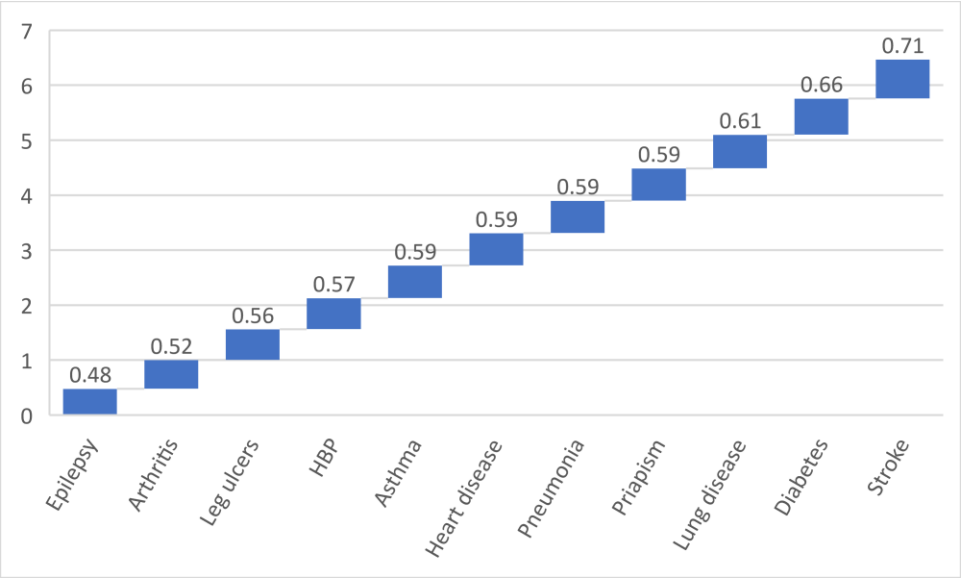


Figure 5-7: Mean Utility Score of Participants by Comorbid Disease

Utility score decreased with an increase in number of co-morbidities ($r = -0.32$, $p < 0.01$), depression ($r = -0.35$, $p < 0.01$), anxiety ($r = -0.41$, $p < 0.01$), somatic symptoms ($r = -0.39$, $p < 0.01$), DSEI ($r= -0.26$, $p < 0.01$) but exhibited a positive relationship with level of education ($r = 0.14$, $p < 0.05$). The association with age was also negative as expected but not statistically significant ($r = -0.13$, $p > 0.05$).

All the independent variables explained 27.9% of the variation (see Table 5-24). The bio-physiological variables were responsible for 13.2% with both measures, disease severity and number of comorbidities as predictors of health utility. The psychosocial variables were responsible for 9.4% variation in the model with anxiety as a major predictor of health utility in the patients. The sociodemographic factors of age and level of education added 5.3% percent variation. Thus, increased anxiety, disease severity and number of co-morbidities predicted reduced utility score while higher level of education predicted better utility score.

Table 5-246: Predictors of Health Utility Score

Variables	B	SE (B)	Stand. β	Statistic (t)	P	R^2	95% CI for β L	U
Block 1								
Constant	0.768	0.037				0.132	0.696	0.840
Disease Severity Index	-0.035	0.013	-0.182	-2.618	< 0.05		-0.062	-0.009
Number of comorbidities	-0.080	-0.021	-0.266	3.830	< 0.01		-0.122	-0.039
Block 2								
Constant	0.894	0.058					0.779	1.00
Disease Severity Index	-0.025	0.013	-0.127	-1.830	0.069		-0.051	0.002
Number of comorbidities	-0.017	0.024	-0.055	-0.696	0.487	0.226	-0.064	0.031
Anxiety	-0.067	0.026	-0.237	-2.592	< 0.05		-0.118	-0.016
Depression	-0.008	0.012	-0.063	-0.724	0.470		-0.031	0.015
Somatic Symptoms	-0.025	0.016	-0.139	-1.558	0.121		-0.057	0.007
Block 3								
Constant	0.969	0.060		16.190			0.673	0.920
Disease Severity Index	-0.028	0.013	-0.144	-2.125	< 0.05		-0.054	-0.002
Number of comorbidities	-0.025	0.024	-0.083	-1.044	0.298	0.279	-0.073	0.022
Anxiety	-0.059	0.025	-0.209	2.352	< 0.05		-0.109	-0.010
Depression	-0.008	0.011	-0.056	-0.664	0.508		-0.030	0.015
Somatic Symptoms	-0.029	0.016	-0.162	-1.859	0.065		-0.060	0.002
Age	-0.009	0.006	-0.091	-1.380	0.169		-0.021	0.004
Level of Education	-0.043	0.012	-0.237	-3.694	< 0.01		0.02	0.066

*P < 0.05, ** P < 0.01, ***=F statistic

CHAPTER SIX

DISCUSSION

6.0 Introduction

This study was undertaken to understand health-related quality of life and its predictors among adults with sickle cell disease in Nigeria. Some studies have been carried out in some high income nations to analyse predictors of HRQL in chronic diseases (Halvorsrud *et al.*, 2010; Taylor *et al.*, 2011; Carlson *et al.*, 2014; Kumar, Kroon and Lalloo, 2014; Vilhena *et al.*, 2014; Grove *et al.*, 2016; Yeng, Gallagher and Elliott, 2016) including SCD (Edwards *et al.*, 2001; Panepinto, 2012; Ivo and Pinto, 2013; Beverung *et al.*, 2015; Mastandréa *et al.*, 2015). However, in view of the different healthcare systems, cultural differences and other socioeconomic realities, such studies are unable to reflect the prevailing situation from a lower-middle income country like Nigeria because of the differences in weightings attached to the various factors (Curtis, 2000) which makes measuring quality of life a challenging task (Szabo, Orley and Saxena, 1997). This chapter discusses the findings of this study as related to the objectives of the study.

6.1 Characteristics

The mean age of participants in the current study was 27.9 which was comparable to similar studies in Nigeria, Cameroun 28.2 (Chemegni *et al.*, 2018), Saudi Arabia (Ahmed *et al.*, 2015) but younger when compared to about 30 years in UK (Anie, Steptoe and Bevan, 2002) and between 31-34 years in in US (Schaeffer *et al.*, 1999; Jenerette, Funk and Murdaugh, 2005; McClish *et al.*, 2006; Levenson *et al.*, 2008; Dampier *et al.*, 2011). This age difference could be related to the substantial difference between developed and developing nations in general life expectancies both in the SCD population as well as in the general population. In the SCD population, life expectancy in UK was 67 (Gardner *et al.*, 2016) compared with 21 in Nigeria (Chijioke and Kolo, 2009). Furthermore, while life expectancy in UK was 80 for

males and 83 for females, in Nigeria it was 55 for males and 56 for females (WHO global health observatory data, 2016). The low mean age in Nigeria reflected the low life expectancy common to people with SCD. SF-36 has been known to decrease with age of patients, the fact that people with SCD are younger and yet with substantially poorer scores in the subscales of SF-36 is quite revealing and of great concern that calls for effective intervention from healthcare providers and healthcare policy-makers.

Females were more in number than the male participants similar to reports of other studies (Kotila and Shokunbi, 2001; Jenerette, Funk and Murdaugh, 2005; Anie *et al.*, 2012). SCD is not a gender selective disease therefore the higher number of women could be explained in terms of health-seeking behaviour; women have been reported to be a more frequent seeker of information and healthcare services than men (Tudiver and Talbot, 1999; Courtenay, 2000a; Galdas, Cheater and Marshall, 2005). For example, Friedman (1989) has argued that the symptoms of weakness or fainting may be interpreted differently based on sex. Nathanson (1975) has suggested that women are more likely to use health services more than men because it is more socially acceptable for women to disclose information about their health status and to admit weakness while men are reluctant to engage in healthcare seeking (Jewkes and Morrell, 2010). Studies have shown that men show poorer health maintenance and fewer health-seeking behaviours than women (Schofield *et al.*, 2000). This behaviour is a product of gender constructions of masculinity, which affects self-management of chronic conditions (Courtenay, 2000b; Oliffe, 2004). These constructions of masculinity seem to be stronger among men of African origin as reported in African American men compared with European American men (Levant, Majors and Kelley, 1998; Levant *et al.*, 2003). In African culture, males are expected to show strength and endurance during times of crisis, to be the bread winners and leaders in their family and to endure pain (Ampofo and Boateng, 2007). Furthermore, studies of self-reported health status have shown that women have poorer health profiles than men across a range of chronic conditions

(Waldron, 1983) and they report or complain more than males when they are suffering from different types of illnesses (Ilesanmi, 2013). This result is therefore in line with findings in literature.

The HbSS genotypes which is the more severe type (Platt *et al.*, 1994) outnumbered the less severe HbSC. This is consistent with findings in other studies where the more severe HbSS was always reported to be more than HbSC in any sample (McClish *et al.*, 2006; Adams-Graves *et al.*, 2008; Mann-Jiles and Morris, 2009; Anie, Egunjobi and Akinyanju, 2010; Mastandréa *et al.*, 2015; Anim, Osafo and Yirdong, 2016).

