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MEASURING AND UNDERSTANDING HEALTH-RELATED QUALITY OF LIFE AMONG
ADULT PATIENTS WITH HEMOPHILIA

A Dissertation presented in partial fulfillment of requirements
for the degree of Doctor of Philosophy
in the Department of Pharmacy Administration
The University of Mississippi

by

RUCHIT SHAH

August 2016

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ABSTRACT

Objectives

The objectives of this study are to: 1) examine the psychometric properties of the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2); 2) assess the measurement invariance of the SF-12v2 with respect to age, disease severity, and treatment regimen; 3) identify psychosocial predictors of health-related quality (HRQOL) among adults with hemophilia in the United States.

Methods

This cross-sectional study was conducted using both a web-based and paper-based self-administered survey. Adults with hemophilia were recruited using an online panel, a Facebook community of hemophilia patients, and at the University of Mississippi Medical Center hemophilia treatment clinic. Psychometric properties of the SF-12v2 were established in terms of its construct validity and internal consistency reliability using confirmatory factor analysis (CFA). The measurement invariance of the scale was examined using a multi-group CFA based approach. Finally, structural equation modeling (SEM) was used to test a theory driven model to identify psychosocial predictors of HRQOL in the study sample.

Results

A total of 218 adults with hemophilia completed the survey. The SF-12v2 was found to be psychometrically valid in the study population. The CFA revealed a two-factor model for the SF-12v2 instrument similar to what has been previously established in the literature. The instrument was found to invariant with respect to age, disease severity, and treatment regimen. Results from the SEM analysis suggested that disability, social support, maladaptive coping, and self-efficacy were key predictors of HRQOL among adults with hemophilia.

Conclusions

The study results indicated that the SF-12v2 is a psychometrically sound instrument to assess HRQOL of adults with hemophilia. Considering that the assumption of measurement invariance was met, future studies can consider that sub-group comparisons among hemophilia patients in terms of HRQOL reflect true differences between groups and are not artifacts of measurement bias. Clinicians and caregivers of hemophilia patients should consider factors such as improving social support provided, emphasizing on the reduction of maladaptive coping strategies, and increasing patient self-efficacy while making key treatment decisions.

DEDICATION

This dissertation is dedicated to my *Appa, Amma, parents* and *Jhankrut* who have always supported me.

LIST OF ABBREVIATIONS AND SYMBOLS

ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AVE	Average Variance Extracted
Brief-COPE	Brief Coping Orientation to Problem Experiences
BP	Bodily Pain
CDC	Centers for Disease Control and Prevention
CFA	Confirmatory Factor Analysis
CI	Confidence Interval
CFI	Comparative Fit Index
CE	Cost–Effectiveness
FDA	Food and Drug Administration
GH	General Health
GSES	Generalized Self-Efficacy Scale
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCV	Hepatitis C Virus
HIV	Human Immuno-deficiency Virus
HTC	Hemophilia Treatment Center
HUGS	Hemophilia Utilization Group Study
HRQOL	Health–Related Quality Of Life

IADL	Instrumental Activities of Daily Living
IQR	Interquartile Range
ISOQOL	International Society for Quality of Life Research
LMF	Latent Mental Factor
LPF	Latent Physical Factor
ML	Maximum Likelihood
MCS	Mental Component Score
MH	Mental Health
MOS	Medical Outcomes Study
MSE	Missing Score Estimation
MI	Modification Indices
MSPSS	Multidimensional Scale of Perceived Social Support
NHF	National Hemophilia Foundation
PCS	Physical Component Score
PGI-S	Patient Global Impression of Severity
PF	Physical Functioning
QALY	Quality Adjusted Life Years
RE	Role Emotional
RP	Role Physical
RMSEA	Root Mean Square Error of Approximation
SD	Standard Deviation
SE	Standard Error
SF-12v2	Short Form Health Survey version 2

SF	Social Functioning
SRMR	Standardized Root Mean Square Residual
SPSS	Statistical Package for Social Sciences
SEM	Structural Equation Modeling
TLI	Tucker Lewis Index
UK	United Kingdom
US	United States
UM-IRB	University of Mississippi's Institutional Review Board
VT	Vitality
WHO	World Health Organization
WLSMV	Weighted Least Squares Minimum Variance

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CHAPTER I: INTRODUCTION

STUDY OVERVIEW

Hemophilia is a rare X-linked chronic genetic blood coagulation disorder among males that is caused by a deficiency of clotting factors VIII or IX. It impacts about 400,000 people across the world and about 20,000 in the United States (US) (Center for Disease Control and Prevention, 2014; The National Hemophilia Foundation, 2014). Patients with hemophilia experience bleeding into joints and muscles which in severe cases can lead to chronic pain, reduce the range of joint motion and eventually progress to chronic arthritis (Dolan et al., 2009). Also, patients with hemophilia often suffer from comorbidities such as infections due to hepatitis C virus (HCV), human immunodeficiency virus (HIV), or tolerance to clotting factors in the form of an inhibitor (Franchini & Mannucci, 2009). Thus hemophilia places a significant burden on the health-related quality of life (HRQOL) of patients.

Several studies in the existing literature have assessed the HRQOL of patients with hemophilia. These studies have largely reported that hemophilia impacts the physical HRQOL of patients rather than the mental HRQOL, which was found to be comparable to the general population (Lindvall, Von Mackensen, & Berntorp, 2012; Miners et al., 1999). The majority of these studies have overlooked the role of psychosocial variables such as social support, coping, and self-efficacy and their impact on the HRQOL of hemophilia patients. Also, none of the studies which have evaluated HRQOL among patients with hemophilia have examined the psychometric properties of the HRQOL measure used. An examination of the psychometric

properties is essential in order to ensure the appropriateness of the use of an instrument in a particular population. Another key aspect of measuring HRQOL is to make sure that observed differences in the HRQOL of the study population are true differences and not measurement artifacts. This can be ensured by assessing the measurement invariance of the HRQOL instrument in the study population.

Therefore the general purpose of this dissertation is to 1) assess the psychometric properties of the HRQOL measure used to evaluate the HRQOL of adults with hemophilia; 2) to assess measurement invariance of the HRQOL measure used among adults with hemophilia; and 3) identify psychosocial predictors of HRQOL among adults with hemophilia.

The remainder of this chapter will provide a brief overview of hemophilia in terms of disease etiology, epidemiology, treatments, comorbidities, and impact on patient HRQOL. Chapter 1 will also explain the need for and the research significance of this dissertation study. Chapter 2 will provide an evaluation of the psychometric properties of an instrument used to measure HRQOL (i.e., Short-Form 12 [SF-12v2] in case of this study) among adults with hemophilia. Chapter 3 will assess the measurement invariance of the SF-12v2 among adults with hemophilia. Finally, chapter 4 will assess psychosocial determinants of HRQOL among adults with hemophilia by employing a theoretical framework.

Hemophilia

Overview of the disease

Hemophilia is a rare X-chromosome linked, recessively inherited disorder characterized by excessive bleeding and impaired coagulation (Gater, Thomson, & Strandberg-Larsen, 2011). Genetically, hemophilia is caused by the transmission of a recessive gene for blood clotting

factor/s on the X-chromosome. Therefore hemophilia occurs mostly in males although females can be affected in rare instances. The two most common forms of hemophilia are hemophilia A (Factor VIII deficiency or classic hemophilia) and hemophilia B (Factor IX deficiency or Christmas disease). Hemophilia A and B are considered to be comparable in terms of genetic inheritance and clinical manifestation, although recent studies have indicated hemophilia B to be less severe (Mannucci & Franchini, 2013) in terms of bleeding frequency and long-term outcomes such as joint arthroplasty (Tagariello et al., 2006). Depending upon the level of residual plasma coagulation factor (i.e., Factor VIII or IX), three levels of disease severity can be distinguished among patients with hemophilia. Individuals are defined as being 'severe' with the representative clotting factor activity level below 1%, 'moderate' with factor activity level between 1% and 5%, and 'mild' with factor activity level between 5% and 40% (White et al., 2001) of normal. About 50% - 70% of patients with hemophilia have severe hemophilia (National Hemophilia Foundation, 2012).

Epidemiology

Hemophilia is the most common bleeding disorder and its current worldwide prevalence is about 400,000 individuals. Hemophilia A affects about 80-85% of the hemophilic population and occurs in about 1 in every 5000 male births (National Hemophilia Foundation, 2014). The incidence of hemophilia B is approximately 1 in 30,000 male births (Bolton-Maggs & Pasi, 2003). The exact prevalence of the disease in the US is not known. A 1994 study by Soucie and colleagues estimated about 17,000 prevalent cases of hemophilia in the US (Soucie, Evatt, & Jackson, 1998). Based on the expected births and deaths since 1994, the CDC estimates the current US prevalence of the disease to be at about 20,000 (Centers for Disease Control and Prevention, 2014).

Disease etiology

Patients with hemophilia suffer from frequent bleeding into joints and muscles especially into the knees, ankles and elbows and to a lesser extent into hips, shoulders and larger muscle groups. Repeated and prolonged bleeding episodes progressively damage the joints and result in irreversible hemophilic arthropathy, chronic pain and reduction in the joint range of motion (Choinière & Melzack, 1987; Dolan et al., 2009). Arthropathy is especially common among adults who did not have any access to factor replacement home therapy when they were younger (Franchini & Mannucci, 2009). In mild hemophilia, bleeding usually ensues after sustaining an injury or after dental or surgical procedures. However, in more severe cases, patients may experience spontaneous bleeds which can affect daily functioning and contribute to disability (Poon, Pope, & Tarlov, 2013).

Treatment of hemophilia

Replacement of the deficient coagulation factor by intravenous infusion, in order to stop bleeding when it occurs or to prevent it altogether, is the basis of hemophilia treatment irrespective of the disease type and/or the severity level (Lindvall, Colstrup, Loogna, Wollter, & Grønhaug, 2010). Providing treatment when bleeding occurs is called ‘on-demand’ treatment. During on-demand therapy, intravenous infusions are administered once or twice a day until complete healing occurs. The length of treatment could range from a day in case of minor bleeds to a month for more severe episodes. During preventive therapy or ‘prophylaxis’ patients are infused with the missing clotting factor regularly (2-4 times a week) for long periods of times (from a few months to years) in order to decrease the frequency or completely stop the occurrence of bleeding episodes. Prophylaxis is considered to be the treatment of choice for children and for patients suffering from severe hemophilia. Prophylaxis started within the first

three years of life before repeated joint bleeds is known as ‘primary prophylaxis’ while that which is started after the first few bleeds to prevent joint damage is known as ‘secondary prophylaxis’ (Berntorp et al., 1995). Prophylaxis has been linked to fewer bleeding episodes and reduced rate of joint deterioration as compared to on-demand therapy (Nilsson, Berntorp, Löfqvist, & Pettersson, 1992).

Comorbidities in patients with hemophilia

Before the introduction of efficacious viral inactivation methods in 1985-1987, more than 90% of patients with hemophilia who were treated with plasma derived factor concentrates became infected with HCV. Almost 20-30% of these individuals developed a chronic infection which progressed to liver cirrhosis (Franchini & Mannucci, 2009). About half of the HCV-infected patients with hemophilia also suffer from concomitant HIV infection. Concomitant HIV infection promotes HCV replication which leads to greater liver inflammation and can ultimately progress to liver failure (Franchini, 2004). Angelotta et al. (2007) estimated that about 30% and 11% of patients with hemophilia in the US were infected with hepatitis C virus (HCV) and human immune-deficiency virus (HIV) respectively (Angelotta et al., 2007).

Also, the development of inhibitor antibodies to clotting factor concentrates can interfere with effective replacement therapy and cause bleeds that are difficult to treat. As many as 20% to 33% of patients with moderately severe and severe forms of hemophilia develop inhibitors (DiMichele, 2000). These patients are at a high risk of suffering from debilitating physical limitations and progressive joint bleeds (Leissinger, Cooper, & Solem, 2011).

Economic burden of hemophilia

Management of hemophilia is associated with high costs for patients, payers and for the overall healthcare system. The primary driver of cost for managing hemophilia, irrespective of the treatment regimen, is the cost incurred for the clotting factor concentrates. Other direct costs such as those associated with treatment visits, hospitalizations, emergency room visits, and laboratory tests form only a fraction of the total expense (Globe, Curtis, Koerper, & HUGS Steering Committee, 2004). As a part of the Hemophilia Utilization Group Study (HUGS), Globe et al. (2004) estimated the annual direct cost of hemophilia A care to be \$139,102 per person. Clotting factor consumption alone accounted for between 45% (for mild hemophilia) to 83% (for severe hemophilia) of the total direct cost of care (Globe et al., 2004). Other studies have reported similar findings among Medicaid as well as commercially insured patients with hemophilia (Guh, Grosse, McAlister, Kessler, & Soucie, 2012a, 2012b; Tencer, Friedman, Li-McLeod, & Johnson, 2007; Zhou et al., 2015).

Johnson et al. estimated the indirect cost of care among adults with hemophilia to be \$12,721 per person annually (Johnson et al., 2012). Indirect costs were calculated in terms of productivity losses due to absenteeism from work, time spent in arranging hemophilia care and unpaid caregiver support. These costs form a small, albeit an important, portion of the total burden of the disease and could have a significant impact on patients and their families.

Health-related quality of life (HRQOL)

The World Health Organization (WHO) defines health as “not merely the absence of disease or infirmity, but as a state of complete physical, mental and social well-being” (Bullinger & von Mackensen, 2004). HRQOL refers to “patients’ appraisal of their current level of

functioning and their satisfaction with it compared with what they perceive to be ideal health” (Fischer, van der Bom, & van den Berg, 2003). HRQOL is thus a subjective representation of the patient’s health. It incorporates those physical, mental, social, and emotional aspects of well-being and functioning which matter to patients because patients may not be sensitive to changes in clinical or physiologic disease measures (Bullinger & von Mackensen, 2004). In fact people with similar disease severities could have different evaluations of their HRQOL (Guyatt, Feeny, & Patrick, 1993). Thus HRQOL has become an important outcome which must be assessed in order to ensure optimum treatment and resource allocation decisions (Fischer et al., 2003).

For a patient living with hemophilia, merely treating and preventing bleeding episodes and other physical symptoms using clotting factor concentrates is not enough. Patients with hemophilia must be careful about participating in activities such as contact sports because immediate bleeding may ensue. Long-term impairments in mobility and impact on functional status due to reduced range of joint motion may also limit the activities in which patients can participate. This can affect social participation and peer integration (Aznar, Magallón, Querol, Gorina, & Tusell, 2009; Mackensen, 2007). Employment and occupational disabilities can occur as well. Also, the disease can influence the mental well-being of patients within whom signs of depression, anxiety and psychological distress are common (Ghanizadeh & Baligh-Jahromi, 2009). Thus the physical, mental and social consequences of the disease serve to reduce the HRQOL of patients. Therefore HRQOL assessment is now recognized as an important health outcomes endpoint which can help decide and optimize treatment options among patients with hemophilia (Fischer et al., 2003).

Several studies have assessed the HRQOL of patients with hemophilia. The majority of these studies have reported that patients with hemophilia suffer from worse physical HRQOL as

compared to the healthy population. The mental HRQOL of patients with hemophilia was found to be similar to the general population (Aznar et al., 2009; Lindvall et al., 2012; Molho et al., 2000; Poon, Doctor, & Nichol, 2014). Studies have also reported the beneficial impact of prophylaxis as compared to on-demand treatment on the physical HRQOL of patients with hemophilia (Royal et al., 2002; Szucs, Öffner, and Schramm, 1996). Higher disease severity, greater age and the presence of comorbidities such as HCV, HIV or inhibitors have also been associated with significant impairments in HRQOL among hemophilia patients (Brown, Lee, Joshi, & Pashos, 2009; Djulbegovic et al., 1996; Posthouwer et al., 2005).

Types of HRQOL measures

A key consideration in HRQOL assessment is the use of an appropriate instrument. A good HRQOL tool should have the ability to discriminate between individuals based on their health status (Guyatt et al., 1993). Therefore it is recommended that the psychometric properties of a HRQOL measure be established in terms of its validity, reliability, and responsiveness before its use in a particular population (Patrick & Deyo, 1989). Studies in the literature have used three types of measures to assess HRQOL among patients with hemophilia: generic measures, disease-specific instruments, and utility-based measures. Generic instruments allow for comparison of patients' health status across disease states and conditions (Coons, Rao, Keininger, & Hays, 2000). However, they are often criticized as being less sensitive to certain key aspects or symptoms of a particular disease state and as a result may not be able to capture small but important changes in the HRQOL of patients (Guyatt et al., 1993).