A fifth of participants were married, similar to the findings in previous studies (Levenson *et al.*, 2008; Santos and Gomes Neto, 2013; McClish *et al.*, 2016). The low percentage of people with SCD who are married could be due to fear of being a burden on their spouse, or giving birth to a child with SCD (Adzika *et al.*, 2017), or inability to find a partner due to stigma (Jenerette, Funk and Murdaugh, 2005; Adeyemo *et al.*, 2015) or to consummate a relationship. A study conducted in Saudi Arabia found that more than 60% of adults with SCD were likely to cancel an at risk marriage, that is, marriage likely to produce an offering with haemoglobinopathy (Al Sulaiman *et al.*, 2008). Only 17% of participants in this study had a child compared with another study which reported 26%. Further study may be required to establish wheather this is due to financial and psychological implications of child rearing in their condition and associated burden. Chemengi *et al*, (2018) reported that having a child negatively affected their finances and could be a factor for anxiety and depression.

Eighty-nine percent of the participants had secondary education and beyond similar to other studies in literature. In a study of 78 adults with sickle cell in Cameroun 87.2% were reported to have level of education of secondary school and beyond (Chemegni *et al.*, 2018). Also, 86.5% of the 232 subjects in the US Pain in Sickle Cell Epidemiology Study (PiSCES) Cohort had secondary education and beyond (Levenson *et al.*, 2008). On the contrary, some

studies found low level of education among sickle cell patients (Santos and Gomes Neto, 2013). The reason for the high percentage of participants with higher education in the current study may be because this was a hospital-based survey and those attending hospital were those educated and are likely to be better informed about the disease and its management outcomes (Adzika *et al.*, 2017). Also, like the study in Cameroun, the University College Hospital, Ibadan is located in an area populated with University students, lecturers and top civil servants. Moreover Ibadan, where the study was carried out, is one of the most educationally more advantaged states in Nigeria (States in Nigeria were categorised as educationally advantaged and educationally less advantaged). About 36.5% had either full-time or part-time employment compared with Nigeria's unemployment rate 0f 18.8% and 21.2% underemployment rate (National Bureau of Statistics, 2017) . This is comparable to the findings of Belgrave et al (1991), Santos and Neto (2013) and Chemegni et al (2018) who reported 32%, 31.2% and 30.8.%, respectively. These low rates of employment reflect the impact of the disease. Another study in Brazil however reported that 88% of their participants were employed, although this high rate could be attributed to the low sample size of 25 enrolled in the study due to limited facility at their centre (Vilela *et al.*, 2012).

6.2 Objective one.

To Describe the HRQL profile of adult living with sickle cell disease

Chronic diseases have been widely reported to affect health-related quality of life with age, type of pathology, family support, values, beliefs and socio-economic level indicated to affect the perception of HRQL (Moreno *et al.*, 1996; Santos and Gomes Neto, 2013). This section of the study examined the health-related quality of life profile in a population of sickle cell disease. The findings of this study reveal a low quality of life in the SF-36 domains compared with the standardised norm scores. Using the norm-based score for comparability with the general population and other diseases, all the SF-36 domains were below the general population score except vitality which was similar to the general population mean. This is

consistent with other studies (Dampier *et al.*, 2011; McClish *et al.*, 2016) which reported decrement in SF-36 domains. In a study of 408 SCD patients in the PiSCES cohort, patients with SCD experienced worse HRQL compared to the general population and similar to patients undergoing haemodialysis (McClish *et al.*, 2016).

Compared with the norm, very low scores were observed in functioning, Physical Functioning (below 40) and Role Physical (below 45) were similar to findings in previous studies (Santos and Gomes Neto, 2013). This underscores the limitations experienced by people with SCD in daily activities due to the effects of the disease on physical health resulting in reduced quality of life. McClish et al (McClish *et al.*, 2016) compared their results in thePiSCES cohort with three cohorts' studies of other chronic diseases; asthma, cystic fibrosis and haemodialysis. They found that SCD patients had significantly lower scores than the general population in all domains of SF-36 except Mental Health. Compared with cystic fibrosis, SCD patients reported significantly lower scores in all the domains except Mental Health. In addition, when compared with asthma, scores were similar in physical functioning, Role Physical, Role Emotional and Mental Health but significantly worse in Bodily Pain, General Health, Vitality and Social Functioning. When compared with haemodialysis patients, sickle cell patients scored significantly worse in Bodily Pain, General Health and Vitality but similar in Role Physical, Social Functioning, Role Emotional and Mental Health. SCD patients were however significantly better in Physical Functioning; this may be due to the coping strategy of the sickle cell patients. According to Anie et al, (Anie, Steptoe and Bevan, 2002) coping mechanisms differ between people such that functional ability may not reflect the level of disease severity. Another study in the UK which compared SF-36 subscales with the general population and people with haemochromatosis reported that adults with sickle cell had poorer quality of life on all eight subscales of SF-36 compared to the general population (Anie, Steptoe and Bevan, 2002). The authors also showed that the quality of life in adults with sickle cell was similar to the quality of life in

people with hemochromatosis but worse in Role Emotional. HRQL domain scores of participants in the current study were compared with scores of hypertensive patients in southwest Nigeria, the same geographical location where this study took place. The scores were similar in Role Physical, and Mental Health. Sickle cell patients had higher scores in Physical Functioning but worse scores in Bodily Pain, Social Functioning, Vitality and Role Emotional.

The highest mean score was observed in Vitality, this was similar to the result obtained in Brazil in a study of 32 SCD patients (Santos and Gomes Neto, 2013) and the study of 1046 US adults with sickle cell from the Comprehensive Sickle Cell Centres Consortium (Dampier *et al.*, 2011). Better Vitality reflects the tendency of patients with SCD to seek better coping strategies against feelings of tiredness and exhaustion due to pain, fatigue and depressive symptoms that they often experience (Santos and Gomes Neto, 2013). Also, spirituality, belief system and optimism may have offered some support (Adegbola, 2011) According to Anie et al (2010), coping responses, acquisition of new skills to deal with the sickness, and modification of daily lifestyle are likely to reduce the effect of the disease on the individual. Recourse to spiritual healing (prayer) has also been reported among Africans as an alternative approach to or in addition to medical treatment (Omonzejele, 2008). In a study, Mann-Jilles and Morris (2009) reported that African-Americans tend to use religious/spiritual practices as a primary means of coping. People of Africa origin are highly spiritual by nature and culture (Adegbola, 2011). Santos and Neto (2013) also opined that health conditions improve when optimism is part of the individual's psychological condition.

Mental Health had the next highest mean score after Vitality, in fact the non-normed score was highest for Mental Health in the present study. Similarly, McClish and colleagues reported that SCD patients in their study did not report poorer Mental Health than the general US population (McClish *et al.*, 2016). Studies have shown that though chronically ill people may report worse health than the general population, they appear to have comparable

wellbeing (Schlenk *et al.*, 1997; Alonso *et al.*, 2004; Rijken *et al.*, 2005). Such reports of good psychological wellbeing despite a chronic disease condition, has been attributed to increased social support, lack of other stressors or a 'response shift' (changes in one's internal standards which affects changes in one's values, priorities and evaluation of a construct) connected with managing their chronic disease (Schlenk *et al.*, 1997). Such 'response shift' could be associated with scale recalibration which implies change in the patients' values, or reconceptualization of their mental health and wellbeing (Rapkin *et al.*, 2004; Sprangers *et al.*, 2010) over time to accommodate their disease condition. However, in a study of haemodialysis patients, Ris et al (2005) disagreed with the concept of scale recalibration but rather argued that people have only adapted to their condition. In contrast, a study of 27 adults with sickle cell in Brazil reported mental health as the most affected, the authors (Ohara *et al.*, 2012) suggested that pain crises, and frequent hospitalisation may cause anxiety, depression, aggressive behaviour and fear (Ohaeri *et al.*, 1995; Ohaeri and Shokunbi, 2002; Adegoke *et al.*, 2012). Also, limitations in achieving some tasks due to pain may trigger feelings of inferiority and low self-esteem which affect mental health (Ohara *et al.*, 2012).

Mean bodily pain in this study was comparable to findings found elsewhere (Ahmed *et al.*, 2015; Mastandréa *et al.*, 2015; McClish *et al.*, 2016). Female participants reported significantly worse scores in bodily pain and social functioning than their male counterparts, similarly to previous studies (McClish *et al.*, 2006). Other studies have also shown that women reported worse bodily pain not only in sickle cell (Cleeland *et al.*, 1994; Fillingim *et al.*, 2003) which may be attributed to physiological gender difference rather than response bias factors (McClish *et al.*, 2006). Laboratory studies have shown that women have a heightened neurophysiological response to heat and physiological response to noxious stimuli (Fillingim and Maixner, 1995; Fillingim, Edwards and Powell, 1999), higher pain intensity and pupil dilation has also been reported in women at high heat pressure levels

(Ellermeier and Westphal, 1995), Some have also suggested that differences may be due to men's tendency to ignore pain or at least avoid public expression of pain (McClish *et al.*, 2006).

Forty-two percent of participants in this study had a pain frequency equal or greater than 3 times within 6 months before the study. In a study of 6-month pain diary of adults with SCD, 29% reported sickle cell pain everyday (Smith *et al.*, 2008). Pain in SCD is both acute and chronic, with acute pain having the potential to develop into a chronic sickle cell pain (Smith *et al.*, 2008). The mean number of pains reported in this study was 2.37 in the last six months with women reporting significant higher mean number of pain than their male counterpart ($P < 0.05$) similar to results of previous studies (McClish *et al.*, 2006; Chemegni *et al.*, 2018). Pain has a negative impact on the financial, emotional, functional, physical, social, occupational dimension of life (Ferrell, Wisdom and Wenzl, 1989).

High utilisation of healthcare resources as measured by emergency department visits ≥ 3 (Aisiku *et al.*, 2009) was reported by 12% of the participants in this study. In a study of 232 adults with sickle cell enrolled in the PiSCES project, high emergency department utilisation was estimated at 35% (Aisiku *et al.*, 2009) which was much higher than in this study. This could be because the PiSCES participants had better medical facilities, access and financial support for healthcare usage than the population in the current study. Due to government low spending on health, Nigerian hospitals lack medical facilities for quality care, additionally, the out of pocket heath financing system makes good healthcare inaccessible and unaffordable to the majority (Ogunbekun, Ogunbekun and Orobaton, 1999; Asuzu, 2004; Galadanci *et al.*, 2013; Obansa and Orimisan, 2013). Aisiku and colleagues reported that higher emergency department users reported higher mean pain and distress level than other sickle cell patients (Aisiku *et al.*, 2009). Three or more emergency admissions is a likely marker of disease severity (Aisiku *et al.*, 2009) and severe enough to require hydroxyurea therapy (Samuel Charache *et al.*, 1995). High emergency department utilisation

was associated with worse Social Functioning, General Health, and Mental Health similar to the result of Chemegni and colleagues (2018). Also, a high frequency of hospital admissions was associated with limitations in Role Physical, Role Emotional, worse Bodily Pain, reduced General health and Mental health in agreement with previous study (Chemegni *et al.*, 2018).

In the current study, 83% had history of blood transfusion similar to the study in Saudi Arabia where 85.9% of the 629 participants reported history of blood transfusion (Ahmed *et al.*, 2015). According to Ugwu *et al* (2011), the higher frequency of blood transfusion may be associated with higher frequency of sickle cell related complications including chronic leg ulcers.

Sickle cell is a debilitating genetic disease in which the number of complications increases significantly with advancing age (Dampier *et al.*, 2011). The presence of other comorbid conditions was therefore expected in the population. Thirty-two percent (32%) of participants reported at least one comorbid disease. Similar studies have reported comparable high prevalence of comorbid conditions in SCD. For example, in the study of adults with sickle cell in Cameroun, a comorbidity prevalence of 23% was reported (Chemegni *et al.*, 2018). Number of comorbidities in the present study correlated positively with age, in agreement with previous studies (Dampier *et al.*, 2011). The prevalence and effect of different comorbid diseases in this study was found in most cases to be comparable to existing literature on the subject.

Leg ulcers had the highest prevalence in this study estimated at 12.5%. Leg ulcers are the most common cutaneous manifestation associated with sickle cell disease and responsible for impaired quality of life (Minniti *et al.*, 2010; Umeh *et al.*, 2017). Leg ulcers have been reported to cause pain, negatively affect physical and emotional function and with the potential to impact on multiple dimensions of an individual's daily life in chronic diseases

(Phillips *et al.*, 1994). The prevalence of leg ulcers in this study was similar to the findings in related studies. Ugwu *et al* (2017) reported 12% in their study carried out in the South Eastern part of Nigeria. In a cohort study of 505 adults with SCD in US, a prevalence of 18% was reported (Minniti *et al.*, 2010). In the data of Comprehensive Sickle Cell Centres Clinical Trial Consortium (CSCCTC), a prevalence of 12% was reported (Dampier *et al.*, 2011). Another study in Nigeria (Kotila and Shokunbi, 2001) however reported 8% prevalence, this low percentage could be attributed to the sample used as most of the subjects in their study were much younger with expected fewer complications. Leg ulcers were associated with reduced scores in seven domains of SF-36 as well as in Physical and Mental component summary except in Vitality where they appeared to have no significant impact. Percentage of patients with priapism in this study was 8.5% which was lower than the 16 % in the CSCCTC study (Dampier *et al.*, 2011). A similar result was obtained for hypertension; 8% in this study compared with 12% in the CSCCTC study. The CSCCTC study had a larger sample and wider coverage and could be considered more representative of the population. Also, the data were from different countries and cultures with different medical orientations, significant differences in health experience and behaviour (Marks *et al.*, 2005), access to health facilities and affordability of healthcare. Priapism was associated with worse health in Mental Health and the Mental component summary score. Hypertension was associated with limitations in Role Physical, Bodily Pain, Vitality, General Health and Mental Health and the Physical and Mental Health summary scores. The prevalence of arthritis was 5.5% and arthritis was associated with limitations in Role Physical, Role Emotional, Bodily pain, Mental Health and MCS. This is in line with previous studies which suggested that people with arthritis were more likely to report lower scores on physical functioning-related measures, suggested to be related to pain (Maddigan, Feeny and Johnson, 2005). Asthma in this study did not associate with HRQL contrary to the findings of CSCCTC study (Dampier *et al.*, 2011). Diabetes, and Epilepsy associated with reduced General Health and reduced

Mental health respectively. Pneumonia was associated with all domains of SF-36 except Role Physical and Role Emotional while stroke was associated with limitations in Physical Functioning. A study of US Medical Expenditure Panel Survey data also showed that emphysema, heart disease, stroke, high BP, diabetes and asthma associated with lower scores of EQ5D, a measure of quality of life (Lubetkin *et al.*, 2005; Singh *et al.*, 2017).

Older participants reported worse scores in Role Physical, Role Emotional, General Health and Mental Health but reported similar scores in the other subscales. This was supported by related previous studies. In a study of 256 adults with SCD in Jamaica, increasing age was associated with Physical Health Summary score (Asnani *et al.*, 2008). Also, a US study by Dampier et al (2011) reported that age was associated with impaired health. Another study reported that older patients had worse Physical Health, Social Functioning and Mental Health (Woods et al, 1997). Participants who were married reported limitations in Role Emotional ($p < 0.05$) than those who were single, divorced, separated or widowed. In the current study, participants living alone had worse score in Social Functioning, a similar study reported that unsatisfactory social support associated with worse quality of life in adults with SCD (Chemegni *et al.*, 2018). Participants in this study who had confidants reported better health in General Health and Mental Health domains of SF-36 than participants without confidants.

The prevalence of anxiety symptoms (GAD7 $\geq$ 10) in this study was 12%. This was comparable to 14% in Cameroun (Chemegni *et al.*, 2018) but higher than reported by some other authors (Levenson *et al.*, 2008; Sogutlu *et al.*, 2011) where 6.5 % of participants reported anxiety. There was no gender difference in anxiety.

Asnani et al (2010), showed that complications in sickle cell tend to increase psychiatric complications in the patients especially depression. Nineteen percent of participants in the current study presented depressive symptoms (PHQ9 $\geq$ 10). This is in the range reported

from previous studies of patients with SCD which ranged from 13.2% to 27% (Ohaeri *et al.*, 1995; Schaeffer *et al.*, 1999; Hasan *et al.*, 2003; Levenson *et al.*, 2008; Asnani *et al.*, 2010; Sogutlu *et al.*, 2011; Gibson *et al.*, 2013) and similar to results obtained for other chronic illnesses such as coronary artery disease and diabetes mellitus. However, because different measures were used, the result of the comparison is interpreted with caution.

Depression has been reported to be more among people with SCD compared with healthy controls (Molock and Belgrave, 1994) and also among people with other chronic diseases with consequent negative influence on general quality of life ratings (Skevington, 1998). Causes of depression in adults with SCD could be due to disease progression or reaction to stigma (Jenerette, Funk and Murdaugh, 2005), or repeated hospitalisation (Comer, 1998). Studies have shown that SCD patients are being stigmatised (Smith *et al.*, 2006; Adeyemo *et al.*, 2015) by healthcare providers, who sometimes see them as people addicted to opiates (Jenerette, Funk and Murdaugh, 2005; Jenerette and Brewer, 2010; Haywood Jr, 2013) as well as by society and peers (Jenerette, Funk and Murdaugh, 2005; Adeyemo *et al.*, 2015). According to Hasan et al, (2003) factors that associated with depression include increase in blood transfusion, low level of pain control, low income, female gender and medication with hydroxyurea. Levenson et al (2008) identified increasing age and low income as factors that associated with depression symptoms. The display of anxiety and depressive symptoms by a substantial proportion of patients in this study requires that attention be given by healthcare personnel to them. For example, patients could be screened for symptoms of anxiety and depression and strategies be evolved to improve their psychological well-being in addition to use of medications to manage physical symptoms (Wan *et al.*, 2016).

High somatic symptoms (PHQ15≥ 15) was 13.5% comparable to 18.3% in Sogutlu *et al* (2011). Worse somatic symptoms was observed in female participants similar to findings in the PiSCES cohort (Sogutlu *et al.*, 2011). There is a high correlation among somatic symptoms anxiety and depression. This result is similar to findings in studies of sickle cell

patients (Sogutlu *et al.*, 2011). Low anxiety and depression were observed among patients who were aged above 50 years compared to younger participants in the present study. There is need for further study to investigate whether this was due to their been able to live beyond their expectation especially since the average age at death was 21.3 years (Ogun, Ebili and Kotila, 2014) in Nigeria and life expectancy at birth in the general population was around five decades. (WHO, 2015). Further study is also required to find out whether living above the average lifespan was responsible for less expression of anxiety or depression at this age especially since they are aware from early age that they have shortened lifespan (Thomas and Taylor, 2002). Moreover, at this age, they might have learnt some coping strategies that has enabled them to live better while the fear of early death associated with younger age (Anie, Egunjobi and Akinyanju, 2010) would have been overcome. Worthy of note is that quality of life is a dynamic construct which implies that people may redefine their internal standards of what constitutes health and change their idea of quality of life as they grow older (Schwartz *et al.*, 2004). This response shift may influence them to lower their expectations about what they value as good quality of life (Camacho et al., 2002). Gibson and colleagues also found higher depressive symptoms among younger individuals with SCD and suggested that this was a pointer to emotional maturity resulting in greater ability to cope with the disease as patients grow older (Gibson *et al.*, 2013)

6.3 Objective two.

To Characterize predictors of HRQL in adults with sickle cell disease

The current study examined the relationship between bio-physiological, psychosocial and sociodemographic variables and health-related quality of life measured by the SF-36.