Disease-specific measures of HRQOL on the other hand concentrate on problems that are relevant to the patients of a particular disease and its treatment consequences (Bullinger, Globe, Wasserman, Young, & Von MacKensen, 2009). However, they cannot be used to compare

HRQOL across different disease states. Such information may be important to clinicians and policy makers in making key treatment and resource allocation decisions. Utility-based measures summarize the positive and negative aspects of HRQOL into a single health-state preference (Bennett, Torrance, & In, 1996). Health utilities are an important component of cost-utility analyses because they are used as weights for the calculation of quality-adjusted life-years (QALYs). Availability of newer and more expensive hemophilia treatment options, the scarcity of resources available at the disposal of payers, and the rarity of this disease make health utilities essential to justify resources allocated to a particular treatment option (Guyatt et al., 1993; Torrance, 1976).

It is very important to assess the psychometric properties of measures of HRQOL before they can be employed across different patient populations. Psychometric assessments provide evidence about the appropriateness of use of measures of HRQOL in a particular group of patients. When testing HRQOL differences between groups of patients using a well-established measure of HRQOL, it is also fundamental that members of different groups assign the same meaning to questionnaire items. If it can be shown that patient characteristics (such as age, gender, type of disease, disease severity) do not affect the psychometric properties of the observed indicators (i.e., questionnaire items), then the assumption of measurement invariance is not violated. If the assumption of measurement invariance holds, then the observed differences in HRQOL among groups defining the study populations are true differences in HRQOL and not measurement artifacts.

Generic measures of HRQOL

The most commonly used generic HRQOL instrument among patients with hemophilia was the Medical Outcomes Study (MOS) Short-Form 36 (SF-36) (Ware & Sherbourne, 1992). A

handful of studies have used the Short Form-12 health survey (SF-12) (Brown et al., 2009; Poon et al., 2013) which is a shorter version of the SF-36 (Ware, Kosinski, & Lincoln, 2001). These instruments capture information regarding eight dimensions of patient health (i.e., physical functioning, role-physical, bodily pain, general health, vitality social-functioning, role-emotional, and mental health). These eight dimensions can be further aggregated into two summary scores: the physical component summary (PCS) and the mental component summary (MCS) score.

A German study found that patients on prophylaxis had better HRQOL as compared to those on on-demand treatment specifically in terms of three dimensions: general health, role-physical and role-emotional (Szucs, Öffner, and Schramm, 1996). Szucs et al. also found that patients with hemophilia had significantly greater limitations in terms of physical activity, pain and general health as compared to healthy men. Royal et al. (2002) reported similar findings in a study comparing the HRQOL of prophylaxis and on-demand therapy patients across 16 European hemophilia clinics. In a United Kingdom (UK) study, Miners et al. (1999) showed that irrespective of age, patients with severe hemophilia recorded a lower HRQOL as compared to both the general population as well as moderate/mild hemophiliacs (Miners et al., 1999). Poon and colleagues conducted a retrospective analysis of HRQOL data which were collected using the SF-12v1 as a part of the HUGS. This is a multicenter cohort study of patients from six hemophilia treatment centers (HTCs) across the US. The analyses revealed that adults with severe hemophilia A had a lower physical HRQOL as compared to the US norm population but a comparable mental HRQOL. Physical HRQOL was poorer for patients with severe form of the disease (i.e., those who reported greater joint pain and reduced range of motion) as compared to patients suffering from mild/moderate forms of the disease (Poon et al., 2013). Duncan et al. (2012) showed that adults with hemophilia in the US who had always been on prophylaxis

therapy reported better physical functioning and physical HRQOL, assessed using the SF-12v2, than those who had not been on prophylaxis throughout their life (Duncan, Kronenberger, Roberson, & Shapiro, 2012). Impairments in the physical HRQOL of patients with hemophilia as compared to the healthy population were found in studies conducted in Spain, Sweden, France, and the US (Aznar et al., 2009; Klamroth et al., 2011; Lindvall et al., 2012; Molho et al., 2000).

Disease-specific measures of HRQOL

Four disease-specific measures of HRQOL have been developed and tested among adults with hemophilia. These are the Hem-A-QOL, HAEMO-QOL-A, Hemofilia-QOL, and the Hemolatin-QOL (Arranz et al., 2004; Remor et al., 2005; Rentz et al., 2008; von Mackensen & Bullinger, 2004). However, the HAEMO-QOL-A is the only measure which has been validated in a sample of patients with hemophilia in the US (Rentz et al., 2008). In addition to capturing information about the impact of hemophilia on the physical and mental health of patients, these instruments also assess the detrimental impact of the disease in terms of consequences of bleeding, joint damage, treatment satisfaction, treatment concerns, treatment difficulties, and impact on relationships and social activity.

Studies which have employed disease-specific HRQOL instruments among patients with hemophilia have reported a similar pattern of findings as compared to those which utilized generic HRQOL measures (Arranz et al., 2004; Rentz et al., 2008). Disease severity and type of treatment were found to be significantly associated with physical HRQOL. Overall, the disease was found to have a considerable negative impact on the physical functioning of patients.

Theoretical framework for understanding HRQOL in hemophilia

There is a lack of clarity on what dimensions of a patient's life (i.e., physical, psychological, emotional, and social) contribute to their HRQOL in case of rare genetic blood coagulation disorders. Most of the studies which have assessed predictors of HRQOL among patients with rare diseases have been limited in their use of a conceptual framework. Using a theoretical framework can help researchers better understand HRQOL and its underlying determinants. Wilson and Cleary's (1995) conceptual model of patient outcomes is the most commonly used conceptual model for understanding and identifying predictors of HRQOL (Wilson & Cleary, 1995). Wilson and Cleary's model causally links five key dimensions of patient outcomes: (1) biological and physiological factors; (2) symptom status; (3) functional status; (4) general health perception; and (5) overall quality of life.

The use of theories of adaptation have been recommended in order to frame a holistic understanding of quality of life (QOL) among patients with rare genetic disorders (Cohen, Biesecker, & Part, 2010). QOL is a broad construct which includes an individual's physical, psychological, and social health, and its relationship with the environment. It includes both health and non-health related factors such as financial status, housing and living conditions, and environment. Adaptation, in the context of a chronic disease, can be defined as "the process of coming to terms with the implications of a health threat and the observable outcomes of that process" (Biesecker & Erby, 2008). QOL has been previously treated as an adaptation outcome (Stanton, Collins, & Sworowski, 2001). HRQOL refers to the impact of an individual's health and illness on their QOL (Bennett et al., 1996). Therefore HRQOL can be conceptualized as an outcome of the adaptation process as well.

Biesecker and Erby (2008) have suggested that stress and coping are concepts which can be influenced by clinicians and therefore theoretical models based on stress and coping theories are particularly well suited for HRQOL research in rare genetic disorders. The Lazarus and Folkman's (1984) cognitive-behavioral model is based on a theory of stress, appraisal, coping, and adaptation. According to this theory, individuals respond to stressors, such as living with hemophilia, by making cognitive and emotional appraisals of the stressor. An individual's appraisal of these stressors depends upon the personal significance of the stressor, its cause, severity, one's susceptibility to the stressor as well as the ability to cope with the problems and the emotions associated with the stressor (Lazarus & Folkman, 1984). These appraisals govern coping behaviors because the likelihood that one can change or adapt to a stressor will direct one's ability to cope with it and also determine the coping mechanism which will be adopted (Bombardier, D'Amico, & Jordan, 1990). These coping strategies in turn gradually help attain or restore optimal HRQOL. Therefore an individual's ability to adapt to a stressor is mediated by cognitive appraisal of the stressful event and the associated coping response. This model can therefore be adapted to identify psychosocial predictors of HRQOL among patients with rare diseases such as hemophilia.

A Dutch study has previously adapted Lazarus and Folkman's theory of stress and appraisal to examine the influence of appraisal, health beliefs, psychological characteristics and social support on well-being among hemophilia patients (Triemstra et al., 1998). Psychological characteristics were found to be the strongest determinants of patient well-being and partially mediated the negative impact of disability on well-being. The mediating role of cognitive appraisal and social support in the relationship between disability and well-being remained unclear. The study by Triemstra et al. (1998) was by far the most comprehensive study which

outlined the development and evaluation of a structural equation model in establishing the consequences of hemophilia. However, this study was carried out in a non-US setting and did not measure HRQOL as the adaptation outcome of interest among patients with hemophilia. Also the impact of key variables, such as self-efficacy and coping, which have been shown to significantly impact HRQOL among patients with hemophilia (Binnema, Schrijvers, Bos, Schuurmans, & Fischer, 2014; Catalan et al., 1992; Lock et al., 2014) was not assessed.

NEED FOR THE STUDY

1. Need to test the psychometric properties of the health status measure among adult patients with hemophilia.

The SF-12 has been previously used to assess HRQOL among patients with hemophilia (Poon, 2013; Duncan et al., 2012). However, its psychometric properties in this population have not been assessed. In order to obtain evidence about the appropriateness of use of the SF-12v2 among hemophilia patients, it is imperative to test its psychometric properties. Psychometric assessments are necessary to ensure the broad application of such generic HRQOL instruments across different populations. Therefore this study determined the psychometric properties of the SF-12v2 among adult patients with hemophilia in the US. The psychometric properties of the SF-12v2 were determined in terms of its convergent validity, discriminant validity, known-groups validity, factorial validity, and internal consistency reliability. Floor and ceiling effects were also examined on a per item basis for the HRQOL instrument under consideration.

2. Need to assess measurement invariance of the health status measure among adult patients with hemophilia

The assumption of measurement invariance must be tested in order to ensure that the differences observed in the HRQOL of the study populations are true differences and not measurement artifacts. An important question to keep in mind when using a HRQOL measure to assess the health status of patients with a given disease state is whether different members of the study population assign the same meaning to questionnaire items. In the context of the current study, the assumption of measurement invariance was said to be met if specific characteristics such as age, disease severity, and treatment regime did not influence observed responses to the items on the SF-12v2. If this assumption is violated then differences in HRQOL between hemophilia patients may not be true differences. In fact inherent differences in terms of factors such as age, disease severity, and treatment regimen may be manifested as differences in HRQOL among patients with hemophilia.

3. Need to assess psychosocial predictors of HRQOL among adult patients with hemophilia.

While previous studies have emphasized on clinical and socio-demographic determinants, this was the first US-based study which critically shifts focus to an assessment of psychosocial predictors of HRQOL among patients with hemophilia. An adapted version of the Lazarus and Folkman's cognitive-behavioral model of stress, appraisal, and coping was employed in order to help us examine the interplay between the patient's use of resources (i.e., social support, coping strategies, and self-efficacy) and adaptational health outcomes such as HRQOL. Employing a theory-based approach is essential to truly

understand the impact of hemophilia on patient well-being. Knowledge about these psychosocial factors will not only assist healthcare providers and caregivers in improving care provided to individuals with hemophilia, but will also enable patients to better understand and self-manage their disease condition. Such assessments can assist both clinicians and healthcare policymakers in designing programs aimed at increasing the level of social support provided, fostering the use of adaptive coping strategies, and overall ensuring better health among these patients.

SPECIFIC AIMS AND OBJECTIVES

1. To examine the psychometric properties of the SF-12v2 among adult hemophilia patients in the United States
 - a. Assess the construct validity (convergent validity, discriminant validity, known-groups validity, factorial validity) of the SF-12v2 instrument.
 - b. Assess the reliability and floor and ceiling effects of the SF-12v2 instrument.
2. To assess the measurement invariance of the SF-12v2 among adult hemophilia patients in the United States
 - a. Assess the presence of measurement invariance bias in a sample of US adults with hemophilia, specifically focusing on whether age, disease severity, and treatment regimen result in biased HRQOL scores measured using the SF-12v2.
3. To evaluate psychosocial predictors of HRQOL among adult hemophilia patients in the United States
 - a. Identify psychosocial determinants of HRQOL in a sample of US adults with hemophilia by employing an adapted version of the Lazarus and Folkman's cognitive-behavioral model of stress, appraisal, and coping. This study will specifically assess the relationship between disability, social support, coping, self-efficacy, and HRQOL among adult hemophilia patients using a structural equation model.

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**CHAPTER II: AN EVALUATION OF THE PSYCHOMETRIC PROPERTIES OF
THE SHORT FORM-12 (SF-12) AMONG ADULTS WITH HEMOPHILIA IN
THE UNITED STATES**

INTRODUCTION

Hemophilia is a rare X-linked chronic genetic blood coagulation disorder predominantly among males that is caused by a deficiency of clotting factors VIII or IX in blood plasma. It affects about 400,000 people across the world and about 20,000 in the United States (US) (Center for Disease Control and Prevention, 2014; National Hemophilia Foundation, 2014). Patients with hemophilia experience bleeding into joints and muscles which in severe cases can lead to chronic pain, reduce the range of joint motion and eventually progress to chronic arthritis (Dolan et al., 2009). Also, hemophilia patients often suffer from comorbidities such as infections due to hepatitis C virus (HCV), human immunodeficiency virus (HIV), or tolerance to clotting factors in the form of an inhibitor (Franchini & Mannucci, 2009).

According to the International Society for Quality of Life Research (ISOQOL), health-related quality of life (HRQOL) is “the functional effect of a medical condition and/or its consequent therapy upon a patient.” (International Society for Quality of Life Research, 2015). Thus HRQOL is a multidimensional, subjective concept which incorporates physical functioning, psychological functioning, social interaction, and somatic sensation. Hemophilia places a significant burden on the HRQOL of patients. Therefore, HRQOL has evolved as an important outcome which must be assessed among patients with hemophilia in order to truly quantify the burden of this disease.

The SF-12 Health Survey version 2 (SF-12v2) is a commonly used generic health status measure (Ware, Kosinski, & Keller, 1996). The SF-12 is an abbreviated version of the SF-36, a

widely used generic self-report measure of HRQOL. Like the SF-36, the SF-12 captures information regarding eight dimensions of patient health (i.e., physical functioning, role-physical, bodily pain, general health, vitality social-functioning, role-emotional, and mental health). It also provides two summary measures: the physical component summary score (PCS) and mental component summary score (MCS), which aggregate the eight domains.

The SF-12 was first psychometrically validated in the general US population by Ware and colleagues in 1996 using data from the National Survey of Functional Health Status (NSFHS) and the Medical Outcomes Study (MOS). The instrument has since been validated among general populations in several different countries such as Denmark, Germany, United Kingdom, Netherlands, and others (Gandek et al., 1998; Hanmer, Lawrence, Anderson, Kaplan, & Fryback, 2006; Kontodimopoulos, Pappa, Niakas, & Tountas, 2007; Montazeri, Vahdaninia, Mousavi, & Omidvari, 2009) as well as among patients with several diseases such as Parkinson's disease, stroke, diabetes mellitus, inflammatory rheumatic disease, hemodialysis and others (Jakobsson, Westergren, Lindskov, & Hagell, 2012; Maurischat, Ehlebracht-König, Kühn, & Bullinger, 2006; Maurischat, Herschbach, Peters, & Bullinger, 2008; Okonkwo, Roth, Pulley, & Howard, 2010; Pakpour et al., 2011). The results of these past studies suggest that the SF-12 has good psychometric properties.

Although the SF-12 has been used to assess the HRQOL of hemophilia patients (Duncan, Shapiro, Ye, Epstein, & Luo, 2012; Poon, Doctor, & Nichol, 2014), the psychometric properties of the SF-12v2 have never been established among patients with hemophilia. In order to obtain evidence about the appropriateness of use of the SF-12v2 among hemophilia patients, it is imperative to test its psychometric properties. Psychometric assessments are necessary to ensure the broad application of such generic HRQOL instruments across different populations (Patrick

& Deyo, 1989). Therefore this study determined the psychometric properties of the SF-12v2 among adult patients with hemophilia in the US. The psychometric properties of the SF-12v2 were determined in terms of its convergent validity, discriminant validity, known-groups validity, factorial validity, and internal consistency reliability. Floor and ceiling effects were also examined for the HRQOL instrument under consideration.

METHODS

Study Design

The current study employed a prospective, cross-sectional, descriptive design by means of a web-based self-administered survey which was distributed to a national convenience sample of adults with hemophilia in the United States. Study approval was obtained from the University of Mississippi Institutional Review Board under the exempt status.