SCD Genotype did not associate with any of the subscales of SF-36. Therefore, this study has shown that the more severe genotype HbSS was not responsible for worse quality of life in the patients. Conflicting results have been reported in literature as to the effect of genotype

on quality of life of sickle cell patients. For example, in the study of both the CSCCTC and PiSCES cohorts of sickle cell patients in US, genotype did not associate with quality of life domains (Dampier *et al.*, 2011; McClish *et al.*, 2016). Additionally, a study of 256 patients (Asnani *et al.*, 2008) and another independent study of 277 sickle cell patients and 65 controls (Asnani *et al.*, 2010) both in Jamaica did not show any correlation between genotype and quality of life. Furthermore, van Tujin et al (2010) in a study of 94 adults with sickle cell in Amsterdam, reported that genotype and the presence of chronic injury in organs were unrelated to quality of life while pain rate and social circumstances did. However, Panepinto (2012), reported that laboratory markers for sickle cell such as genotype, foetal haemoglobin (HbF) and dehydrogenase were associated with diminished quality of life Mastandrea and colleagues also reported that more severe genotype decreased role physical and general health in adult sickle cell patients in Brazil (Mastandréa *et al.*, 2015). Different methods of treatment, patients' adherence to treatment regime and affordability of treatment medications might be responsible for these differences. According to Mastandrea et al, results from studies on genotype and quality of life may be related to the quality of treatment given to the patients, whether treatment was well managed by the physician and adhered to by patients and whether the patient can afford to buy medication (Mastandréa *et al.*, 2015). Anie *et al* has argued that how patients cope with the disease rather than its severity may be responsible for differences in psychosocial functioning(Anie, Steptoe and Bevan, 2002; Anie, 2005).

In this study, the presence of comorbidity resulted in lower scores in all the domains of SF-36 and statistical significance was observed in all, except in physical functioning and vitality where the difference was not significant. A negative correlation was observed between increase in number of comorbidities and all the domains of SF-36 ($p < 0.01$) with non-significance only in Physical Functioning. This association is consistent with previous studies. In a type-2 diabetic population, number of comorbidities was significantly negatively correlated with six domains of the SF-36 (Anderson *et al.*, 1997). A study in the

Saudi Arabian population of adults with sickle cell disease revealed that other chronic diseases significantly associated with Vitality, Mental Health and Social Functioning (Ahmed *et al.*, 2015). Increase in the number of comorbidities predicted worse health in seven domains of the SF-36 and the physical and mental summary scores of SF-36 but did not predict Physical Functioning. A one-point increase in comorbidities will lead to between 0.20 to 0.82 decrease in scores on the subscales. For example, a unit increase in number of comorbidities will lead to a12.2 points (conventional score) or 8.7 points (normed score) reduction in Role Emotional. This result is consistent with findings in literature. Ahmed *et al.,* (2015) reported that other diseases in SCD predicted worse health in Vitality, social functioning and Mental Health. In a population of 331 diabetic veterans, increase in diabetic complications was associated with significant decrease in six of the domains of SF-36 namely Physical Functioning, Role Physical, Social Functioning, Bodily Pain, Vitality and General Health). Disease severity predicted worse Role Emotional, Social Functioning, Bodily Pain, Physical Health Summary and Mental Health Summary.

Anxiety symptoms was correlated with all the SF-36 domains except Physical Functioning and predicted limitations in Role Physical, Role Emotional, Social Functioning, worse General Health, Mental Health and Mental component summary scores. This is consistent with previous findings (McClish *et al.*, 2006). A similar result was reported in haemodialysis, where anxiety symptoms predicted worse Social Functioning, Mental Health, and Mental component score (Birmelé *et al.*, 2012) and in coronary artery disease (Höfer *et al.*, 2005)

More depressive symptoms predicted worse Physical Functioning, Vitality, and Physical component summary in this study. In a related study of 77 adults wiSCD in Brazil, depression associated with both the Physical and Mental components of quality of life (Treadwell *et al.*, 2005). Another study reported that depression and anxiety predicted more daily pain and poorer Physical and Mental quality of life in adults with sickle cell (Levenson

et al., 2008). In the PiSCES cohort, depression predicted Physical and Mental Health. In other chronic diseases, depression was a strong predictor of domains of HRQL. For example, in chronic coronary artery disease, depression was associated with more Physical limitations and worse quality of life. Depression also predicted reduced quality of life in other chronic diseases including hepatitis C (Olson *et al.*, 2005) and diabetes mellitus (Egede, 2004). Studies have shown that depression had similar or higher impact on quality of life than objective bio-physiological factors (Bair *et al.*, 2003; Katon, Lin and Kroenke, 2007). Depressed patients are more likely to entertain a negative perception of their health status which affects their HRQL (Sullivan *et al.*, 2000). Depressive symptoms in patients with sickle cell disease also appear to be a function not only of demographics but also disease severity (Hasan *et al.*, 2003). The impact of depression on the quality of life of sickle cell patients is important; Molock and Belgrave (1994) has suggested that when there is evidence of poor psychological adjustment in patients with sickle cell disease, the role of socioeconomic status needs to be explored, as factors such as financial difficulties, racial discrimination, and lack of social support are known to contribute to depression in physically healthy African Americans. However, Hilton et al (1997) did not find any significant relationship between depression and sickle cell in adults. Alao and Cooley (2001) suggested that small sizes, retrospective design and self-report may be responsible for the conflicting results.

Somatic symptoms were found to be significantly negatively correlated with all the subscales of SF-36. This was similar to findings in the PiSCES project where somatic symptoms burden significantly associated with all subscales of SF-36 (Sogutlu *et al.*, 2011). Earlier studies of primary care patients have shown that people with high somatic symptoms reported poorer quality of life (Kroenke, Spitzer and Williams, 2002; Kroenke *et al.*, 2010). In this study, somatic symptoms also predicted Bodily Pain, Vitality and General Health. A similar study also showed that subjects with more somatic symptoms reported higher pain

and that high somatic symptoms predicted increased sickle cell disease related healthcare utilisation including hospitalisation, and frequency of visits to physicians (Sogutlu *et al.*, 2011).

Sociodemographic variables that predicted quality of life domains in this study include older age predicted limitations in Role Physical similar to results of Treadwell et al (2015), female gender predicted worse Bodily Pain, being married predicted worse Role Emotional and Social Functioning similar to findings of Ahmed *et al.*, (2015) which showed that being married predicted worse Role Emotional, Vitality, Social Functioning and Mental Health; and having confidants predicted better General Health and Mental Health. This contrasts with a study of people with heart failure where having a confidant or marital status were not associated with quality of life (Heo *et al.*, 2005). Furthermore, living with others predicted better Social Functioning and Mental Health component Summary.

6.4 Objective three.

To Test the Wilson-Cleary HRQL model in the population of adults with sickle cell disease.

This section examined the determinants of quality of life in SCD using the Wilson and Cleary (1995) model. The aim was to test the structural paths of relationship between biophysiological factors, symptoms status, functioning, general health perception and overall health-related quality of life as hypothesised by Wilson and Cleary. The effect of characteristics of the individual and of the environment on the main factors were also examined as suggested by the authors. Structural equation modelling (SEM) was used to evaluate the model because the structural modelling techniques permits simultaneous estimation of a set of measurement models and structural paths coefficients (Höfer *et al.*, 2005), and has been recommended for development of models in HRQL research (Smith, Avis and Assmann, 1999). Several studies that empirically evaluated Wilson and Cleary

model in chronic diseases have also used SEM techniques (Höfer *et al.*, 2005; Baker, Pankhurst and Robinson, 2007; Shiu *et al.*, 2014; Mayo *et al.*, 2015; Santos *et al.*, 2015b)

The findings of the current study supported the usefulness of the Wilson and Cleary model as a theoretical framework to understand relationships among clinical and psychosocial factors in chronic diseases and offers insight to enhance quality of life in patients with sickle cell disease. The result supported the main structural relationships as hypothesised in the model. Bio-physiological factors predicted symptoms, symptoms predicted functioning, functional status predicted general health perception and general health perception predicted overall quality of life. The data also supported the hypothesis that characteristics of the individual influenced functional status but did not support paths between the characteristics of the environment to symptoms, health perception and overall quality of life. The data did not support the influence of the characteristics of the environment on any of the main factors as well.

The study established a significant path between bio-physiological factors and symptoms status. Worsening health conditions indicated by increased disease severity and increased number of comorbidities or complications predicted more symptoms in the patients. Forty-four percent of variance in symptoms status was explained by bio-physiological factors. Furthermore, bio-physiological factors had an indirect effect on functioning through symptom status as hypothesised by Wilson and Cleary. Similar results have been reported for xerostomia (Baker, Pankhurst and Robinson, 2007), coronary artery disease (Höfer *et al.*, 2005) and stroke (Mayo *et al.*, 2015). The effect size of the present study was fairly large (Cohen, 1988) indicating a strong impact. The large effect may be as a result that SCD is a debilitating life-threatening disease which is often accompanied with, and /or is responsible for triggering symptoms in patients. However, some studies failed to support such relationships between bio-physiological factors and symptoms (Arnold *et al.*, 2005; Shiu *et al.*, 2014); Shiu et al (2014) who studied community-dwelling older Chinese with diabetes

explained that the failure to support relationship between bio-physiological factor and symptom status may be due to their sample which consisted of older adults with stable diabetes control, moreover, Wilson and Cleary also stated that bio-physiological factors may be unrelated to symptoms status in some disorders.

Symptoms status (anxiety, depression, bodily pain, mental health, somatic symptoms) had a direct significant link with functional status demonstrating that more symptoms significantly predicted reduced daily functioning. About 39% of variance in function status was explained by symptom status and characteristics of the individual. In addition, symptoms had a significant indirect pathway through functional status to general health perception indicating that more symptoms led to limitations in functioning and reduced general health perception leading to impaired quality of life. Furthermore, symptoms had a direct link to general health perception leading to a low health perception and reduction in quality of life. Wilson and Cleary did not draw a direct link between symptoms and health perception but suggested that such non-adjacent pathways are possible (Wilson and Cleary, 1995). This result is therefore consistent with the intent of the model. Several studies including those on oral health, HIV/IDS and coronary artery disease (Höfer *et al.*, 2005; Sousa and Kwok, 2006; Baker, Pankhurst and Robinson, 2007) supported the direct pathway between symptoms status and functioning and an indirect link to general health perception mediated by functional status. Some studies also supported the direct pathway between non-adjacent latent constructs. In a study of people recovering from stroke (Mayo *et al.*, 2015), a non-adjacent link between symptoms and general health perception was supported. Similarly in a study of people with xerostomia (Baker, Pankhurst and Robinson, 2007), the non-adjacent link between symptoms and general health perceptions, between symptoms status and overall quality of life and between functional status and quality of life were supported. Furthermore, study of chronic obstructive pulmonary disease and chronic heart failure supported non-adjacent relationships (Arnold *et al.*, 2005).

The direct effect of functional status on general health perception and the indirect effect of functional status on overall quality of life mediated by general health perceptions as revealed in this study is consistent with the Wilson and Cleary model. Patients who experienced limitations in daily functioning had lower health perception and impaired quality of life. Related studies reported similar findings, for example, in HIV (Sousa and Kwok, 2006). On the contrary, Mayo and colleagues did not find a direct link between functional status and general health perception in people with stroke. They suggested that this might be due to their sample which consisted of older persons in a community dwelling and only functional older persons with stroke could return and remain at home (Mayo *et al.,* 2015).in the current study, 55% of variance in general health perception was explained by the direct pathway from functional status and the non-adjacent direct pathway from symptom status.

The path from general health perception to overall quality of life was positive and significant in agreement with the model indicating that a positive general health perception predicted better overall quality of life. Comparable results have been obtained from several studies in diabetes (Shiu *et al.*, 2014), heart failure (Heo *et al.,* 2005; Krethong *et al.*, 2008) oral health (Santos *et al.,* 2015b), generalised anxiety disorder (Wyrwich *et al.*, 2011) and coronary artery disease (Höfer *et al.*, 2005).

Although Wilson and Cleary did not draw any path to connect the characteristics of the individual and the characteristics of the environment to the main concepts in their diagram, they however indicated that these two concepts (characteristics of the individual and the characteristics of the environment) would influence symptom status, function status, general health perception and the overall quality of life (Wilson and Cleary, 1995). The data in this study were only able to support a significant path between the characteristics of the individual and function status but did not support significant path between the characteristics of the environment and any of the main concepts. This is similar to the result in coronary artery disease where a path from the characteristics of the individual to functioning status

was supported (Höfer *et al.*, 2005). However, several previous studies did not investigate the influence of the characteristics of the individual and of the environment (Sousa and Kwok, 2006; Baker, Pankhurst and Robinson, 2007).

These findings provide insight into the predictors of health-related quality of life in people with sickle cell disease and highlight the importance of assessing subjective symptoms alongside biological factors both in research and clinical practice geared towards the management of the disease. The model has depicted health-related quality of life in sickle cell disease as grossly impaired and influenced by a combination of bio-physiological, sociodemographic and psychosocial factors suggesting the necessity for a multidisciplinary approach to the management of the disease because physiological treatment is insufficient to help improve the quality of life of patients. Furthermore, the model is useful to direct choice of study design, research instruments and intervention and rehabilitation programmes (Wettergren, Björkholm, Axdorph, Langius-Ekiöf, *et al.*, 2004).

6.5 Objective four.

To Create a hierarchy of importance of the determinants as targets for potential intervention.

Evidence from this study shows that symptoms was the most important predictor of general health status and quality of life in SCD. Symptoms monitoring, and management are important to the improved quality of life of the patients. Symptom status in this study were measured by anxiety, depression, bodily pain, somatic symptoms and mental health. Hofer et al (2005), in their prospective study of 432 people with coronary artery disease reported that depression was the most important indirect influence on the course of HRQL in coronary artery disease followed by anxiety symptoms. Additionally, in a study of 422 Thai patients with heart failure, symptom status had the most significant impact on HRQL both directly

and indirectly through functional status and general health perception (Krethong *et al.*, 2008). According to Heo et al (2005), general health perceptions and symptom status are the strongest and most consistent factors associated with HRQL in heart failure. In sickle cell disease, pain and depression are the most common symptoms that reflect patients' subjective perception of presence and severity of abnormal physical and physiological sensations (Heo *et al.*, 2005).

6.6 Objective five.

To determine the health utility score and its associated factors in people with sickle cell disease.

This study also investigated the preference-based measure or utility scores of HRQL in sickle cell disease. Preference-based measures or health utilities are designed to investigate across domains of health to provide a single score that incorporates how patients (or the general population) value experiencing a given health state that is defined by level of functioning and well-being in those domains. Such scores are important to measure the burden of diseases. The mean utility score for SCD patients, in the present study, (0.65±0.12) compares with the utility score (0.66±0.14) reported for people with age-related macular degeneration (Espallargues *et al.*, 2005) and those with chronic kidney disease (0.67±0.13) (Davison, Jhangri and Feeny, 2009) but lower than the utility score of (0.745±0.137) reported in adults with type 1 diabetes (Peasgood *et al.*, 2016), and that for overweight and obese women with urinary continence (0.75±0.10) (Pinto *et al.*, 2011). Anie *et al*,(Anie *et al.*, 2012) reported a utility score of 0.39±0.40 for SCD patients on admission for pain which improved to 0.65±0.29 after treatment which is similar to our result. Lower utility values indicate that SCD can substantially diminish the HRQL of the affected individual.

The lower utility scores in women than men found in this study might not be statistically significant, but this difference and its 95% CI could be of clinical importance and requires

further study. The same conclusion goes for the difference between those living alone and those living with others, because a difference of 0.03 could be clinically important (Walters and Brazier, 2003; Khanna *et al.*, 2007). The finding of a significant difference between those who had at least one co-morbidity compared to those who had none deserves some comments. SCD patients are a vulnerable, chronically ill population with a high prevalence of co-morbidities which contributes to reduced quality of life in chronic diseases (Rijken *et al.*, 2005).

Age was negatively associated with utility, as expected, because SCD patients are exposed to increased clinical complications as they age. This supports findings from a general UK population where utility score was reported to decrease as age increases (Berg, 2012) as a result of age-dependent end-organ dysfunction associated with the disease. The negative associations of anxiety and depression with health utility found in this study, support previous studies where these variables were reported to associate negatively with HRQL in SCD (Edwards *et al.*, 2001; McClish *et al.*, 2006; El-Shinnawy *et al.*, 2013; Mastandréa *et al.*, 2015). The regression modelling showed that disease severity, anxiety, number of co-morbidities and education were strong predictors of health utility score. In terms of the direction of effects, these impacts were as expected. This result also has implications for new therapy and healthcare costs. For example, if a new treatment or service, at a cost of £100 produces a difference of 0.02 on the utility scale compared to existing treatment this would be cost effective as it translates to £5,000 (£100/0.02) per QALY (Hays *et al.*, 2014). Such a saving would be substantial in sub-Saharan Africa which are generally low-income countries.

The beta coefficients ranged between -0.01 and 0.04 on the 0-1 health utility score. These have the minimally clinically important difference (Walters and Brazier, 2003; Khanna *et al.*, 2007). The predictors all had the unstandardized beta coefficients with absolute values

equal or greater than 0.03 indicating that beyond statistical significance, they are of clinical importance in the management of SCD.

6.7 Implications

This study has implications for the healthcare professionals, sickle cell patients and the policymakers. These are discussed in the following sections.

6.7.1 Healthcare providers

Due to better medical attention and treatment leading to increased survival rates of SCD patients, better education and awareness, healthcare providers will increasingly encounter adults with SCD. It is therefore important for these professionals to understand both the clinical complications of the disease and the subjective psychological impacts of the disease on patients.