Study Sample

For the purposes of the current study, the study sample included adults (≥ 18 years of age) with hemophilia A or B. Patients with other blood coagulation disorders such as Von Willebrand's disease were excluded from the study sample. The sample was recruited with the help of a market research vendor company called Rare Patient Voice which maintains a panel of hemophilia patients. The majority of these patients were recruited at hemophilia-related conferences and patient advocacy group meetings across the US. Considering hemophilia is a rare disease, patients were also recruited using a Facebook community of hemophilia patients called Hemo Friends and at the University of Mississippi (UMMC) hemophilia treatment center (HTC) in order to maximize the analyzable sample size for the current study. Given the nature of the statistical analysis plan for this study (i.e., structural equation modeling), an a priori sample size of 200 patients with hemophilia was considered to be adequate (Kline, 2005).

Study methodology

This study was a part of a bigger study assessing psychosocial predictors of HRQOL among patients with hemophilia. However, only information pertinent to the current study has been reported here. The survey instrument for the current study included the following measures: SF-12v2, and the demographic and health information form. Study participants were initially sent an email explaining the objective and scope of the study. This email assured the respondents that their information would be kept confidential. The email also contained a URL link to the survey which was programmed in Qualtrics (Qualtrics Inc, Provo, UT). The survey was open for a period of 3 months from October 31, 2015 to January 31, 2016. All respondents were provided \$10 Amazon gift cards for participation in the study.

Study Measures

SF-12 Health Survey Version 2 (SF-12v2). The SF-12 is the shorter version of the SF-36 which was also developed as a part of the Medical Outcomes Study. The SF-12v2 is a generic health profile instrument with 12-items which compose 8 health concepts forming a health profile (Ware et al., 1996). These eight sub-domains are: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). These eight sub-domain scores can be weighted and summarized into two component scores – the physical component summary (PCS) score and the mental component summary (MCS) score. According to the theoretical test model, the items from the physical functioning, role-physical, bodily pain, and general health domain are indicators of PCS while vitality, social functioning, role-emotional, and mental health items are indicators for the MCS. The items have different levels of response categories (two, three, five or six). Using item-specific indicator weights, the PCS and MCS scores are calculated using the QualityMetric SF Health Outcomes™ Scoring Software. The SF-12 scores obtained using the scoring software

can be transformed onto a 0 to 100 scale with higher scores indicating better HRQOL. For the SF-12v2, the norm-based scores for the general US population have a mean of 50 and a standard deviation of 10 with higher scores indicating a better health status (Ware & Kosinski, 2001). The SF-12v2 takes about two minutes to complete.

Patient Global Impression of Severity (PGI-S). The PGI-S is a single self-reported measure that asks respondents to rate the severity of their disease condition. In this study, the PGI-S was specifically worded as “When thinking about all of the hemophilia-related symptoms that you may have experienced during the past 7 days, please circle the one number that best describes how your symptoms overall have been; on a 4-point scale scored as: (1) “no symptoms”, (2) “mild symptoms”, (3) “moderate symptoms”, or (4) “severe symptoms”. A similar self-report symptom severity measure has been previously used among male subjects with lower urinary tract symptoms secondary to benign prostatic hyperplasia and women with stress urinary incontinence (Viktrup, Hayes, Wang, & Shen, 2012; Yalcin & Bump, 2003).

Demographic and health information form. Information was collected for the following socio-demographic and clinical characteristics: (1) age, (2) race/ethnicity, (3) education status, (4) marital status, (5) occupation status, (6) disease severity, (7) monthly bleeding frequency, (8) type of treatment, (9) hemophilia-related comorbidities.

Statistical Analysis

Sample description

Descriptive statistics were calculated in the form of frequencies and percentages for categorical variables, and means and standard deviations for the continuous variables.

Item-level analysis and floor and ceiling effects

Item-level descriptives were calculated in terms of means, and standard deviations (SD). The item-response patterns were presented as the frequency and percentage of each response (missing data, if any, was treated as a category with the number of subjects with missing responses included in the calculation of the percentages). Kurtosis and skewness coefficients were calculated in order to check for multivariate normality. Variables with absolute value of the skew index > 3.0 and kurtosis index > 10.0 were considered to be non-normal and warranted further examination (Kline, 2005).

Missing data analysis

The missing score handling technique (Missing Score Estimation) developed by QualityMetric™ was used for handling missing responses on the SF-12v2. For confirmatory factor analysis which was used for establishing the factorial validity of the SF-12v2, the total available sample was used for the analysis rather than the listwise deletion approach (Asparouhov & Muthén, 2010).

Factorial validity. Confirmatory factor analysis (CFA) was applied to the raw data in order to evaluate the factor structure of the SF-12v2 among patients with hemophilia. CFA is a structural equation modeling technique which is used to evaluate the fit of a theoretically-based measurement model (Hair, Black, Babin, Anderson, & Tatham, 2009). Three measurement models for the SF-12v2 were tested. The first was a 1-factor model which forced all the items on the SF-12 to load onto a single latent factor. The second was a 2-factor model based on the approach adopted by Okonkwo and colleagues (2010) where the PF, RP, and BP sub-domain items were allowed to load onto a latent physical health factor (LPF) while the RE and MH items were allowed to load onto a latent mental health factor (LMF). The three items from the GH, VT, and SF domain were allowed to cross load onto both latent factors. The residuals for the

two PF items were allowed to be correlated in both the 1-factor and 2-factor models. Model 3 was based on the 2-factor model employed by Maurischat and colleagues (2008) where the GH, PF, RP, and BP sub-domain items were allowed to load onto a LPF. The RE, MH, VT, and SF sub-domain items were allowed to load onto a LMF. The residuals for each of the two PF, RP, RE, and MH items were allowed to be correlated. The LPF and LMF were also correlated in models 2 and 3.

Considering that the items on the SF-12 are measured on an ordinal scale with a limited number of response options, weighted least squares estimation (WLSMV) for categorical indicators was used to quantify the hypothesized relationships (Muthén, 1984). All CFA models were estimated using Mplus version 7.31 (Muthen & Muthen, Los Angeles, CA).

Model fit for each model was assessed using the following five fit statistics: χ^2 statistic, the root mean square error of approximation (RMSEA), the Tucker Lewis Index (TLI), the comparative fit index (CFI), and the weighted root mean square residual (WRMR). Bagozzi and Yi (2012) suggest that for a well-fitting model, the RMSEA, TLI, CFI must be ≤ 0.08 , ≥ 0.92 , and ≥ 0.93 respectively (Bagozzi & Yi, 2012). For a good fitting model, WRMR must be less than or equal to 1 (Yu, 2002).

Convergent validity. Items which are indicators of a particular latent construct must share a high proportion of variance in common. This is known as convergent validity. Factor loadings and average variance extracted (AVE) from the CFA models and item-scale correlations were used to estimate the relative amount of convergent validity among item measures.

The size of the factor loading is an indication of the amount of variance in a particular item that is explained by the latent construct. For the current study, standardized factor loadings of 0.5 or higher were considered to be indicative of good construct validity (Hair, Anderson,

Tatham, Black, & River, 2010). Statistical significance of the factor loadings was the minimum requirement because a significant loading could be weak or moderate in strength.

AVE for each latent construct was computed as the total of all squared standardized factor loadings divided by the number of items loading onto that factor. An AVE of 0.5 or higher was considered to be suggestive of good convergent validity because an AVE below 0.5 indicates that the error variance remaining in the indicators is higher than the variance explained by the latent factor (Hair et al., 2010).

Higher item-scale correlations (Pearson's correlation between score on an individual item in a sub-domain with the total score on the underlying sub-domain) indicate that expected items in the same sub-domains correlate strongly with each other. This approach of establishing convergent validity has been used by previous studies (Khanna, Jariwala, & West-Strum, 2015). Item-scale correlations of 0.1-0.29 were considered small, 0.3-0.49 as moderate, and ≥ 0.45 was considered to be suggestive of strong (Cohen, 1988). It was hypothesized that the correlation between an item and its underlying sub-domain will be higher than with other sub-domains. A strong correlation of the items which belong to the GH, PF, RP, and BP sub-domains with PCS was hypothesized. Similarly, a strong correlation between items representing the RE, MH, VT, SF sub-domains with MCS summary scale score was hypothesized.

Discriminant validity. Discriminant validity is the extent to which a construct is distinct from other constructs. The following methods were used to assess the discriminant validity of the physical and mental health dimensions of the SF-12v2.

First, after freeing all factor loadings for the items on the SF-12v2, the correlation between the LPF and LMF was fixed to one in the 2-factor model. Following this, it was assessed whether the fit of the 2-factor model was significantly different from the 1-factor

model. A significant difference in the model fit between the two models was suggestive of discriminant validity. This is not a very strong test of discriminant validity because even a very correlation between the two constructs (≥ 0.90 or higher but not exactly 1) would indicate adequate discriminant validity.

Second, the difference between the AVE for each latent construct and the square of the correlation estimate between the two constructs was calculated. A positive difference (i.e., the two AVE's exceed the sum of the square of the correlation between LMF and LPF) is indicative of the fact that the latent construct explains a higher proportion of the variance in its indicator items as compared to the variance shared with another latent construct, suggesting discriminant validity (Fornell & Larcker, 1981).

Third, lower item-to-other scale correlations (≤ 0.40) were suggestive of adequate discriminant validity. The reasoning behind this technique was that items from different domains should have low or no correlations with each other. It was hypothesized that the correlation between an item and other sub-domains will be weaker than with its underlying sub-domain. A weak correlation of the items which belong to the GH, PF, RP, and BP sub-domains with MCS was hypothesized. Similarly, a weak correlation between items representing the RE, MH, VT, SF sub-domains with PCS summary scale score was hypothesized.

Known-groups validity. Known-groups validity is the ability of an instrument to differentiate among individuals who have levels of disease severity. One-way ANOVA was used to compare the PCS and MCS from the SF-12v2 across hemophilia patients with different symptom severity levels obtained using the PGI-S.

Internal consistency reliability. In order to evaluate the internal consistency reliability of the PCS and MCS for the SF-12v2, Cronbach's alpha (α) was calculated. An $\alpha \geq 0.70$ was

considered to be suggestive of adequate internal consistency reliability for the PCS and the MCS (Okonkwo et al., 2010).

Floor and ceiling effects. In order to assess the floor and ceiling effects of the SF-12v2, the percentage of adults with hemophilia with the least possible and the maximum possible PCS and MCS were determined. Floor and ceiling effects were considered to be present if more than 20% of the respondents received the lowest or the highest possible PCS or MCS summary scale score (Holmes & Shea, 1997; Khanna et al., 2015).

RESULTS

Socio-demographic characteristics

The final study sample consisted of 218 adults with hemophilia (Table 2.1). The majority of the study population included patients with hemophilia A (77.5%), males (79.5%), and Caucasians (68.5%). 169 (77.5%) of these patients were recruited using an online panel of hemophilia patients (i.e., Rare Patient Voice), 44 (20.2%) were recruited using a Facebook community of hemophilia patients (i.e., Hemo Friends), and 6 (2.3%) were recruited at the UMMC HTC. The mean age of the study sample was 35.45 (12.3) years. Patients also commonly suffered from comorbidities such as hepatitis C (36.5%) and depression (38.4%).

Table 0.1: Demographic and clinical characteristics the study sample

Characteristics	N (%)
<u>Diagnosis</u>	
Hemophilia A	169 (77.5)
Hemophilia B	49 (22.5)
<u>Gender</u>	
Male	174 (79.5)
Female	24 (11.0)
<u>Age, mean (sd)</u>	35.45 (12.3)
<u>Race/Ethnicity</u>	
White/Caucasian	150 (68.5)
Other*	47 (21.5)
<u>Marital Status</u>	
Never Married	66 (30.1)
Married	98 (44.7)
Other†	34 (20.1)
<u>Education level</u>	
Less than high school	9 (4.1)
High school or technical school	30 (13.7)
College degree	128 (58.4)
Masters degree	17 (7.8)
Doctoral degree	6 (2.7)
Professional degree	8 (3.7)
<u>Employment Status</u>	
Employed/self-employed full time	103 (47.0)
Employed part-time	23 (10.5)
On disability	16 (7.3)
Other‡	56 (25.6)
<u>Region of the country</u>	
Northeast	46 (21.0)
Midwest	40 (18.3)
South	54 (24.7)
West	58 (26.5)
<u>Health Insurance</u>	
Public	61 (27.9)
Private	113 (51.6)
Both	6 (2.7)
None	18 (8.2)
<u>Disease severity</u>	
Mild (5%-40% clotting factor activity)	42 (19.2)
Moderate (1%-5% clotting factor activity)	25 (11.4)
Severe (>1% clotting factor activity)	127 (58.0)
Not sure	3 (1.4)

<u>Symptom Severity</u>	
No symptoms	31 (14.2)
Mild symptoms	67 (30.6)
Moderate symptoms	61 (27.9)
Severe symptoms	39 (17.8)
<u>Treatment Regimen</u>	
Always received on prophylaxis therapy	121 (55.3)
Received both prophylaxis and on-demand therapy	31 (14.2)
Always received on on-demand therapy	45 (20.5)
<u>Number of bleeding episodes in the past year, mean (sd)</u>	11.69 (19.1)
<u>Hemophilia-related surgery</u>	
Yes	73 (33.3)
No	124 (56.6)
<u>Number of hemophilia-related surgeries in the past year, mean (sd)</u>	3.64 (3.9)
<u>Comorbidities</u>	
Hepatitis C	80 (36.5)
HIV ^v	26 (11.9)
Depression	84 (38.4)
Inhibitors to clotting factor	41 (18.7)
<u>Annual number of hemophilia-related visits, mean (sd)</u>	
Hemophilia Treatment Center (HTC)	2.23 (3.1)
Hematologist outside a HTC	0.83 (1.8)
Primary Care Practitioner	2.42 (4.2)
<p>Note: SD, standard deviation; Frequencies for each demographic characteristic may not add up to the total sample size due to the presence of missing data.</p> <p>*Other includes American Indian/Alaskan Native, Asian/Indian Asian, Native Hawaiian/Other Pacific Islander, Hispanic, etc.</p> <p>†Other includes divorced, separated, widowed, and not married, living with partner</p> <p>‡Other includes retired, home-maker, student, seeking work, etc.</p> <p>^vHIV - Human Immuno Deficiency Virus.</p> <p>Patient recruitment – 169 (77.5%) from Rare Patient Voice, 44 (20.2%) from Hemo Friends, and 6 (2.3%) from UMMC HTC.</p>	

Item distribution and quality

Table 2.2 shows the mean scores, and skewness and kurtosis coefficients on a per-item basis for the SF-12v2. The skewness and kurtosis coefficients for all items on the SF-12v2 were found to be within a range of -1.00 and 0.63. Based on these ranges, the data appear to be normally distributed. The mean PCS was 43.68 (± 10.19) and the mean MCS was found to be

46.48 (± 10.09) among adults with hemophilia. The mean score for each of the eight SF-12v2 domains as well as the PCS and the MCS were lower than the norm score for the general healthy US population. The distribution of the PCS and MCS scores across the study sample can be found in Figure 2.1 and 2.2 below. This indicated that adults with hemophilia had a worse overall HRQOL as compared to the US norm population. There was no missing data for any of the SF-12v2 items.