Health-related quality of life research in SCD has been limited by a lack of a theoretical framework. The WCM is useful to healthcare professionals and researchers who want to explore how changes in specific clinical characteristics may affect a patient's overall health outcomes. The results indicate the importance of including HRQL along with clinical indicators, symptom measures and subjective well-being.

This study has shown that individuals with more comorbidities and worse symptoms have reduced GHP and HRQL. This may lead to reduced capacity of the patient to cope with SCD resulting in adverse effects on their daily lives. If healthcare providers are in possession of such information, they may be able to easily identify 'high risk' individuals, design the most effective treatment management for them and educate them on stress management and how to develop effective coping strategies.

The findings show that objective health relates to functioning through symptoms status (see Table 5-20). This suggests that rather than the physical disorder often emphasised by

clinicians, it is the resultant limitations in physical functioning that are important determinants of the HRQL of the patients. The findings that symptoms status is the most important relative predictor of HRQL in SCD (see 5.5.1) means that measures of symptoms burden are important to capture the full effect of the disease on HRQL. These suggest the need for healthcare providers to know the symptoms expressed and the physical limitations experienced and their HRQL because these factors are directly related to GHP which determine HRQL and therefore may inform treatment protocol of patients. Effective interventions to control symptoms are also desirable.

Number of comorbidities was significant predictor of reduced HRQL, pointing to the need for healthcare professionals to be sensitive to cumulative burden of additional comorbidities in the management of SCD patients.

Based on the systematic reviews (Chapters 2 and 3) and the present findings, it is essential that healthcare providers adopt a comprehensive care protocol that can optimise both the physiological and the psychological well-being of the patients. Several researchers have also proposed that psychological interventions should be a standard part of care in the routine management of sickle cell disease in addition to treatment (Anie, 2005). Combining medical treatment with regular assessment of daily psychosocial experience and the long-term effects of both psychological and medical therapies in the management protocol would allow patients to cope better, perform activities and enjoy better quality of life.

HRQL is a distinct health entity (Höfer *et al.*, 2005) and should routinely be examined as part of standard care. Physicians should pay more attention to the quality of life characteristics of the patients. For example, physicians could monitor patients by asking them about their ability to work and their involvement in leisure activities. This routine challenge of the functionality of the patients could assist in helping physicians understand the extent of the effect of the diseases on patients' daily activities (Mastandréa *et al.*, 2015).

Similar to the published principles to improve quality of life in multiple sclerosis (https://www.msif.org/), sickle cell patients should be empowered and allowed to fully participate in decisions about their treatment, care and lifestyle in harmony with their personal beliefs and values. Additionally, healthcare providers should listen to individual needs and respect the knowledge that comes from lived experience which only the patient can provide, this implies that clinicians must rely on and believe the patient's self-report of pain rather than assuming that they are addicted to their pain medications or being disparaged as 'sicklers' (Haywood Jr, 2013). It has been argued that not having sufficient participation in their care, or having a problematic relationship with clinicians can lead to harmful clinical and behavioural outcomes for the patient (Haywood *et al.*, 2010). On the other hand, when patients were allowed self-assessment of mood, pain health and quality of life at three instances: upon admission to hospital, prior to discharge and a week after discharge, better self-assessment of health, general mood and quality of life led to significant improvement in pain reduction for these patients upon hospital admission, prior to discharge and after one week of follow up (Anie *et al.*, 2012).

There is need for training and re-orientation of healthcare providers to relate appropriately and effectively with individuals who have sickle cell disease in order for them to be able to discuss the problems experienced by patients and to provide necessary care (Alao and Cooley, 2001). Inappropriate assumptions or attitudes from caregivers could contribute to depressive thoughts in patients with a consequent effect on their health status. There is the need to properly understand the nature of the disease especially the unremitting pain nature of the disease which are yet to be properly understood by the physicians. Pack-Mabien *et al.*, (2001) has suggested that nurses for example, would benefit fom training that focus on attitudes toward pain and drug addiction in SCD. Suspecting drug dependence, may lead to patients being undertreated (McClish *et al.*, 2016) making them reluctant to seek medical attention (Maxwell, Streetly and Bevan, 1999; Elander *et al.*, 2003).

This thesis has shown that depression significantly affects HRQL in SCD (see section 6.2-6.4); therefore, integrating routine depression screening for individual patients as part of management strategies so that patients at risk can be adequately treated on time should be taken as a priority. This is to reduce further suffering, morbidity and suicidal thoughts which according to Jenerette, Funk and Murdaugh, (2005) are associated with depression. Moreover, depression may also adversely affect the ability to cope with the disease, reduce active care seeking resulting in increased practice of self-care management activities (Cooper, 2004) and diminished quality of life (Whitter, 2001). Healthcare professionals should strive to follow and improve on recommended standards of care for patients with SCD (Health, 2002).

6.7.2 People with SCD

In line with evidence in literature on the effectiveness of self-management interventions, there is need to provide counselling or psychoeducation which could help to mediate psychosocial outcome (e.g depression) by enhancing self-efficacy as well as deliberate empowerment to engage in proactive coping. Educating sickle cell patients on methods of selfcare is important to help the patients take control of their own health (see 1.8.2, pp.1) for better quality of life. For example, previous study showed that older patients aged 48-73 associated their longevity with learning how to take care of themselves (Jenerette, Leak and Sandelowski, 2011). They referred to this method as “listening to their bodies” which was responsible for selfcare practices that reduced the effect of the disease on the daily living of the participants. Patients should be encouraged to practice early health-seeking, be aware of their right to health resources and disabuse their minds of the stigma attached to frequent hospital visits (Galloway-Blake *et al.*, 2014). Sickle cell patients should also be encouraged

to organise social activities among themselves and to participate in educational forums that will further enlighten them on the high possibility of a better quality of life if they adhere to good self-health-management practices.

The systematic reviews (see 2.4 and 3.13) show that depression is an important symptom responsible for reduced HRQL in SCD, it may therefore be beneficial to engage in therapeutic communication about depression with SCD patients during their visit to the hospital. Living with others (social support) was associated with increased HRQL, this should be encouraged through public education, to reduce stigma and promote social support for SCD patients.

6.7.3 Policymakers

The model is useful for policy makers who are expected to take a comprehensive look at various issues when making decisions about treatment for SCD as it provides insight into understanding the mechanisms that drive changes in health that may occur during natural course of the disease or treatment of patients. This could guide policymakers to evolve strategies for how healthcare is delivered, design appropriate training to raise awareness about symptoms management in sickle cell disease.

One important step would be the creation of a national record of all patients with sickle cell disease, newborns affected, and haemoglobinopathy-related deaths such as that developed in Greece (Voskaridou *et al.*, 2012) and neonatal clinics like in Midwest Brazil where sickle cell screening for children helped to significantly reduce child mortality (Ivo and Pinto, 2013). A register of all patients with sickle cell disease at local government level should be established with adequate budgetary provisions made for them. Also, government should be responsible for the medical expenses of people with sickle cell as currently applies to people with HIV/AIDS to ensure patients have access to good and free healthcare services,

furthermore, rehabilitating centre should be created to cater for patients already disabled due to the disease (Olaniyi, 2008). Currently, unlike the high-income countries, Nigeria lacks a national programme of health insurance or a social welfare system, what is currently available is restricted to employees of the Federal government. The current out-of-pocket system of healthcare financing has made it difficult for sickle cell disease patients to have acces to medical facilities or to receive quality healthcare. Some patients have to depend on families, relatives, and friends for financial assistance to get minimal healthcare. Th e financial burden could further worsen the poverty level, increase anxiety and depression due to the burden of the disease and the barriers at securing healthcare. Inaugurating a social welfare programme for people with sickle cell might go a long way to relieve the patients and their caregivers of the financial burden that often translates to the neglect of other members of the family (Adegoke and Kuteyi, 2012).

Hospital management should establish, in their emergency departments, a comprehensive programme specific to sickle cell patients and aimed at timely delivery of compassionate, pain-management services to better the patients' quality of life (Aisiku *et al.,* 2009). Free genotype counselling should be available in community health centres for people with sickle cell traits especially those yet to be married to possibly educate on possible consequences when two people with sickle cell tratis are married as this will predispose the couple to a 25% risk of giving birth to a child with sickle cell disease.

SCD, like other chronic illness is expensive to treat, creates disability and requires life changes. Policymakers should therefore address the welfare, income generation and education for people with SCD. There is a need for policies to assist patients financially and to make healthcare accessible and affordable for them to help reduce the burden of the disease. Such assistance will protect patients from stress and potentially a lack of treatment. In addition, having a guaranteed source of income will protect against barriers to self-care created by low financial capacity. In addressing their education, one method is the Brazil

model. Brazil operates a policy that guarantees continuity of studies to compensate for classes missed due to the illness (Ivo and Pinto, 2013). It will also be necessary to organise vocational and professional training tailored to their specific condition and aimed at providing them with better integration in the job market. Additionally, education policies should recognise open and distance education that gives better opportunities to people with sickle cell disease and enables them to study at their own pace. Furthermore, governments should develop policies to insulate sickle cell patients from being discriminated against either overtly or covertly in the job market and to protect those who have jobs from being relieved of their jobs because of frequent absences due to illness.

The activities of social groups such as the Nigerian Sickle Cell Association and the Sickle Cell Disease Clubs have been reported to be at present of little community impact (Ohaeri and Shokunbi, 2002). Religious organisations should also be enlisted to raise awareness and provide proper counsel to their yet to be married adherents to know the genotype of their partner as part of measures of compatibility before going into the union. A premarital genetic screening project should be instituted by the government following the example of Saudi Arabia where premarital screening has helped to reduce instances of marriages likely to produce sickle cell child (Al Sulaiman *et al.*, 2008).

6.8 Limitations

This is a cross sectional study. One of the conditions to make a causal inference is that there must be temporal precedence which implies that the independent variable, X must precede the dependent variable, Y in time. A cross sectional study violates this principle; hence it is not possible to infer causal relationship from this study. A longitudinal analysis which combines autoregressive and latent curve models (Curran and Bollen, 2001) is required to further support the causal relationship suggested by the Wilson and Cleary model. However, the analysis has shown that the relationships depicted were supported by the data and could

lead to a more comprehensive testing of the Wilson and Cleary conceptual model (Sousa and Kwok, 2006).

The clinic setting for the data collection also posed some limitations to the study. All the participants were SCD patients who attended hospital on a clinic day either for an appointment or for specific complaints. The views of patients not receiving medical treatment or without access to conventional medical care could be different if study was carried out in a community setting (Anie, Egunjobi and Akinyanju, 2010). In addition, data were collected from only one state, this may not be representative of the wider SCD population in the country. A population-based study with appropriately designed sampling techniques may yield more objective results and generalisable conclusions. It is difficult to determine if the findings are representative of the wider SCD population group in Nigeria because of the lack of population-based SCD cohorts with which to compare.

This study relied on self-reported co-morbid conditions which could be subject to bias. However, evidence have shown good agreement between self-report and clinical measures of conditions (Bush *et al.*, 1989; Heliövaara *et al.*, 1993; Macintyre, Ford and Hunt, 1999; Bombard *et al.*, 2005) and high agreement between self-reported co-morbidities and medical records abstractions (Van Den Bos, 1995; Kriegsman *et al.*, 1996; Penninx *et al.*, 1996; Bayliss, Ellis and Steiner, 2005; Miller *et al.*, 2008).

The SF-36 is a generic instrument which measures HRQL as patients' perception of their health status in broad areas of physical, social and psychological functioning and being not diseases specific, does not measure patients' HRQL from their SCD peculiar experience. A disease-specific measure would have been more sensitive to detect specific quality of life issues in the patients. The available quality of life instrument for sickle cell, the Adult Sickle Cell Quality of Life Measurement System, ASCQ-Me (Keller *et al.*, 2014; Treadwell *et al.*, 2014) is still being validated. The SF-36 has however been used widely in sickle cell and

chronic diseases and has been reported to be valid for use in patients with SCD (Asnani, Lipps and Reid, 2007, 2009).

The Wilson and Cleary model has significantly contributed to our understanding of the predictors of quality of life by proposing a conceptual model that integrate the objective and subjective health concepts. Currently, guidelines for selecting indicator variables for the model is at best flexible. For example, Wilson and Cleary have suggested that depression or any other psychological factor could be considered as a bio-physiological variable, as a symptom status variable or as a functioning status variable. Many studies have arbitrarily selected indicator variables for the latent factors based on their own understanding of the model or simply using what has been used in previous studies. Such situations may lead to the choice of inappropriate indicator variables or inconsistent conclusions in literature. For example, Höfer *et al.* (2005) used depression as indicator for individual characteristics in coronary artery disease, Saensgisri et al (2014), also for coronary artery disease, used depression as indicator of symptoms. The choice of variables in this study was constrained by the available data. The guidelines of Wilson and Cleary were followed in the choice of the variables. However, such variables may not be the most ideal to measure the constructs. This may be responsible for the non-significance of, for example, the characteristics of the environment in the model. Furthermore, to obtain a good fit for the model, errors of non-adjacent variables were correlated as suggested by the modification index in AMOS, this suggests the need for future work to investigate possible partial mediation of latent variables identified in Wilson and Cleary as well as the use of alternative indicators of the latent factors in the model.

SF-6D was used to obtain a utility score for the study. SF-6D may have a floor effect and different derivations of utility measures have been reported to yield different results (Feeny *et al.*, 2012; Peasgood *et al.*, 2016), although SF-6D is relatively better in discriminating

between health states than other measures of utility such as EQ-5D and EQ-VAS (Richardson, Iezzi and Khan, 2015; Peasgood *et al.*, 2016).

6.9 Further work

In the absence of national record of sickle cell disease in Nigeria, regional and state and community studies of sociodemographic aspects and quality of life of people with SCD will be necessary to provide current and continuing information on the dynamics of the illness to help understand their quality of life. Such studies will also shed light on the urban-rural dynamics and the role of cultural practices in the study of quality of life. Furthermore, quality of life is a multidimensional construct with wide variations in its measures, therefore qualitative data to inform quality of life dimensions in the specific illness (Skevington, 1999) of sickle cell is important to add to knowledge on the impact of the disease on patients' quality of life. A qualitative study will also be necessary to help understand some of the cultural practices and health decisions and to further clarify factors affecting quality of life in the population.

As mentioned in section 6.8, there is need to establish the direction of relationship and causality. A longitudinal study is therefore required both for this and also to compare the use of disease-specific and generic instruments for measuring quality of life in SCD. A longitudinal study using disease-specific instrument like the ASCQ-Me (Treadwell *et al.*, 2014) may be necessary to establish causality and its direction in adults with sickle cell disease.

Furthermore, a longitudinal study of utility in people with SCD using both direct and derived methods is also required to broaden our knowledge of preference-based quality of life status in sickle cell patients.

6.10. Recommendations

This study has identified determinants of quality of life in people with sickle cell disease and has established the appropriateness of using the Wilson and Cleary model to guide further studies. A comprehensive model for managing a patient with SCD is imperative to help improve his or her quality of life. Symptoms status indicated by pain, depression, anxiety and somatic symptoms in patients have a significant impact on their quality of life. Similar to the published principles to improve quality of life in multiple sclerosis (https://www.msif.org/), sickle cell patients should be empowered and allowed to fully participate in decisions about their treatment, care and lifestyle in harmony with their personal beliefs and values. Routine investigation of patients' psychiatric status should be integrated into the disease management protocol to be targeted for immediate attention once SCD is diagnosed. Healthcare providers should design a more effective management programme for persistent pain and depression while policymakers should, ensure the passage of the national policy on SCD by the national assembly, embark on education of the patients on self-care and habits that could help reduce the frequency of pain occurrence. Furthermore, in line with the WHO African region SCD strategy, general individual and community awareness about the disease should be promoted. Also, specific periodic education for families and caregivers on disease management at home and routine practices to prevent crisis should be implemented.

6.11 Conclusion

The paradigm shift in healthcare demands a holistic definition of health and consequently points of care with emphasis now on health, functioning, quality of life and focus on health care instead. This shift comes with a challenge of how to identify and appropriately measure patient outcomes for the purpose of improving the quality of patient care; the Wilson and Cleary model can be used to help tackle these challenges, as supported by empirical analysis in this study. The insight gained by examining the relationship between subjective and

objective health outcomes in SCD can be used by clinicians to understand how changes in specific clinical characteristics affect a patient's overall health outcomes.

The effects of symptoms especially pain, depression and anxiety on functioning and overall quality of life should be considered when designing or redesigning protocols for the management of the disease. For interventions to be fully effective, patients' experiences of their symptoms must be taken into consideration along with the bio-physiological variables because two patients with identical health status or clinical characteristics may have a very different quality of life experience, as well as expectations and perceptions regarding their health. Factors like living conditions, disease severity, socioeconomic status and nationality are also determinants of clinically important differences in the SCD population.

This study provides insight into the predictors of health-related quality of life in people with sickle cell disease and highlights the importance of assessing subjective symptoms alongside biological factors both in research and clinical practice geared towards the management of the disease. Additionally, health utilities are important values necessary to understand the preferences of an individual for different health outcomes and when combined with survival estimates can be employed in cost utility analysis of medical treatment. The predictors of preference-based measures also have clinical importance in the management of sickle cell disease.

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APPENDICES

QUESTIONNAIRE ON QUALITY OF LIFE OF ADULTS WITH SICKLE CELL ANAEMIA

This questionnaire is to collect some information from you as a participant. Kindly fill answer the questions as they apply to you. The exercise is for research purpose and all information shall be treated as confidential. Thank you for completing this survey.

SECTION A: BACKGROUND INFORMATION

Age group (*circle*): (a) 18-30 (b) 31-40 (c) 41-50 (d) Above 50

Sex (c*ircle*): (a) Male (b) Female State of origin……

Education (*circle*): (a) No education (b) Primary (c) Secondary (d) ND/NCE
(e) 1st degree/equivalent (f) Higher degree

Marital status: (a) Single (b) Married (c) Separated/Divorced
(d) Widowed

Number of children:

Employment (*circle*): (a) Fully-employed (b) Employed-part-time (c) Not employed

Employment type (*circle*): (a) Government (b) Private (c) Self (d)Not applicable

Income (*per month)*: (a) Below ₦18,000 (b) ₦18,000-50,000 (c) ₦51,000-100,000
(d)₦101,000-200,000 (e) ₦201,000-300,000 (f) above ₦300,000

Living situation (*circle*): (a) Living alone (b) Living with parent/siblings
(c) Living with friends (d) Living with spouse/children

Do you have a confidant? (a) Yes (b) No

Religion (*circle*): (a) Christianity (b) Islam (c) Traditional (d) None

Genotype (*circle*): (a) SS (b) SC (c) Sβ Weight (kg)……. Height (m)……

In the last 6 months, how many times did you do any of the following?