Table 0.2: Item-level and domain-level characteristics for the SF-12v2 among adults with hemophilia

Items	N	Missing	Mean (SD)	Skewness		Kurtosis	
				Statistic	Std. error	Statistic	Std. error
Health in general (GH01)	218	0	2.89 (0.94)	0.28	0.164	-0.22	0.327
Limitation in moderate activities (PF02)	218	0	2.25 (0.69)	-0.36	0.164	-0.86	0.327
Limitation in climbing stairs (PF03)	218	0	2.17 (0.78)	-0.3	0.164	-1.00	0.327
Accomplished less due to physical health (RP04)	218	0	3.31 (1.28)	-0.24	0.164	-0.88	0.327
Limited in health due to physical health (RP05)	218	0	3.25 (1.26)	-0.12	0.164	-0.96	0.327
Pain interfered with work (BP08)	218	0	2.91 (1.18)	0.09	0.164	-0.94	0.327
Have a lot of energy (VT10)	218	0	3.09 (1.03)	0.1	0.164	-0.50	0.327
Physical health or emotional problems interfered with social activities (SF12)	218	0	3.56 (1.13)	-0.43	0.164	-0.42	0.327
Accomplished less due to emotional problems (RE06)	218	0	3.54 (1.30)	-0.46	0.164	-0.95	0.327
Less careful due to emotional problems (RE07)	218	0	3.8 (1.20)	-0.63	0.164	-0.62	0.327
Felt calm and peaceful (MH09)	218	0	2.62 (0.98)	0.42	0.164	-0.36	0.327
Felt downhearted and depressed (MH11)	218	0	3.65 (1.10)	-0.55	0.164	-0.47	0.327
Physical Component Score (PCS)	218	0	43.68 (10.19)	-0.62	0.164	0.61	0.327

Mental Component Score (MCS)	218	0	46.48 (10.09)	-0.72	0.165	1.23	0.328
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Responses to the items on the SF-12v2 were measured using 3 or 5-point response scales

Figure 0.1: Distribution of SF-12v2 Physical Component Score

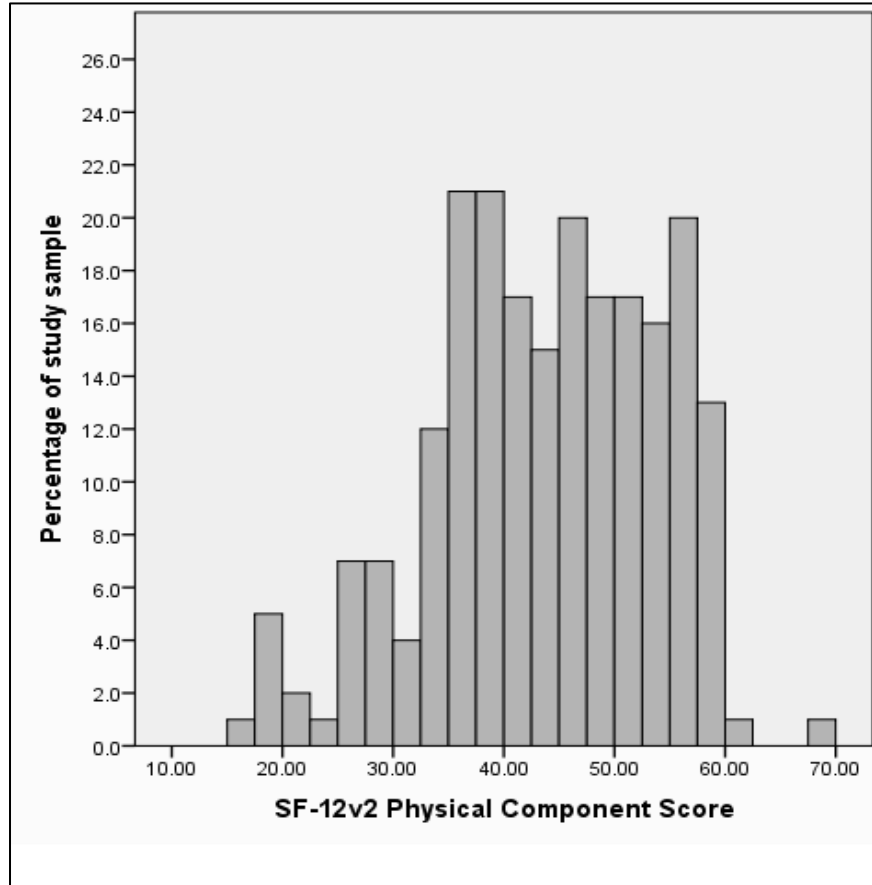
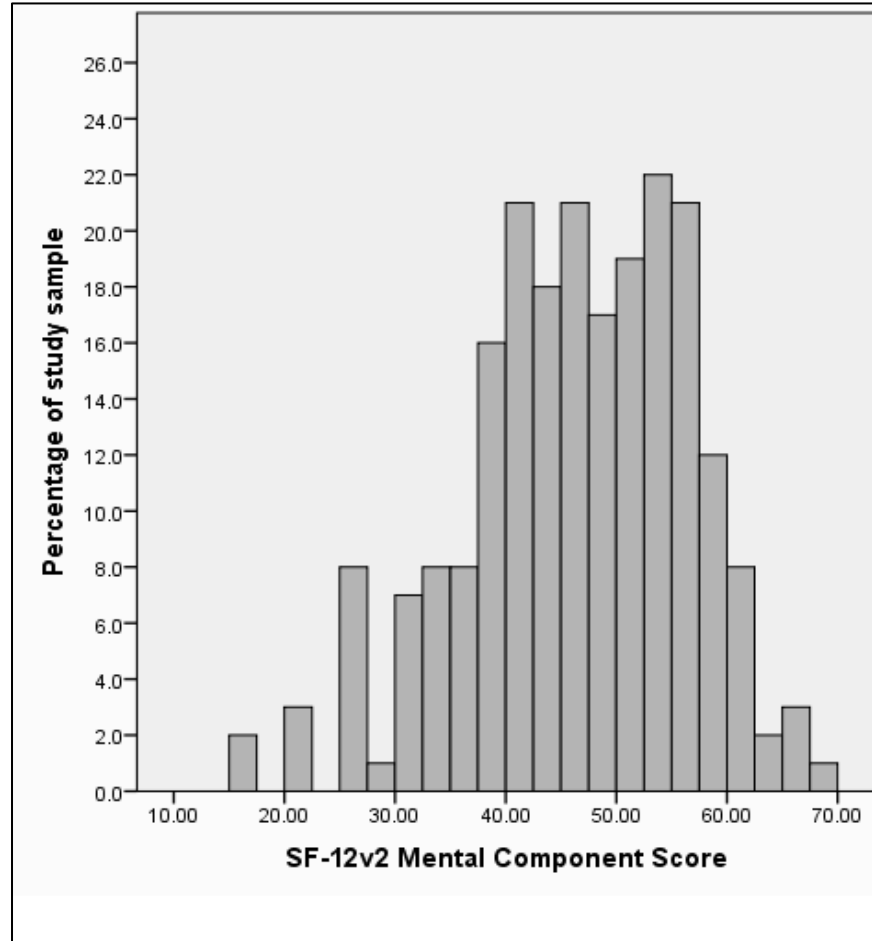


Figure 0.2: Distribution of SF-12v2 Mental Component Score



Factorial validity. Figures 2.3, 2.4, and 2.5 depict the three SF-12v2 factor models which were tested in order to examine the factorial validity of the instrument among adults with hemophilia. The model fit indices for the three models can be found in Table 2.3. The single factor model where all items loaded onto a single latent HRQOL factor had a poor fit (Chi-square [df] = 531.807 [53]; CFI = 0.896; TLI = 0.870; RMSEA [90% CI] = 0.203 [0.188-0.209]; WRMR = 2.011). The two-factor model tested by Okonkwo et al. (2010) had a moderate-mediocre fit (Chi-square [df] = 340.418 [49]; CFI = 0.936; TLI = 0.914; RMSEA [90% CI] = 0.165 [0.149-0.182]; WRMR = 1.409). The two-factor model based on the approach used by Maurischat et al. (2008) had the best fit among the three models which were tested (Chi-square [df] = 270.183 [49]; CFI = 0.952; TLI = 0.935; RMSEA [90% CI] = 0.144 [0.127-0.162]; WRMR = 1.250). Based on the modification indices, the error terms for items 9 and 10 (i.e., MH09 and VT10) were correlated in model 3 in addition to the corrected residuals already specified in the Maurischat et al. (2008) model. This improved the model fit of the final model significantly (Chi-square [df] = 172.778 [48]; CFI = 0.972; TLI = 0.962; RMSEA [90% CI] = 0.109 [0.092-0.127]; WRMR = 0.947).

Table 0.3: Summary of model fit indices for the SF-12v2 confirmatory factor models

Fit Statistics	Model 1	Model 2	Model 3
Chi-square (<i>df</i>)	531.807 (53)	340.418 (49)	172.778 (48)
CFI	0.896	0.936	0.972
TLI	0.870	0.914	0.962
RMSEA (90% <i>CI</i>)	0.203 (0.188 - 0.219)	0.165 (0.149 - 0.182)	0.109 (0.092 - 0.127)
WRMR	2.011	1.409	0.947
Model 1 - All items load onto a single latent health-related quality of life factor; Model 2 - SF-12 CFA model based on Okonkwo et al. (2010); Model 3 - SF-12 CFA Model based on Maurischat et al. (2008). Note: <i>df</i> , degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation; WRMR, Weighted Root Mean Square Residual; <i>CI</i> , Confidence Interval.			

Figure 0.3: Single Factor Model for the SF-12v2

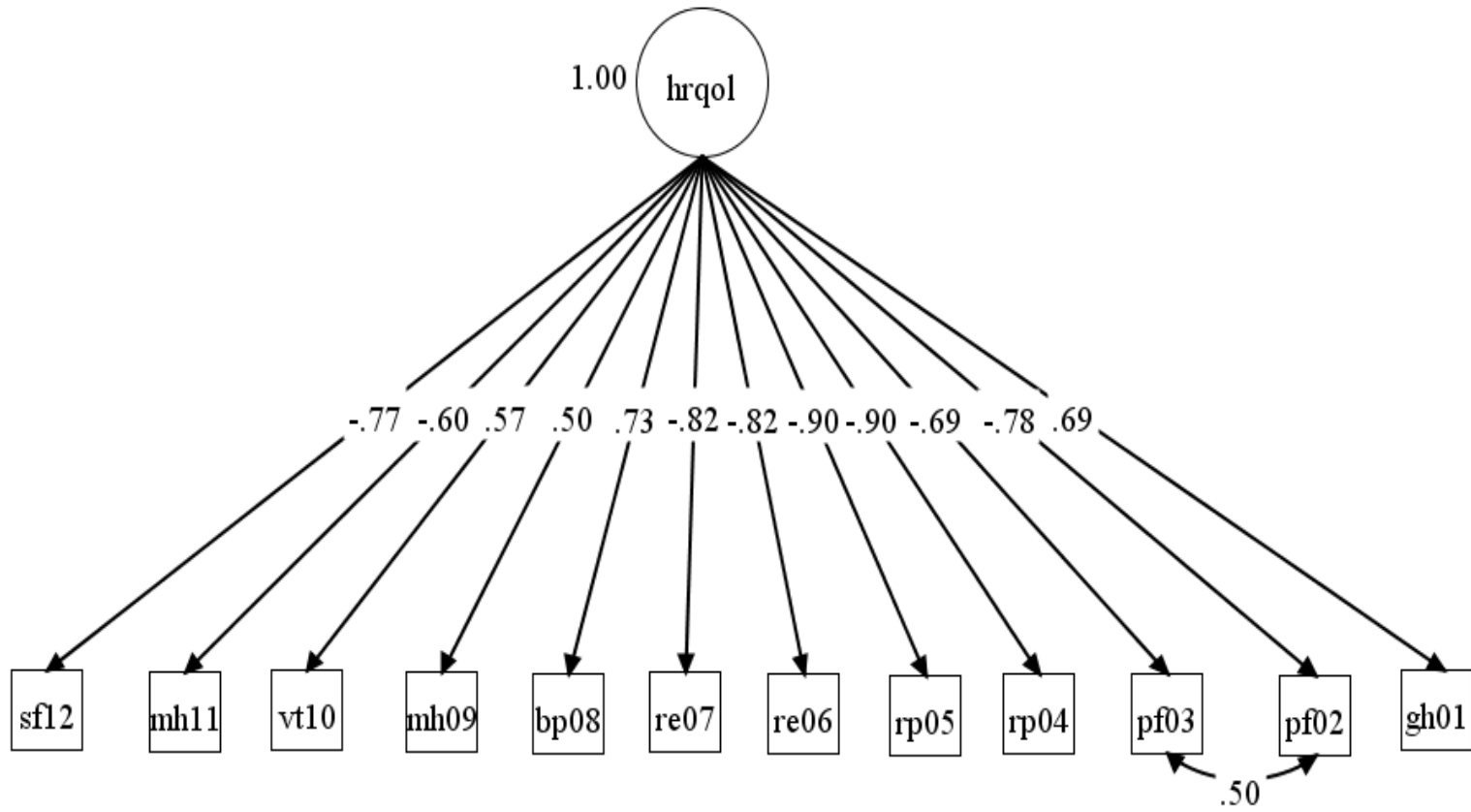


Figure 0.4: Two Factor Model for the SF-12v2 based on Okonokwo et al. (2010)

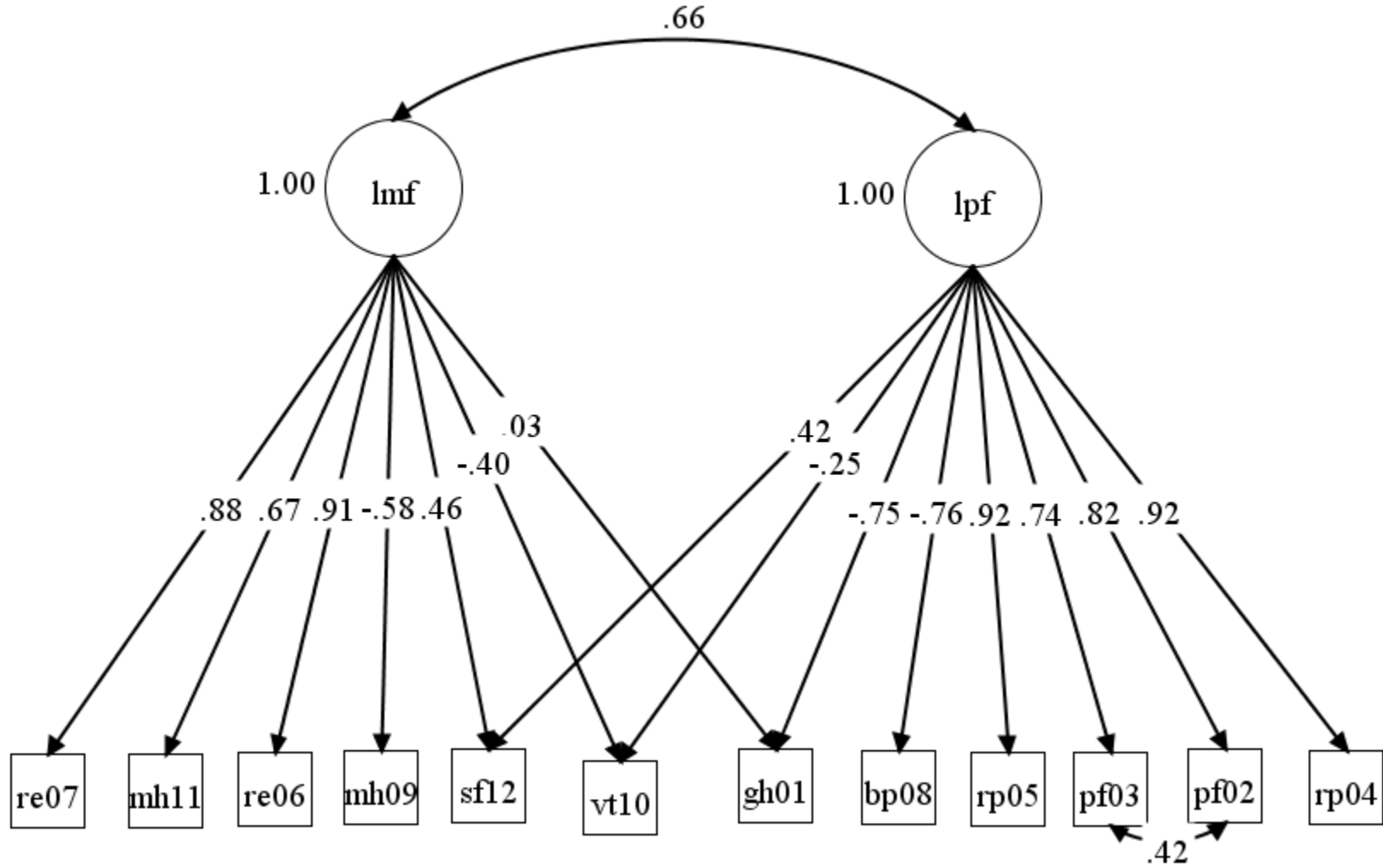


Figure 0.5: Two Factor Model for the SF-12v2 based on Maurischat et al. (2008)

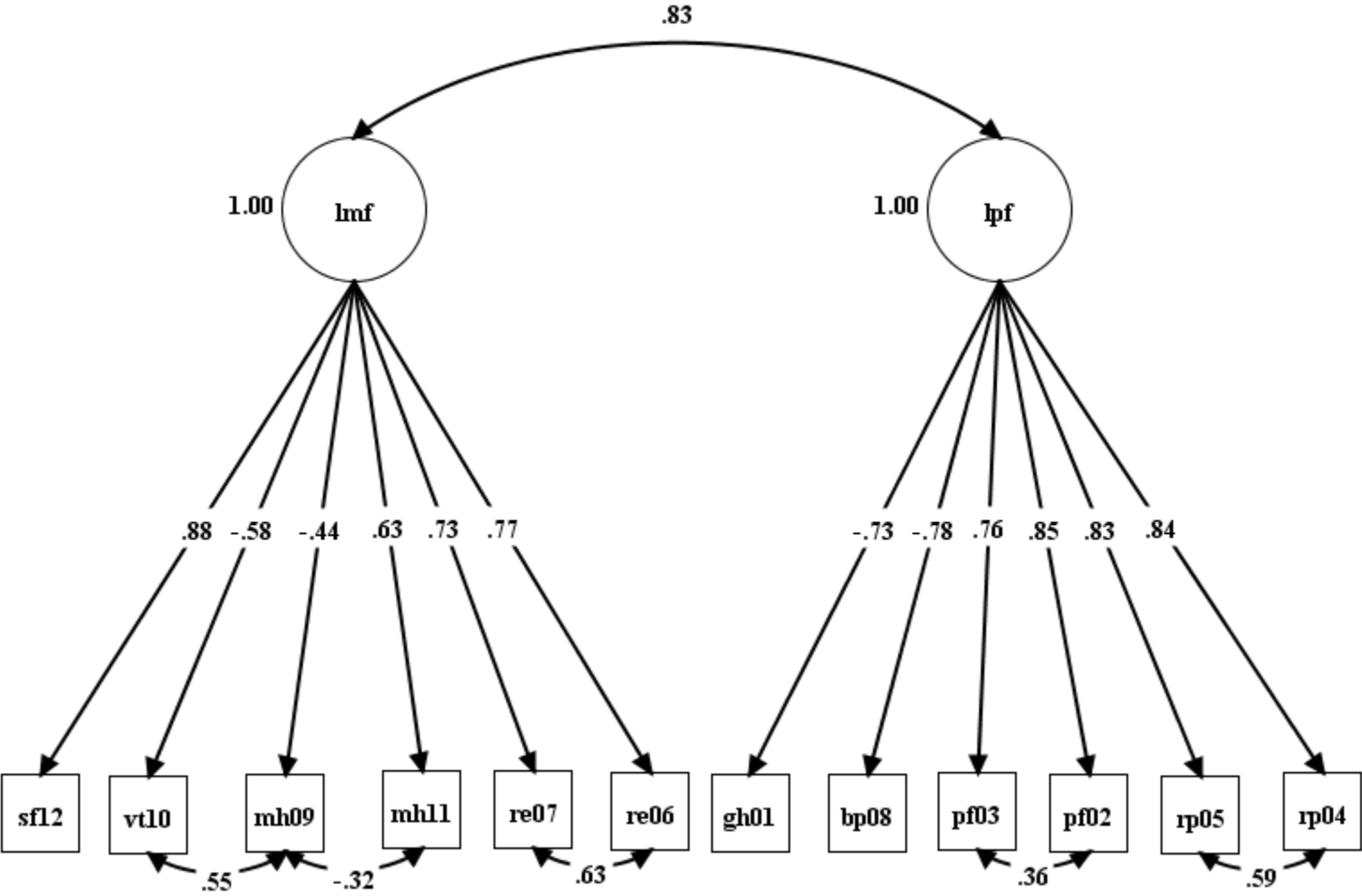


Table 0.4: Standardized factor loadings for the final two factor model of HRQOL for the SF-12v2 among adults with hemophilia

Items	Estimate [∧] (SE)
Latent Physical Factor	
Health in general (GH01)	-0.734 (0.040)
Limitation in moderate activities (PF02)	0.848 (0.028)
Limitation in climbing stairs (PF03)	0.758 (0.038)
Accomplished less due to physical health (RP04)	0.842 (0.025)
Limited in health due to physical health (RP05)	0.831 (0.026)
Pain interfered with work (BP08)	-0.785 (0.030)
Latent Mental Factor	
Accomplished less due to emotional problems (RE06)	0.766 (0.044)
Less careful due to emotional problems (RE07)	0.726 (0.037)
Felt calm and peaceful (MH09)	-0.443 (0.054)
Have a lot of energy (VT10)	-0.575 (0.048)
Felt downhearted and depressed (MH11)	0.627 (0.040)
Physical health or emotional problems interfered with social activities (SF12)	0.878 (0.028)
Latent Factor Correlation	
Latent Physical Factor with Latent Mental Factor	0.829 (0.039)
Correlated Residuals	
Item 2 with Item 3	0.355 (0.091)
Item 4 with Item 5	0.591 (0.047)
Item 6 with Item 7	0.627 (0.041)
Item 9 with Item 10	0.552 (0.054)
Item 9 with Item 11	-0.323 (0.049)
<p>Items with negative factor loadings represent those SF-12 questions on which higher scores indicated poorer health status whereas items with positive factor loadings represent the SF-12 questions on which higher scores reflected better health status</p> <p>[∧]All factor loadings were significant at $\alpha = 0.05$</p>	

Convergent validity. The standardized factor loadings for the final study model have been reported in table 2.4 above. All factor loadings were statistically significant at $\alpha = 0.05$. Most factor loadings (except item 9 on LMF) were greater than 0.5. The AVE for the LPF was found to be 0.64 and the AVE for the LMF was 0.47. Table 2.5 depicts the item-scale correlation matrix. The correlation between the eight subdomains and their underlying item(s) were strong and statistically significant. Items comprising the PF, RP, GH, and BP subdomains had a strong and statistically significant correlation with the PCS. While RE, MH, VT, SF items were strongly correlated with the MCS summary scale score. Overall the standardized factor loadings, AVE for each latent factor, and item-scale correlations suggested acceptable convergent validity for the SF-12v2 among adults with hemophilia.

Table 0.5: Item-scale correlations for the SF-12v2 among adults with hemophilia

	GH	PF	RP	RE	BP	MH	VT	SF	PCS	MCS
GH										
GH01	-.990**	-.589**	-.572**	-.291**	-.455**	-.322**	-.502**	-.414**	-.710**	-.256**
PF										
PF02	.521**	.893**	.656**	.477**	.555**	.326**	.339**	.576**	.758**	.304**
PF03	.540**	.918**	.587**	.291**	.514**	.285**	.338**	.444**	.791**	.137*
RP										
RP04	.537**	.646**	.956**	.561**	.600**	.306**	.302**	.563**	.760**	.341**
RP05	.543**	.659**	.955**	.522**	.575**	.315**	.327**	.539**	.769**	.304**
RE										
RE06	.255**	.392**	.569**	.945**	.431**	.460**	.300**	.592**	.282**	.741**
RE07	.275**	.394**	.495**	.936**	.457**	.450**	.287**	.546**	.258**	.717**
BP										
BP08	-.454**	-.588**	-.615**	-.472**	1.000**	-.376**	-.391**	-.577**	-.736**	-.350**
MH										
MH09	-.364**	-.254**	-.203**	-.278**	-.342**	-.834**	-.599**	-.364**	-.141*	-.627**
MH11	.173*	.318**	.346**	.538**	.303**	.872**	.313**	.490**	.095	.761**
VT										
VT10	-.485**	-.374**	-.329**	-.312**	-.391**	-.524**	1.000**	-.425**	-.371**	-.592**
SF										
SF12	.409**	.561**	.580**	.609**	.577**	.496**	.425**	1.000**	.512**	.671**

Note: GH, general health; PF, physical functioning; RP, role physical; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, Physical Component Summary; MCS, Mental Component Summary

** . Correlation is significant at the 0.01 level.

* . Correlation is significant at the 0.05 level.

Discriminant validity. Three separate tests were employed in order to examine the discriminant validity of the SF-12v2. First, the fit of the two factor model (Figure 2.5) was compared to that of a model where the correlation between LPF and LMF was fixed to one. The test yielded a significant difference in the chi-square value (Chi-square [df] = 18.686 [1]; $p < 0.0001$) which was suggestive of adequate discriminant validity (Hair et al., 2010). Second, the difference between the AVE for each latent factor and the square of the latent factor correlation was not found to be positive for either the LPF or the LMF. A non-positive difference was suggestive of lack of adequate discriminant validity (Hair et al., 2010). Last, items comprising the PF, RP, GH, and BP subdomains had a weak correlation with the MCS summary scale score. While RE, MH, VT, SF items had a weak to moderate correlation with the PCS summary scale score. Overall the SF-12v2 was found to have acceptable discriminant validity among adults with hemophilia.

Known-groups validity. The ability of the SF-12v2 to discriminate between hemophilia patients with no symptoms, mild symptoms, moderate symptoms, and severe symptoms was assessed using a one-way ANOVA (Table 2.6). Differences in PCS and MCS scores between individual groups were assessed using post-hoc Tukey's honestly significant difference (HSD) tests. The mean PCS (50.10 vs 47.39 vs 40.79 vs 35.24; $p < 0.0001$) and MCS (50.61 vs 46.80 vs 46.96 vs 42.29; $p = 0.007$) summary scale scores were significantly different across the four symptom severity levels. A definite gradation was observed in terms of the PCS and MCS with increasing levels of symptom severity on the PGI-S. Specifically, the mean PCS score for patients with no symptoms over the past 4 weeks (50.10) was significantly higher than the score for patients with moderate (40.79) or severe (35.24) symptoms. Patients with mild symptoms (47.39) had a significantly higher PCS score as compared to those with moderate (40.79) or severe (35.24) symptoms. The PCS summary scale score for those with moderate symptoms (40.79) was

significantly greater than for those with severe symptoms (35.24). Finally, patients with no symptoms (50.69) had a significantly higher MCS summary scale score as compared to those with severe symptoms (42.29).

The SF-12v2 was not able to discriminate across hemophilia severity levels based on self-reported blood clotting factor activity level.

Table 0.6: Known-groups validity for the SF-12v2 components among adults with hemophilia

Component	No symptoms (N = 31)	Mild Symptoms (N = 67)	Moderate Symptoms (N = 61)	Severe Symptoms (N = 39)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i>-value
Physical Component Summary Score (PCS)	50.10 (7.92) [∨]	47.39 (8.25) [*]	40.79 (8.59) ^{∨*‡}	35.24 (10.78) ^{∨*‡}	<0.0001
Mental Component Summary Score (MCS)	50.61 (8.23) [∨]	46.80 (9.53)	46.96 (9.27)	42.29 (12.28) [∨]	0.007
<p>[∨]Significant difference in mean PCS scores between group 1 as compared to group 3 and group 4 at alpha less than or equal to .05 based on Tukey's HSD (Honestly Significant Difference) test. [*]Significant difference in PCS scores between group 2 as compared to group 3 and group 4 at alpha less than or equal to .05 based on Tukey's HSD test. [‡]Significant difference in PCS scores between group 3 and group 4 at alpha less than or equal to .05 based on Tukey's HSD test. [∨]Significant difference in mean MCS scores between group 1 and group 4 at alpha less than or equal to .05 based on Tukey's HSD test.</p>					
<p>Note: SD, standard deviation <i>p</i>-values are based on a one-way analysis of variance</p>					

Internal Consistency Reliability. The internal consistency reliability for the SF-12v2 was found to be satisfactory with the Cronbach’s alpha value of 0.848 for PCS and 0.785 for MCS (Table 2.7).

Table 0.7: Reliability analysis for the SF-12v2 components among adults with hemophilia

Component	Mean (SD)	Cronbach's alpha	No. of items
Physical Component	43.92 (3.02)	0.848	6
Mental Component	45.53 (2.63)	0.785	6

Floor and ceiling effects. Less than 20% of the study sample received the lowest or highest possible PCS or MCS summary scale score which was indicative of the absence of floor and ceiling effects. The minimum and maximum PCS score for the study sample was 16.95 and 67.63 respectively. The minimum and maximum MCS score was 15.75 and 68.91 respectively. The minimum and maximum PCS score for the general US population as per the SF-12 scoring manual is 4.92 and 69.24 respectively. While the minimum and maximum MCS score for the US norm population was 8.14 and 73.24 respectively (Ware, Kosinski, Turner-Bowker, Gandek, 2005). Therefore none of the respondents from our study sample received the lowest or highest possible score as per the general US population.

DISCUSSION

Hemophilia is a rare genetic blood coagulation disorder which impact the physical, mental, and social aspects of the life of an individual. As HRQOL continues to evolve as a key health outcomes endpoint among patients with hemophilia, so does the need for psychometrically-sound generic instruments which measure HRQOL. Such instruments not only allow one to ascertain the burden of hemophilia on patient HRQOL, but also compare their HRQOL to the healthy US population and across subgroups of individuals suffering from other diseases. The current study assessed the validity (factorial, convergent, discriminant, and known-groups) and internal consistency reliability of the SF-12v2, a generic measure of HRQOL, among adults with hemophilia.

The mean PCS for the study population was found to be 43.67 (± 10.67) and the mean MCS was 46.48 (± 10.09). Thus adults with hemophilia had worse PCS and MCS scores as compared to the US norm population (PCS and MCS = 50.0 (± 10.00)). Adults with hemophilia had the lowest mean score on the two physical functioning items (Items 2 and 3). This is understandable because hemophilia patients experience repeated bleeding into joints and large muscle groups. These prolonged bleeding episodes eventually result in hemophilic arthropathy, chronic pain, and reduction in the range of joint motion leading to difficulties with moderate physical activities such as moving a table, pushing a vacuum cleaner or climbing several flights of stairs.

Factorial validity of the SF-12v2 was tested by examining the model fit indices across three different models. The two-factor model based on the approach adopted by Maurischat and colleagues (2006, 2008) was found to be the best fitting model in this population. Previous studies have also conceptualized the SF-12v2 as a two factor model where items related to the GH, PF, RP, BP subdomains loaded onto a LPF while items related to the RE, MH, VT, SF subdomains loaded onto a LMF and the error covariance for items which belonged to the same subdomain (PF, RP, RE, and MH) were correlated (Maurischat et al., 2008; McBride, Adamson, Bunting, & McCann, 2009). Items which belonged to the same subdomain were expected to have commonality which warranted the correlation of the residuals for these items. Previous studies have reported that a similar two-factor model for the SF-12v2 was found to have acceptable fit among patients with inflammatory rheumatic disease (Maurischat et al., 2006), and diabetes mellitus (Maurischat et al., 2008). In the current study based on the modification indices, minor modifications driven by data were made where the error covariance for item 9 (felt calm and peaceful) and item 10 (had a lot of energy). Residuals for these items on the SF-12 have been previously shown to be correlated by McBride et al. (2009) in a sample of diagnostic orphans and by Fleishman and Lawrence (2003) in a population of non-institutionalized US civilians (Fleishman & Lawrence, 2003; McBride et al., 2009).

The SF-12v2 was found to have good convergent validity among adults with hemophilia. Considering the best fitting model, the size of each factor loading was greater than 0.5 indicating that the latent factor explained at least 50% of the variance in each observed indicator. AVE for both latent factors was close to 0.5 which was indicative of the fact that the latent factors explained a higher proportion of the variance in the observed indicators than the error variance which remained unexplained. We did not find evidence of adequate discriminant validity of the

SF-12v2 among adults with hemophilia. This was primarily because of the high correlation between the LPF and the LMF as compared to previous studies (Okonokwo et al., 2010; Maurischat et al., 2006; Maurischat et al., 2008). Future studies must examine and assess the reasons for this correlation between the LPF and LMF. Finally, individual items were more strongly correlated with the subdomain they represented as compared to other subdomains. Items which belonged to the GH, PF, RP, BP subdomains were strongly correlated with PCS and weakly correlated with MCS. Also, the RE, MH, VT, and SF items were strongly correlated with MCS and weakly (or moderately in case of item 12) correlated with PCS. Similar results have been reported by previous studies among adults with autism (Khanna et al., 2015).

The results of the current study lend support to the known-groups validity of the SF-12v2 in terms of its ability to discriminate across different symptom severity levels among adults with hemophilia. Mean PCS and MCS were found to be significantly different across the four symptom severity groups. Additionally with an increase in the symptom severity level mean PCS summary scale scores were found to decrease significantly. A similar distinct downward trend was not seen in case of mean MCS with an increase in symptom severity. The mean MCS for the moderate symptom severity group was greater than the MCS for the mild symptom severity group. However, this increase was not found to be statistically significant. The SF-12v2 was not able to discriminate across hemophilia severity levels based on self-reported blood clotting factor activity level. This may be because 58% of the study sample was classified as having severe hemophilia (i.e., clotting factor activity level less than 1%). There may not have been enough sample size in the mild and moderate hemophilia groups in order to detect differences in PCS and MCS even if there were any.

The internal consistency reliability of the PCS and MCS summary scales was found to be good. Also, PCS and MCS scale scores did not indicate the presence of any floor or ceiling effects and therefore the SF-12v2 was considered to be sensitive in capturing the variation in HRQOL among adults with hemophilia.