(Use "✓" to indicate your answer)

	None	once	2 times	3 times	More than 3 times
1. Visited the Emergency Department					
2. Admitted to the hospital					
3. Have pain episodes/experience					
4. Have other sickle-cell related crisis					

Have you been diagnosed with any of the following diseases?

	Yes	No
Asthma		
Diabetes		
Arthritis		
Leg ulcers		
Stroke		
Epilepsy		
High blood pressure		
Heart disease		
Priapism		
Lung disease		
Pneumonia		
Others (mention)		

Looking at all parts of my life – physical, emotional, social, spiritual and financial in the last two weeks, the quality of my life has been?". Rate from 0, VERY BAD to 10, EXCELLENT.

SECTION B: EXPERIENCES AS A RESULT OF HEALTH CONDITION

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(Use "✓" to indicate your answer)

	Not at all	Several Days	More than half the days	Nearly Every day

	0	1	2	3
1. Little interest or pleasure in doing things				
2. Feeling down, depressed, or hopeless				
3.Trouble falling or staying asleep, or sleeping too much				
4. Feeling tired or having little energy				
5. Poor appetite or overeating				
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down				
7.Trouble concentrating on things, such as reading the newspaper or watching television				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual				
9. Thoughts that you would be better off dead or of hurting yourself in some way				

During the last 4 weeks, how much have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*

	Not bothered (0)	**Bothered a little (1)**	**Bothered a lot (2)**
1. Stomach pain			
2. Back pain			
3. Pain in your arms, legs, or joints (knees, hips, etc.			
4. Feeling tired or having little energy			
5. Trouble falling or staying asleep, or sleeping too much			
6. Menstrual cramps or other problems with your periods			
7. Pain or problems during sexual intercourse			
8. Headaches			
9. Chest pain			
10. Dizziness			
11. Fainting spells			
12. Feeling your heart pound or race			
13. Shortness of breath			
14. Constipation, loose bowels, or diarrhoea			
15. Nausea, gas, or indigestion			

Over the last 4 weeks, how often have you been bothered by any of the following problems?
(Use "✓" to indicate your answer)

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Feeling nervous anxiety or on edge				
2. Not being able to stop or control worrying				
3. Worrying too much about different things				
4. Trouble relaxing				
5. Being so restless that it is hard to sit still				
6. Becoming easily annoyed or irritable				
7. Feeling afraid as if something awful might happen				

SECTION C: HEALTH STATUS

1. In general, would you say your health is (*circle*): (1) Excellent (2) Very good (3) Good (4) Fair (5) Poor

2. Compared to one year ago:
(1) Much better now than one year ago
(2) Somewhat better now than one year ago
(3) About the same
(4) Somewhat worse now than one year ago
(5) Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
*(Circle One Number on Each Line***)**

	Yes, Limited a Lot (1)	Yes, Limited a Little (2)	No, Not limited at All (3)
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	**1**	**2**	**3**
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	**1**	**2**	**3**
c. Lifting or carrying groceries	**1**	**2**	**3**
d. Climbing **several** flights of stairs	**1**	**2**	**3**
e. Climbing **one** flight of stairs	**1**	**2**	**3**

f. Bending, kneeling, or stooping	**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**? *(Circle One Number on Each Line)*

	Yes (1)	No (2)
a. Cut down the amount of time you spent on work or other activities	**1**	**2**
b. **Accomplished less** than you would like	**1**	**2**
c. Were limited in the **kind** of work or other activities	**1**	**2**
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 (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes (1)	No (2)
a. Cut down the amount of time you spent on work or other activities	**1**	**2**
b. Accomplished less than you would like	**1**	**2**
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? (1) Not at all (2) Slightly (3) Moderately (4) Quite a bit (5) Extremely

7. How much bodily pain have you had during the past 4 weeks?
(1) None (2) Very mild (3) Moderate (4) Severe (5) 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)?

(1) Not at all (2) A little bit (3) Moderately (4) Quite a bit (5) Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.** *(Circle One Number on Each Line)*
9. How much of the time during the past 4 weeks **. . .**

	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
a. Did you feel full of pep?	**1**	**2**	**3**	**4**	**5**	**6**

b. Have you been a very nervous person?	**1**	**2**	**3**	**4**	**5**	**6**
c. Have you felt so down in the dumps that nothing could cheer you up?	**1**	**2**	**3**	**4**	**5**	**6**
d. Have you felt calm and peaceful?	**1**	**2**	**3**	**4**	**5**	**6**
e. Did you have a lot of energy?	**1**	**2**	**3**	**4**	**5**	**6**
f. Have you felt downhearted and blue?	**1**	**2**	**3**	**4**	**5**	**6**
g. Did you feel worn out?	**1**	**2**	**3**	**4**	**5**	**6**
h. Have you been a happy person?	**1**	**2**	**3**	**4**	**5**	**6**
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.)? *(Circle One Number):*

(1) All of the time (2) Most of the time (3) Some 0f the time
(4) A little bit of the time (5) None of the time

11. How TRUE or FALSE is each of the following statements for you.
(*Circle One Number on Each Line*)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people	**1**	**2**	**3**	**4**	**5**
b. I am as healthy as anybody I know	**1**	**2**	**3**	**4**	**5**
c. I expect my health to get worse	**1**	**2**	**3**	**4**	**5**
d. My health is excellent	**1**	**2**	**3**	**4**	**5**

INFORMED CONSENT FORM

IRB Research Approval number:

This approval will elapse on:

TITLE OF THE RESEARCH:

HEALTH RELATED QUALITY OF LIFE AND ITS PREDICTOR MARKERS AMONG SICKLE CELL PATIENTS IN IBADAN, SOUTH WEST NIGERIA.

Name(s) and affiliation(s) of researcher(s):

The study is being conducted by Adedokun O. Ojelabi, a PhD student of the Department of Pharmacy, Health and Well-being of the University of Sunderland, United Kingdom.

Sponsor of research: this is part of a Ph.D programme sponsored by the University of Ibadan

Purpose of Research:

The purpose of this research is to investigate the quality of life of adults (18 years and older) living with sickle cell disease and to examine the effects of sickle cell disease on quality of life.

Why have I been chosen?

As a person living with SCD your views are important. As part of the investigation, the researcher would like to collect information from a sample of patients, 18 years and above, living with SCD. You along with other people in the same condition are being asked if you would like to take part in this project

Do I have to take part?
It is entirely voluntary. Whether or not you take part should be your decision. Any identifying information about those taking part will be kept confidential. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form. If you decide to take part you are free to withdraw at any time without giving a reason. If you do chose to withdraw, any data collected up to the point of withdrawal will be destroyed and will not be used in the study.
A decision to withdraw at any time, or a decision not to take part, will not affect you in any way.

What will happen to me if I take part?
You may be asked to take part in completing a questionnaire and your height and weight might be taken. The entire process will last about one hour. A token may be given to cover cot of transportation of participants.

What do I have to do?
If you decide that you would like to take part, please sign the consent form that is attached to this information sheet and return to me. You will be contacted on the date and time, the activities will take place.

What will happen to the results of the research study?
The report of the analysis will be used for a PhD and may be used in published journal articles, which is expected to generate further research to improve quality of life of people living with SCD, however participants will not be named, and you will not be able to be recognised by any comments you make.

Will my taking part in this study be kept confidential?
All information supplied will be treated as confidential and will be used for research purposes only.

Who is organising and funding the research?
This is a research project in partial fulfilment for the award of a PhD from the University of Sunderland.

Ethical approval.
This research has been approved by UI/UCH Ethics Committee. If you have any concerns regarding the conduct of this study please contact the Chairman, UI/UCH Ethics Committee, Biode Building, Room 210, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, email: uiuchirc@yahoo.com and uiuchec@gmail.com.
In addition, if you need any further information, please contact AO Ojelabi,
Department of Pharmacy, Health and Well-being, University of Sunderland,
United Kingdom or via email at adedokun.ojelabi@research.sunderland.ac.uk.

STATEMENT OF PERSON GIVING CONSENT

- Please put your initials in the column provided beside each statement to show that you agree with the statement and give consent.
- Please sign and date this form to show you give consent to all statements that you have initialled.

Statement	**Initials**
I consent to take part in this research project.	
I understand that a researcher from the University of Sunderland is carrying out a study on Health-related quality of life among people living with sickle cell disease (SCD). I understand that the data collection is for research purposes.	
I confirm that I have read and understood the enclosed Information Sheet for this study, and have had plenty of time to decide whether or not I wish to participate.	
I understand that my participation is voluntary, and that I am free to withdraw at any time, without giving a reason.	
I understand that I will be given a copy of this signed consent form.	
I have been told that the completed questionnaires will be securely kept until after the end of the project when they will be destroyed. I am aware that all documents will remain confidential and these will be securely stored with only the researcher having access to them.	
I am aware that information on the questionnaire may be used in a final report, but understand that individual participants will not be identified.	

Signed …….....……..Date ……

Name…… ……..

TO BE COMPLETED BY RESEARCHER on attendance at the interview:

I can confirm that I have explained to the above-named participant the nature of this study, and I have given adequate time for any questions to be asked and answered regarding the study.

Signed …… Date ……

Name (in capitals) ……

Post ……