The results of the current study must be interpreted in the light of certain limitations. The cross-sectional nature of the study precluded us from assessing the predictive validity as well as test-retest reliability of the SF-12v2 in the study population. Future studies should adopt a longitudinal design in order to explore these aspects of the psychometric profile of the SF-12v2. Adults with hemophilia who participated in this study are likely to have higher physical functioning because of their ability to participate in survey research. This may limit the generalizability of the study results.

This was the first US-based study to psychometrically validate a generic measure of HRQOL among adults with hemophilia. Considering that hemophilia is a rare genetic disorder, most previous published reports have employed smaller sample sizes. The Hemophilia Utilization Group Study (HUGS) employed a larger sample size of hemophilia patients as compared to the current study however all patients were recruited at six HTC's across the country. Patients treated in a non-HTC setting were not included in the HUGS. To the best of our knowledge, this is the first US based study to capture the HRQOL of a large population of adults with hemophilia who are treated in a HTC and non-HTC setting. For the current study, adults with hemophilia were recruited using multiple sources including an online rare disease patient panel, a private Facebook community of hemophilia patients, and at a HTC in the south eastern region of the country. The study sample included an even distribution of patients from

all regions of the country which ensures the generalizability of the study results to most adults with hemophilia in the US.

This study provides evidence about the acceptable psychometric properties of the SF-12v2 among adults with hemophilia in the US. The SF-12v2 was found to be a valid and reliable generic measure of HRQOL among adults with hemophilia. The scale demonstrated adequate factorial, convergent, and known-groups validity. The scale was found to have adequate internal consistency reliability and no evidence of the presence of a floor or ceiling effect was found. Overall, the results provide basis for the future use of the SF-12v2 among adults with hemophilia and incorporating the HRQOL information obtained from these studies into health policy and clinical decision making.

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**CHAPTER III: ASSESSING MEASUREMENT INVARIANCE OF THE SHORT
FORM – 12 (SF-12) AMONG ADULTS WITH HEMOPHILIA IN THE UNITED
STATES**

INTRODUCTION

Hemophilia is a chronic blood coagulation disorder which is caused by the genetic deficiency of clotting factor VIII or IX in the blood plasma. Patients with hemophilia suffer from bleeding into large joints and muscle groups. This causes severe pain, loss of range of joint motion, and could eventually lead to chronic arthropathy (National Hemophilia Foundation, 2014). Health-related quality of life (HRQOL) is considered to be a very important indicator of outcomes among patients with such chronic diseases because complete recovery may not be possible (Okonkwo, Roth, Pulley, & Howard, 2010).

Assessment of HRQOL often involves comparisons of health status among different subgroups of patients. However, before carrying out such planned comparisons, it is essential that the researcher is confident that the items comprising the HRQOL measure operate equivalently across these different patient subgroups. In other words, when testing differences between groups of patients using a well-established measure of HRQOL (such as the Short Form-12 Health Survey [SF-12]), it is fundamental that members of different groups assign the same meaning to questionnaire items. Thus patients at the same level of the underlying latent construct (HRQOL in this case) must respond to an observed item in the same way and patient responses must not be influenced by patient characteristics (such as age, gender). If it can be shown that patient characteristics do not affect the psychometric properties of the observed questionnaire items, then the assumption of measurement invariance is said to be met. If the assumption of measurement invariance holds, then the observed differences in HRQOL among

groups defining the study populations are true differences and not measurement artifacts (Brown, 2015). For example, women are more likely to endorse items about crying rather than men on the Center for Epidemiological Studies Depression Scale (CES-D) given the same underlying level of depression. Thus even though a gender difference exists in terms of crying, depression scores for women, as compared to men, may be inflated due to gender bias in the measurement of depression (Pollard, Johnston, & Dixon, 2013).

Testing the assumption of measurement invariance commonly involves comparisons of the measurement model (i.e., observed indicators, factor loadings, indicator intercepts, and indicator variances) and the structural parameters (i.e., latent factor variances, covariances, and latent means) of the model across population subgroups. The former evaluations are called tests of measurement invariance while the latter comparisons are known as tests of population heterogeneity. Several analytical techniques including item response theory (IRT) and structural equation modeling (SEM) can be employed to test the assumption of measurement invariance. Within the framework of SEM, multi-group CFA and MIMIC (multiple indicators, multiple causes) modeling are commonly used approaches for testing the assumption of measurement invariance (King-Kallimanis et al., 2012). In cross-sectional research, the multi-group CFA approach is used very commonly because it allows the examination of all aspects of measurement invariance and population heterogeneity (i.e., factor loadings, indicator intercepts, indicator variances, factor variances, factor covariances, and latent means). However, multi-group CFA has restrictive sample size requirements because the sample must be split by group membership. In MIMIC modeling, the potential violator of invariance (e.g. age, gender) is dummy coded and included in the model along with other indicators as a single exogenous variable. The MIMIC approach affords greater parsimony (as fewer parameters are freely

estimated), is relatively easier to implement, and has less stringent sample size requirements. However, a key limitation associated with MIMIC modeling, as opposed to multi-group CFA, is the fact that it can only examine two potential sources of invariance (i.e., indicator intercepts, latent means). Therefore the multi-group CFA approach is generally preferred despite its larger sample size requirements (Brown, 2015).

Establishing the reliability and validity of a scale in a particular population does not ensure that the instrument will not violate the measurement invariance assumption. The SF-12v2 is a commonly used generic measure of HRQOL (Ware, Kosinski, & Keller, 1996). It measures eight dimensions of patient health (i.e., physical functioning, role-physical, bodily pain, general health, vitality social-functioning, role-emotional, and mental health) which can be aggregated into the physical component summary score (PCS) and the mental component summary score (MCS). Demographic variations in SF-12 scores have been assessed by previous studies in order to determine whether these are true differences or an indication of measurement invariance. Okonkwo and colleagues (2010) found item factor loadings on the SF-12v2 to be largely invariant across patients with and without a history of stroke. Fleishman and Lawrence tested the assumption of measurement invariance for the SF-12 in a national sample of adults in the United States (US) (Fleishman & Lawrence, 2003). Age was found to be a source of measurement non-invariance for items which load onto the mental health component. The authors also suggested that differences in education, age, and gender must be controlled for when assessing group differences in PCS and MCS scores on the SF-12.

Although the SF-12v2 has been previously utilized to assess HRQOL among patients with hemophilia (Duncan, Shapiro, Ye, Epstein, & Luo, 2012; Poon, Pope, & Tarlov, 2013), the assumption of measurement invariance has not been tested with respect to key predictors of

HRQOL in this population. Most studies in the literature have suggested that patient age, disease severity, and treatment regimen (i.e. prophylaxis or episodic care) are three of the most significant predictors of HRQOL among patients with hemophilia A and B (Brown, Lee, Joshi, & Pashos, 2009; Gringeri et al., 2004; Miners et al., 1999; Royal et al., 2002). However before assessing differences in HRQOL based on patient age, disease severity, and treatment regimen, it is essential to examine measurement bias in HRQOL with respect to these variables.

The current study will examine whether HRQOL measured using the SF-12v2 is invariant with respect to age, disease severity, and treatment regimen among adult diagnosed with hemophilia in the US. This will not only help us obtain deeper insight into the psychometric properties of the SF-12v2 but also better our understanding of the construct of HRQOL among patients with rare genetic blood coagulation disorders.

METHODS

Study Design

This study employed a cross-sectional design by means of an online self-administered survey designed using Qualtrics (Qualtrics Inc, Provo, UT). Institutional Review Board (IRB) approval was for the current study obtained from the University of Mississippi IRB under the exempt status.

Study population

The study sample for the current study included patients with hemophilia A or B who were greater than 18 years of age. Patients with other blood coagulation disorders such as Von Willebrand's disease were not included in the study population. Data for the current study were collected using a panel of hemophilia patients, provided by a market research vendor company called Rare Patient Voice. In order to meet the sample size requirements for multi-group CFA, patients with hemophilia were also recruited at the University of Mississippi Medical Center (UMMC) hemophilia treatment center (HTC) as well as through a private Facebook community called Hemo Friends.

Study procedures

The current study was a part of a larger study which aimed at assessing the psychosocial predictors of HRQOL among adults with hemophilia in the US. Only information relevant to the current study has been reported in this section. Initially an email explaining the nature and scope

of the research was sent out to potential study participants. This email also contained a URL link to the study survey. Data collection was open from October 31, 2015 to February 1, 2016. All respondents were provided with \$10 Amazon gift cards as an incentive to participate in the study.

Study Measures

SF-12 Health Survey Version 2 (SF-12v2). The SF-12v2 includes 12 items and was developed to be a much shorter, yet valid, alternative to the SF-36 for use in specific populations. The SF-12v2 has a 4 week recall period (Ware et al., 1996). The SF-12v2 has 8 domains summarized in Table 1.

Table 0.1. SF-12v2® Domains and Items

Domain	Domain Abbreviation	Total Number of Items in Domain	Items Specific to Domain
Physical functioning	PF	2	Items 2 and 3
Role physical	RP	2	Items 4 and 5
Bodily pain	BP	1	Item 8
General health	GH	1	Item 1
Vitality	VT	1	Item 10
Social functioning	SF	1	Item 12
Role emotional	RE	2	Items 6 and 7
Mental health	MH	2	Items 9 and 11

Items on the SF-12v2 use either a 3- or a 5-point response format. The SF-12v2 is used to compute two general summary measures of HRQOL, Mental Component Summary score (MCS) and Physical Component Summary score (PCS), derived from the 8 domain scores with higher scores indicating better health status. The component and domain scores are transformed to a 0 –

100 scale and subsequently transformed to norm based scores with a mean of 50 and a standard deviation of 10 in the general US population. The software from Optum® was used to calculate the scores for the SF-12v2 domains and components (PCS and MCS).

Patient Global Impression of Severity (PGI-S). The PGI-S is a single self-reported item that asks respondents to rate the severity of their condition. In this study, the PGI-S was specifically worded as “When thinking about all of the hemophilia-related symptoms that you may have experienced during the past 7 days, please circle the one number that best describes how your symptoms overall have been; on a 4-point scale scored as: (1) “no symptoms”, (2) “mild”, (3) “moderate”, or (4) “severe”. The construct validity of the PGI-S has been previously assessed in male subjects with lower urinary tract symptoms secondary to benign prostatic hyperplasia and women with stress urinary incontinence (Viktrup, Hayes, Wang, & Shen, 2012; Yalcin & Bump, 2003).

Demographic and health information. The following socio-demographic and clinical characteristics: (1) age, (2) race/ethnicity, (3) education status, (4) marital status, (5) occupation status, (6) disease severity, (7) monthly bleeding frequency, (8) type of treatment, and (9) hemophilia-related comorbidities.

Statistical Analysis

Demographic and clinical comorbidity related variables were summarized using descriptive statistics. Frequencies and percentages were calculated for categorical variables while means and standard deviations were determined for continuous variables.

Step 1: Establishing a measurement model for the SF-12v2

The two-factor model of the SF-12v2 where items related to the GH, PF, RP, BP subdomains loaded onto a latent physical factor (LPF), items related to the RE, MH, VT, SF subdomains loaded onto a latent mental factor (LMF). The residual for each of the two PF, RP,

RE, and MH items were correlated. The LPF and LMF were allowed to freely correlate as well (Maurischat, Herschbach, Peters, & Bullinger, 2008; McBride, Adamson, Bunting, & McCann, 2009). The final measurement model for the SF-12v2 can be found in figure 3.1 below. Details about the methodology adopted for establishing this measurement model can be found in chapter 2 of this dissertation.

Step 2: Testing measurement invariance with respect to exogenous variables (i.e., age, symptom severity, and treatment regimen)

Multi-group CFA was used for testing the assumption of measurement invariance across patients belonging to different age groups (18-34 versus greater than 34 years of age), disease severity levels (no/mild symptoms versus moderate/severe symptoms as reported on the PGI-S), and treatment regimens (always been on prophylaxis versus been on prophylaxis or on-demand therapy). In multi-group CFA, assessment of invariance includes two distinct parts namely testing of measurement invariance (i.e., the latent construct is being measured in the same way by the indicators across groups of patients) and structural invariance (i.e., the groups of patients differ in their distribution and/or means of the latent construct). The current study focused on assessing only the measurement invariance of the SF-12v2 across sub-groups of adults with hemophilia. The testing of measurement invariance of the SF-12v2 was carried out using a series of tests and nested-model comparisons that imposed successive restrictions on model parameters. Chi-square tests examining statistically significant improvement in model fit between nested models were carried out using the DIFFTEST option in Mplus 7.31 (Muthen & Muthen, Los Angeles, CA) in conjunction with weighted least squares (WLSMV) estimation for categorical (ordinal) indicators. The WLSMV estimation technique with delta parameterization

was used considering that the items on the SF-12v2 are measured on an ordinal scale with a limited number of response options (B. Muthén, 1984).

The current study employed a “step-up” approach to the order in which restrictions on model parameters within multiple-groups CFA were evaluated. In this strategy, invariance testing started with the least restricted solution and analysis proceeds with the evaluation of subsequent models with greater number of restrictive constraints (Brown, 2015). Initially an omnibus test of equality of the overall indicator covariance matrices across patient sub-groups was conducted. This involved testing the CFA separately in each group. On the whole, if the covariance matrices did not differ between groups then it was considered that the assumption of measurement invariance is met and testing was conducted. The first step involved the test of equal factor structures (i.e., whether the number of latent constructs and pattern of indicator loadings on latent dimensions are identical across groups). This is known as the test of equal form or configural invariance (Brown, 2015). The second step entailed placing an additional constraint of equal factor loading on the model from step 1. This test is often referred to as the test of metric invariance or weak factorial invariance (Brown, 2015). The final step included the restrictions from step 2 (i.e., equal factor loadings) plus the additional constraint of equal indicator intercepts (or thresholds) across patient sub-groups. This test has been alternatively termed as scalar invariance or strong factorial invariance (Brown, 2015). Mplus shortcuts for configural, metric, and scalar invariance were also used to ensure that similar results were obtained using both approaches. Further specification of these models can be found in the Mplus user’s guide (Muthén & Muthén, 2015).

The χ^2 statistic for the WLSMV estimator cannot be used for chi-square difference testing in the regular way in Mplus. Therefore the DIFFTEST option in Mplus was used during

invariance testing to evaluate model fit across patient sub-groups (Muthén & Muthén, 2015). If the fit, after adding each restrictive constraint to the model, was found to be significantly worse than the previous less constrained model, then further invariance testing was stopped and an inspection of the modification indices was carried out. Starting from the largest modification index, problematic constraints were removed at each level of invariance testing until the model fit was found not to be worse as compared to the previous model with fewer constraints on model parameters. Thus in cases where full invariance did not hold, an examination of partial measurement invariance was carried out. Further testing by placing more restrictive parameter constraints was only continued if at least one indicator (besides the marker indicator) was found to be invariant across patient sub-groups (Brown, 2015).

RESULTS

Sample Description

The study sample included a total of 218 adults with hemophilia (Table 3.1). 169 (77.5%) of these patients were recruited using an online panel of hemophilia patients (i.e., Rare Patient Voice), 44 (20.2%) were recruited using a Facebook community of hemophilia patients (i.e., Hemo Friends), and 6 (2.3%) were recruited at the UMMC HTC. The study sample largely included Caucasian (68.5%), males (79.5%) with hemophilia A (77.5%). The mean age of adults with hemophilia who were enrolled into the study was 35.45(±12.3) years. Based on the severity of hemophilia-related symptoms in the past 4 week, the study sample included four patient groups namely – no symptoms (14.2%), mild symptoms (30.6%), moderate symptoms (27.9%), and severe symptoms (39%). Based on the treatment regimen, the study sample could be divided into three groups namely – always received clotting factor prophylactically (55.3%), received clotting factor both prophylactically and as episodic therapy (14.2%), and always received clotting factor episodically (20.5%).

Table 0.2: Demographic and clinical characteristics the study sample (N = 218)

Characteristics	N (%)
<u>Diagnosis</u>	
Hemophilia A	169 (77.5)
Hemophilia B	49 (22.5)
<u>Gender</u>	
Male	174 (79.5)
Female	24 (11.0)
Age, mean (sd)	35.45 (\pm 12.3)
<u>Race/Ethnicity</u>	
White/Caucasian	150 (68.5)
Other*	47 (21.5)
<u>Marital Status</u>	
Never Married	66 (30.1)
Married	98 (44.7)
Other†	34 (20.1)
<u>Education level</u>	
Less than high school	9 (4.1)
High school or technical school	30 (13.7)
College degree	128 (58.4)
Masters degree	17 (7.8)
Doctoral degree	6 (2.7)
Professional degree	8 (3.7)
<u>Employment Status</u>	
Employed/self-employed full time	103 (47.0)
Employed part-time	23 (10.5)
On disability	16 (7.3)
Other‡	56 (25.6)
<u>Region of the country</u>	
Northeast	46 (21.0)
Midwest	40 (18.3)
South	54 (24.7)
West	58 (26.5)
<u>Health Insurance</u>	
Public	61 (27.9)
Private	113 (51.6)
Both	6 (2.7)
None	18 (8.2)
<u>Disease severity</u>	
Mild (5%-40% clotting factor activity)	42 (19.2)
Moderate (1%-5% clotting factor activity)	25 (11.4)
Severe (>1% clotting factor activity)	127 (58.0)
Not sure	3 (1.4)

<u>Symptom Severity</u>	
No symptoms	31 (14.2)
Mild symptoms	67 (30.6)
Moderate symptoms	61 (27.9)
Severe symptoms	39 (17.8)
<u>Treatment Regimen</u>	
Always received on prophylaxis therapy	121 (55.3)
Received both prophylaxis and on-demand therapy	31 (14.2)
Always received on on-demand therapy	45 (20.5)
Number of bleeding episodes in the past year, mean (sd)	11.69 (\pm 19.1)
<u>Hemophilia-related surgery</u>	
Yes	73 (33.3)
No	124 (56.6)
Number of hemophilia-related surgeries in the past year, mean (sd)	3.64 (\pm 3.9)
<u>Comorbidities</u>	
Hepatitis C	80 (36.5)
HIV ^v	26 (11.9)
Depression	84 (38.4)
Inhibitors to clotting factor	41 (18.7)
<u>Annual number of hemophilia-related visits, mean (sd)</u>	
Hemophilia Treatment Center (HTC)	2.23 (\pm 3.1)
Hematologist outside a HTC	0.83 (\pm 1.8)
Primary Care Practitioner	2.42 (\pm 4.2)
SD standard deviation	
*Other includes American Indian/Alaskan Native, Asian/Indian Asian, Native Hawaiian/Other Pacific Islander, Hispanic, etc.	
†Other includes divorced, separated, widowed, and not married, living with partner	
‡Other includes retired, home-maker, student, seeking work, etc.	
^v HIV - Human Immuno Deficiency Virus.	
Patient recruitment – 169 (77.5%) from Rare Patient Voice, 44 (20.2%) from Hemo Friends, and 6 (2.3%) from UMMC HTC.	

Step 1: Establishing a measurement model for the SF-12v2

Details related to establishing the best fitting two factor model for the SF-12v2 can be found in chapter 2 of this dissertation. The final measurement model used for the measurement invariance analysis can be found in Figure 3.1 below.

Step 2: Testing measurement invariance with respect to exogenous variables

Three separate multi-group CFA models were used in order to test for measurement invariance of the SF-12v2 across the three exogenous variables of interest (i.e., age, symptom severity, and treatment regimen).

Age. Based on a median split at 34 years of age, the study sample was divided into two age groups (i.e., adults with hemophilia between 18 to 34 years of age [n = 106] and adults with hemophilia greater than 34 years of age [n=91]). Only 197 out of 218 patients with hemophilia responded to the age question on the survey. The results for the measurement invariance analysis can be found in Table 3.2 below.

Figure 0.1: Two Factor Model for the SF-12v2 based on Maurischat et al. (2008)

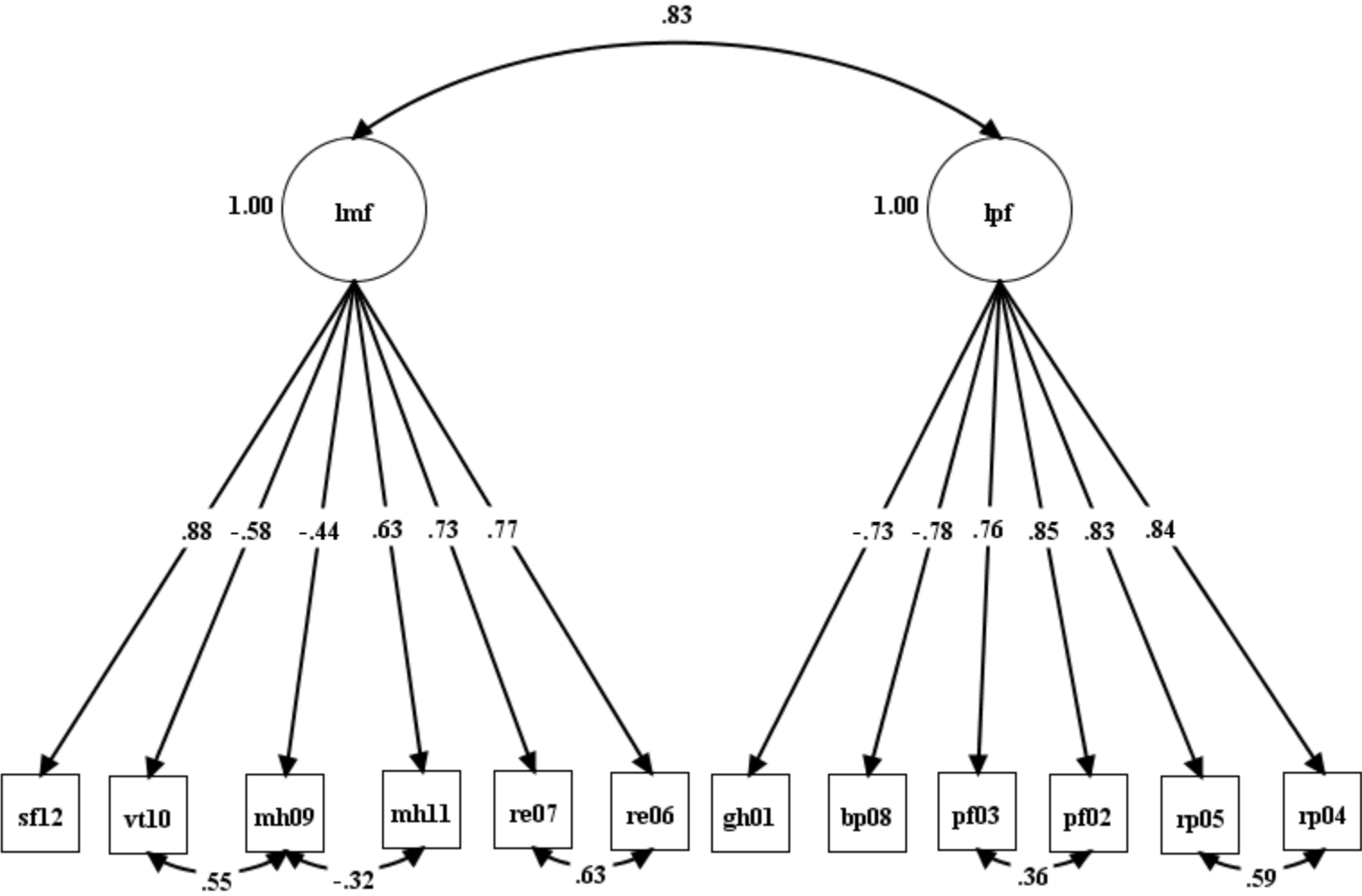


Table 0.3: Test of measurement invariance of the SF-12v2 in adults with hemophilia with respect to age (less than/equal to versus greater than 34 years of age)

	χ^2	<i>df</i>	χ^2 diff	<i>df</i> diff	RMSEA (90% CI)	WRMR	CFI	TLI
<u>Single-group solution</u>								
Age less than or equal to 34 years (<i>n</i> = 106)	129.07*	48			0.126 (0.100-0.153)	0.847	0.962	0.948
Age greater than 34 years (<i>n</i> = 91)	184.55*	48			0.125 (0.106-0.144)	1.061	0.964	0.950
<u>Measurement Invariance</u>								
Equal Form (configural invariance)	230.15*	96			0.119 (0.099-0.139)	1.132	0.967	0.954
Equal Factor Loadings (Metric invariance)	223.18*	106	7.176	10	0.106 (0.086-0.125)	1.158	0.971	0.964
Equal indicator intercepts (Scalar invariance)	245.69*	136	40.01	30	0.090 (0.072-0.108)	1.281	0.973	0.974
<p>Note: <i>df</i>, degrees of freedom; χ^2 diff, nested χ^2 difference; RMSEA, Root Mean Square Error of Approximation; CI, Confidence Interval; WRMR, Weighted Root Mean Square Residual; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.</p> <p>The chi-square (χ^2) value for WLSMV estimator cannot be used for chi-square difference testing in the regular way. WLSMV difference testing is done using the DIFFTEST (χ^2 diff) option in Mplus.</p> <p>*p-value <0.0001</p>								

Initially an omnibus test of equality of the overall indicator covariance matrices was conducted in both the population subgroups (i.e., 18-34 years of age, greater than 34 years of age). The model fit indices were comparable across both age groups. Following the omnibus test, the three invariance tests of equal form, equal factor loadings, and equal indicator intercepts were carried out. All three tests (configural, metric, and scalar invariance) indicated invariance across the two age groups as measured by insignificant differences in χ^2 diff values. The results for the test of equal form (configural invariance) suggest that the number of latent constructs and the pattern of indicator loadings on the LPF and LMF are identical across the two age groups. The test of equal factor loadings (metric invariance) suggested that the indicators evidence equivalent relationships to the two latent constructs of LPF and LMF across both age groups ($\Delta\chi^2 = 7.176$, $df = 10$, $p = 0.7087$). Finally, on the basis of the results of the equal factor loadings and equal indicator intercepts ($\Delta\chi^2 = 40.01$, $df = 30$, $p = 0.1046$) analysis, it was concluded that for any given value of LPF or LMF, the observed values of the SF-12 items are statistically equivalent across the two patient age groups and any observed differences in HRQOL between patient age groups were “true differences” and not systematic measurement artifacts.

Symptom severity. Adults with hemophilia were divided into two groups based on their symptom severity as assessed using the PGI-S. One group included those with no/mild symptoms over the past 4 weeks ($n = 98$) while the other group included those with moderate/severe symptoms ($n = 100$). A total of 197 patients with hemophilia responded to the self-reported symptom severity measure. Symptom severity was dichotomized given the higher sample requirement for assessing measurement invariance across three or more groups. The results for the tests of measurement invariance can be found in Table 3.3 below.

Table 0.4: Test of measurement invariance of the SF-12v2 in adults with hemophilia with respect to symptom severity (no/mild symptoms versus moderate/severe symptoms)

	χ^2	<i>df</i>	χ^2 diff	<i>df</i> diff	RMSEA (90% CI)	WRMR	CFI	TLI
<u>Single-group solution</u>								
No/Mild symptoms (<i>n</i> = 98)	166.86*	48			0.159 (0.133-0.186)	0.984	0.941	0.919
Moderate/Severe symptoms (<i>n</i> = 100)	99.78*	48			0.104 (0.075-0.133)	0.754	0.966	0.954
<u>Measurement Invariance</u>								
Equal Form (configural invariance)	265.11*	96			0.133 (0.114-0.153)	1.24	0.953	0.935
Equal Factor Loadings (Metric invariance)	264.22*	106	17.24	10	0.123 (0.104-0.141)	1.306	0.956	0.945
Equal indicator intercepts (Scalar invariance)	284.69*	136	50.53 ^y	30	0.105 (0.088-0.122)	1.469	0.959	0.96
<p>Note: <i>df</i>, degrees of freedom; χ^2 diff, nested χ^2 difference; RMSEA, Root Mean Square Error of Approximation; CI, Confidence Interval; WRMR, Weighted Root Mean Square Residual; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.</p> <p>The chi-square value for WLSMV estimator cannot be used for chi-square difference testing in the regular way. WLSMV difference testing is done using the DIFFTEST option in Mplus.</p> <p>*p-value <0.0001; ^yp-value = 0.0109</p>								

The overall omnibus test of equality of the indicator covariance matrices across the groups suggested adequate and comparable fit across the two symptom severity groups. The test for equal form (configural invariance) and equal factor loadings (metric invariance) suggested invariance across the symptom severity groups ($\Delta\chi^2= 17.24$, $df = 10$, $p = 0.0691$). However, the test for equal indicator intercepts (scalar invariance) indicated non-invariance across the symptom severity groups as indicated by a significant χ^2 diff value ($\Delta\chi^2= 50.53$, $df = 30$, $p = 0.0109$). After an examination of the modification indices, we proceeded with partial invariance testing by relaxing the constraint on the indicator threshold for item 9 across both the symptom severity groups. Relaxing this constraint not only improved the model fit (RMSEA [90% CI] = 0.103 [0.086 – 0.120]; CFI = 0.960; TLI = 0.961; WRMR = 1.436) but also resulted in an invariant model as indicated by the non-significant difference in the χ^2 value ($p = 0.051$) as compared to the metric model which held only factor loadings to equality across both groups.

Treatment regimen. Adults with hemophilia included in the study sample were divided into two groups based on their treatment regimen – patients who had always been on prophylaxis therapy ($n = 121$) and those who had not always been on prophylaxis therapy (i.e., hemophilia patients who were on both prophylaxis and on-demand therapy, or who had always been on on-demand therapy [$n = 76$]). A total of 197 patients with hemophilia responded to the self-reported treatment regimen item. Treatment regimen was dichotomized into the following two groups based on previous literature (Royal et al., 2002). The results for the tests of measurement invariance based on the treatment regimen can be found in table 3.4 below.

Table 0.5: Test of measurement invariance of the SF-12v2 in adults with hemophilia with respect to treatment regimen (Always on prophylaxis versus prophylaxis or on-demand treatment)

	χ^2	<i>df</i>	χ^2 diff	<i>df</i> diff	RMSEA (90% CI)	WRMR	CFI	TLI
<u>Single-group solution</u>								
Always Prophylaxis (<i>n</i> = 121)	145.06*	48			0.129 (0.105-0.154)	0.901	0.958	0.942
Prophylaxis/On-demand (<i>n</i> = 76)	98.07*	48			0.117 (0.084-0.150)	0.716	0.971	0.960
<u>Measurement Invariance</u>								
Equal Form (configural invariance)	242.41*	96			0.124 (0.105-0.144)	1.151	0.964	0.950
Equal Factor Loadings (Metric invariance)	242.34*	106	13.68	10	0.114 (0.095-0.133)	1.200	0.966	0.958
Equal indicator intercepts (Scalar invariance)	307.59*	136	81.94*	30	0.113 (0.096-0.130)	1.446	0.957	0.959
<p>Note: <i>df</i>, degrees of freedom; χ^2 diff, nested χ^2 difference; RMSEA, Root Mean Square Error of Approximation; CI, Confidence Interval; WRMR, Weighted Root Mean Square Residual; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.</p> <p>The chi-square value for WLSMV estimator cannot be used for chi-square difference testing in the regular way. WLSMV difference testing is done using the DIFFTEST option in Mplus.</p> <p>*p-value <0.0001</p>								

Based on the results of the omnibus test of the equality of indicator covariance matrices, it was concluded that the two factor model of the SF-12v2 had a comparable fit across both the treatment groups. The tests for equal form (configural invariance) and equal factor loadings (metric invariance) suggested invariance across both treatment groups ($\Delta\chi^2 = 13.68$, $df = 30$, $p = 0.187$). However, upon adding the constraint of equality of indicator intercepts to the metric model, the assumption of scalar invariance did not hold ($\Delta\chi^2 = 81.94$, $df = 30$, $p < 0.0001$). Measurement invariance at the scalar level could not be achieved even after an examination of modification indices. In conclusion, the finding of invariance at the configural and metric level assures that comparisons across hemophilia treatment regimens can be made as to relationships between factors (i.e., factor loadings). However, considering the finding of non-invariance at the scalar level indicates that caution must be exercised in analyses involving comparisons of item means between groups.

DISCUSSION

The SF-12v2 is one of the most widely used generic HRQOL instrument. Several studies have established the psychometric properties of the SF-12v2 in the US general population and among patients across several disease states (Fleishman & Lawrence, 2003; Maurischat et al., 2008; McBride et al., 2009; Okonkwo et al., 2010). Before conducting comparisons of patient subgroups in terms of their HRQOL, it must be ensured that patients at the same level of the underlying latent HRQOL construct assign the same meaning to the questionnaire items and that patient responses on these items are not influenced by their demographic and/or clinical characteristics such as age, gender, symptom severity, or treatment regimen. If such patient characteristics do not impact the psychometric properties of the observed questionnaire items then the assumption of measurement invariance is said to be met. The current study assessed whether the measurement properties of the SF-12v2 are invariant with respect to age, symptom severity, and treatment regimen among adults with hemophilia in the US.

The two factor model of the SF-12v2 as per the approach adopted by Maurischat and colleagues was used as the measurement model for the current study. The factorial validity of this measurement model of the SF-12v2 among adults with hemophilia has been previously established in chapter 2 of this dissertation. The results of the current study suggested that the SF-12v2 was invariant across age groups. Differential item functioning (DIF) was seen with respect to item 9 “calm and peaceful” among adults with hemophilia across symptom severity levels. Comparison of the SF-12v2 across hemophilia treatment regimens supported the

presence of “approximate invariance” (Millsap, 2005) such that although non-invariance across treatment groups was seen at the scalar level (i.e., equal indicator intercepts), the association between the SF-12 items and the underlying latent factors was largely equivalent across treatment groups in terms of pattern and coefficients of factor loadings.

The results of the current study suggested that the assumption of measurement invariance with respect to age was satisfied at the configural, metric, and scalar level in the total study sample. This suggests that if younger and older adults with hemophilia had the same underlying HRQOL, they would respond similarly to the items on the SF-12v2. Thus any differences seen in HRQOL across age groups among adults diagnosed with hemophilia can be interpreted as true differences and not artifacts of systematic measurement error. Previous studies have reported the detrimental effects of increasing age on the HRQOL of patients with hemophilia. Miners and colleagues reported that besides age, none of the clinical variables, were found to be significant predictors of HRQOL among patients with severe hemophilia A and B (Miners et al., 1999). Several other studies have reported similar findings (Solovieva, 2001; Trippoli et al., 2001; Wang, Zhang, Li, Zhao, & Yang, 2004). Therefore the finding that HRQOL as measured by the SF-12v2 has the same meaning across age groups holds key importance in allowing future researchers to conduct planned HRQOL comparisons across different age groups of hemophilia patients.

The results from the multi-group CFA across symptom severity levels among adults with hemophilia revealed the presence of measurement invariance at the configural and metric level. Non-invariance was found at the scalar invariance level specifically with respect to item 9 “calm and peaceful”. Previous studies which have assessed measurement invariance of the SF-12 among other populations have found a similar differential item functioning (DIF) effect with

respect to item 9 on the scale. A study examining the measurement invariance of the SF-12v2 among Latina, European-American, and African-American postpartum women in the US reported a DIF effect for item 9 indicating that Latinas were more likely to report feeling calm and peaceful within 2 weeks after their baby was born as compared to European-Americans (Desouky, Mora, & Howell, 2013). In a study assessing the presence of DIF among items on the SF-12v1 in the general US population, Fleishman and Lawrence reported that Latinos were more likely to endorse item 9 as compared to their European-American counterparts (Fleishman & Lawrence, 2003). Perkins and colleagues found the presence of age and education-related DIF for this item while assessing the measurement invariance of the SF-36v1 in a national sample of healthy adults in the US (Perkins, Stump, Monahan, & McHorney, 2006). The authors indicated that older and less educated individuals were more likely to endorse item 9 “calm and peaceful” as compared to their younger and more educated counterparts. Therefore, based on prior evidence and the results of the current study, a revision of item 9 may improve the equivalence of the SF-12v2 in future research. Overall our findings suggest that the items on the SF-12v2 are interpreted equivalently across adults with hemophilia having varying symptom severity levels. Such a finding has key implications in establishing the known-groups validity of the instrument in this patient population and allowing comparisons of the HRQOL across different severity levels of patients with hemophilia.

The results for the test of measurement invariance across treatment regimens among adults with hemophilia suggested the presence of invariance at the configural and metric level. In general, configural and metric invariance is sufficient for establishing psychometric equivalence of the SF-12v2 (Morales, Diamant, & Hays, 2016). This attests that the LPF and the LMF are related to the items on the SF-12v2 in the same way for adults with hemophilia who

have always been on prophylaxis and for those who have not always been on prophylaxis therapy. Further constraints equating the intercepts (scalar invariance) across the two groups resulted in a chi-square difference value which was significant at $\alpha = 0.05$, thereby indicating non-invariance at the scalar level. This may be because of unequal sample sizes between the two treatment groups. Also, invariance analyses based on large sample sizes very often result in a significant chi-square difference value and increased risk of rejection of good models (Clench-Aas, Nes, Dalgard, & Aarø, 2011). In the current study, an examination of other fit indices besides the χ^2 difference value for the scalar model indicated that these were either improved (RMSEA or TLI) or slightly decreased (CFI and WRMR) as compared to the metric model. Based on the suggestion of “approximate invariance”, although the scalar model would be rejected by a statistical test of exact fit (i.e., chi-square difference value), it was retained upon an assessment of other fit indices (Millsap, 2005). The implication of this practice is that some degree of violation of the assumption of measurement invariance is tolerated; resulting in “approximate invariance” rather than exact invariance as defined in theory. In the context of the current study, approximate invariance for the scalar model implies that group means on the latent variables are comparable across treatment groups among adults with hemophilia.

Limitations of the current study include the fact that all data on demographic and clinical variables of interest were self-reported and not verified by a review of medical records. Another limitation relates to sample sizes for each group. In some cases the groups being compared had unequal sample sizes. For example, the number of patients who had always been on prophylaxis were almost one and half times those who had not been on prophylaxis therapy throughout. Third, the current study employed a cross sectional design and therefore it was not possible to assess longitudinal measurement invariance of the SF-12v2 among adults with hemophilia.

Future research should focus on determining whether hemophilia patients interpret items on the SF-12v2 equivalently over a longer period of time. Finally, model fit indices have largely been developed in the context of parametric maximum likelihood estimation. The application of these model fit statistics to non-parametric ordinal models should be made cautiously.

The results of our study have demonstrated that the SF-12v2 can provide accurate estimates of HRQOL among adults with hemophilia in the US. Assessing and ascertaining invariance is essential for improving measurement. The current study indicated that the SF-12v2 was invariant with respect to age of the study participants. The presence of DIF was seen with respect to item 9 “calm and peaceful” while comparing hemophilia patients across different severity levels. This item has shown DIF effects among other patient populations as well as in the general US population and could possibly be considered for revision. Finally, findings for the invariance analysis across hemophilia treatment regimens lend support to the interpretation of “approximate invariance”. Although HRQOL comparisons across hemophilia patients on different treatment regimens can be carried out, these results must be interpreted with caution. Overall, the SF-12v2 was largely invariant with respect to age, symptom severity, and treatment regimen among a sample of US adults with hemophilia.

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**CHAPTER IV: AN ASSESSMENT OF PSYCHOSOCIAL DETERMINANTS OF
HEALTH-RELATED QUALITY OF LIFE AMONG ADULTS WITH
HEMOPHILIA IN THE UNITED STATES**

INTRODUCTION

According to the International Society for Quality of Life Research (ISOQOL), health-related quality of life (HRQOL) is “the functional effect of a medical condition and/or its consequent therapy upon a patient” (International Society for Quality of Life Research, 2015). Hemophilia is a rare genetic blood coagulation disorder affecting men. It is caused by a deficiency of clotting factor VIII or IX. Patients with hemophilia experience bleeding into joints or muscles which may result in chronic pain and reduce the range of joint motion (Dolan et al., 2009). Depression, anxiety, and psychological distress among hemophilia patients lead to a deterioration in their mental well-being (Ghanizadeh & Baligh-Jahromi, 2009). Individuals with hemophilia must be careful about participating in activities such as contact sports because immediate bleeding may ensue. This may impact their social participation and peer integration (Aznar, Magallón, Querol, Gorina, & Tusell, 2009; Mackensen, 2007). Thus the physical, mental and social consequences of the disease serve to reduce the health-related quality of life (HRQOL) of patients. HRQOL is increasingly being considered as an important outcome among hemophilia patients.

Purpose of the study

Several studies have assessed the HRQOL of patients with hemophilia. Majority of these studies have reported that hemophilia patients suffer from worse physical HRQOL as compared to the healthy population. The mental HRQOL of patients with hemophilia was found to be similar to the general population (Aznar et al., 2009; Lindvall, Von Mackensen, & Berntorp, 2012; Molho et al., 2000; Poon, Doctor, & Nichol, 2014). Previous studies which have

evaluated predictors of HRQOL among hemophilia patients have examined the role of clinical (i.e., disease severity, comorbid conditions such as hepatitis C or human immunodeficiency virus [HIV] infection) and socio-demographic determinants (Miners et al., 1999; Royal et al., 2002; Szucs, Öffner, and Schramm, 1996). However, these studies have generally overlooked the role of psychosocial variables such as social support, coping strategies, and patient self-efficacy which have been identified as essential predictors of HRQOL among other disease states including HIV and osteoarthritis (Luszczynska, Sarkar, & Knoll, 2007a; McKnight, Afram, Kashdan, Kastle, & Zautra, 2010). Knowledge about these psychosocial factors not only assist healthcare providers and caregivers in improving care provided to individuals with hemophilia, but also potentially enable patients to better understand and self-manage their disease condition. Such evaluations can assist both clinicians and healthcare policymakers in designing programs aimed at increasing the level of social support provided, fostering the use of adaptive coping strategies, and overall ensuring better health among these patients. Therefore the current study assessed psychosocial factors which affect the HRQOL of individuals with hemophilia using a theory-driven approach.

Conceptual framework

Employing a theory-based assessment is essential to arrive at a holistic understanding of the impact of hemophilia on patient well-being. It has been suggested that stress and coping are concepts which can be influenced by clinicians and therefore theoretical models based on stress and coping theories are particularly well suited for HRQOL research in rare genetic disorders (Biesecker & Erby, 2008). The Lazarus and Folkman's (1984) cognitive-behavioral model is based on a theory of stress, appraisal, coping, and adaptation. According to this theory, individuals respond to stressors, such as living with hemophilia, by making cognitive and

emotional appraisals of the stressor. An individual's appraisal of these stressors depends upon the personal significance of the stressor, its cause, severity, one's susceptibility to the stressor as well as the ability to cope with the problems and the emotions associated with the stressor (Lazarus & Folkman, 1984). These appraisals govern coping behaviors because the likelihood that one can change or adapt to a stressor will direct one's ability to cope with it and also determine the coping mechanism which will be adopted (Bombardier, D'Amico, & Jordan, 1990). The adopted coping strategies in turn gradually help attain or restore optimal HRQOL. Therefore an individual's ability to adapt to a stressor is governed by cognitive appraisal of the stressful event and the associated coping response. This model can therefore be adapted to identify psychosocial predictors of HRQOL among patients with rare diseases such as hemophilia. This framework has been modified and previously used by studies to identify determinants of HRQOL among patients with breast cancer, colon cancer, and diverse chronic conditions (Bombardier et al., 1990; Miller, Gordon, Daniele, & Diller, 1992; Northouse et al., 2002; Northouse, Templin, & Mood, 2001).

For the purposes of the current study, an adapted version of the Lazarus and Folkman's cognitive-behavioral model of stress and coping was employed to identify antecedents and cognitive pathways that influence adaptation responses (i.e., restoring optimal HRQOL) to a chronic disease such as hemophilia (Figure 1). HRQOL has been previously considered as an outcome of the adaptation process among patients with breast cancer, HIV, and osteoarthritis (Luszczynska, Sarkar, & Knoll, 2007; McKnight, Afram, Kashdan, Kastle, & Zautra, 2010; Northouse et al., 2002). Specifically, it is hypothesized that the influence of hemophilia-related disability on HRQOL will be partially mediated by the social support received by the patient and

the adopted coping strategy. Further it is also hypothesized that the impact of coping and social support on HRQOL will depend on the level of patient self-efficacy.

Model Constructs

Disability

Patients with hemophilia experience progressive joint impairments because of repeated bleeding episodes. This can lead to serious functional disabilities (van Genderen et al., 2006). These functional disabilities can significantly impact their HRQOL. Barr et al. (2002) measured health utilities among hemophilia patients and reported major impairments in the domains of mobility, ambulation, and pain (Barr et al., 2002). In another study, functional limitation due to existing joint damage was the major predictor of lower physical HRQOL among adult Canadian hemophilia patients (Walsh et al., 2008). A Dutch study showed that disability, as measured by impairments in activities of daily living (ADL) and joint impairment, significantly influenced well-being of hemophilia patients (Triemstra et al., 1998). In previous research, the relationship between disability and HRQOL has been found to be mediated by perceived social support and the adopted coping style (Newsom & Schulz, 1996; Santavirta et al., 2010).

Perceived Social Support

According to Stewart (1993), social support is defined as “interactions, with family members, friends, health professionals and peers, that communicate information, reliable alliance, aid and esteem” (Stewart, Streiner, & Norman, 1995). A German study suggested that social support and life satisfaction explained the highest proportion of variance in HRQOL among adolescents with hemophilia (Bullinger & von Mackensen, 2008). Iannone and colleagues reported that the perceived lack of social support was significantly and positively

associated with higher depression scores among adults with hemophilia in the US (Iannone et al., 2015). Klein et al. (1994) examined the impact of social support and coping on stress resiliency among adult hemophiliacs with HIV. Social support (i.e. marital satisfaction and peer support) was found to be a significant predictor of patients' functioning and psychological well-being (Klein, Forehand, Armistead, & Wierson, 1994).

Coping

Lazarus and Folkman (1984) define coping as “cognitive and behavioral efforts to master, reduce, or tolerate the internal and/or external demands that are created by the stressful situation”. There are two types of coping mechanisms. Problem-focused/task-oriented coping (TOC) aims at the management of the external environment associated with the stressor by seeking information about what to do or holding back from making premature decisions. This is also known as adaptive coping. Emotion-oriented coping (EOC) is concerned with the regulation of the internal affective emotions which are a consequence of the stressor (Lazarus & Folkman, 1984). EOC strategies do not change a damaging situation but they make a person feel better. Avoidance coping (AC) is a maladaptive coping strategy where an individual completely avoids or is in denial of the illness. This is considered as a sub-strategy of EOC (Fledderus, Bohlmeijer, & Pieterse, 2010) and has been linked to diminished QOL (Cassis et al., 2012). EOC and AC strategies are considered to be maladaptive coping strategies. Binnema et al. (2014) studied coping strategies among adults with severe hemophilia in the Netherlands. Patients with hemophilia were found to use adaptive coping strategies as often as healthy controls. However they used significantly less maladaptive coping as compared to the control group. Use of maladaptive coping was found to be positively and significantly correlated with poor socio-psychological health, lower participation in daily activities and lesser social interactions among

severe hemophilia patients (Binnema, Schrijvers, Bos, Schuurmans, & Fischer, 2014). Klein and colleagues (1994) demonstrated that maladaptive was associated with poorer functioning among hemophilia patients and HIV (Klein et al., 1994). There is evidence that coping mediates the disability and psychosocial well-being relationship among adults with hemophilia (Santavirta et al., 2010).

Perceived Self-Efficacy

Self-efficacy is the amount of confidence that patients have in managing the demands associated with their chronic illness (Bandura, 1994). Among individuals with hemophilia self-management skills are essential for achieving higher treatment adherence, slowing disease progression and restoring optimal HRQOL (Teitel et al., 2004). Lock et al. (2014) assessed the reliability and validity of the hemophilia-specific self-efficacy scale (HSES) among children who were on prophylactic home treatment in the US (Lock et al., 2014). It was found that higher self-efficacy scores were significantly correlated with higher patient HRQOL. Self-efficacy has been previously shown to have a moderating impact on the coping and HRQOL relationship. At higher levels of self-efficacy, the negative impact of maladaptive coping strategies on HRQOL was found to be diminished among patients with acquired brain injury (Brands, Köhler, Stapert, Wade, & van Heugten, 2014). A similar relationship was tested among patients with rheumatoid arthritis where self-efficacy was found to moderate the relationship between coping and emotional outcomes (i.e., anxiety and depression) (Lowe et al., 2008). Previous studies have also suggested that people with lower self-efficacy were likely to be less physically active in spite of having high perceived social support (Dishman et al., 2009; Warner, Ziegelmann, Schuz, Wurm, & Schwarzer, 2011). In the context of the theoretical framework employed by the current study, self-efficacy was treated as a form of appraisal. It was hypothesized that at higher

levels of self-efficacy, the impact of coping strategies and social support on HRQOL will be enhanced among adults with hemophilia. Certain studies in the literature have also found self-efficacy to play the role of a mediator in the disability-HRQOL relationship (Abbott, Tyni-Lenn, & Hedlund, 2010). Therefore in addition to the above hypothesis, we also tested the role of self-efficacy as a mediator.

Research hypotheses

Several hypotheses were tested in this study. First, it was hypothesized that higher levels of disability among adults with hemophilia will be associated with lower HRQOL. Second, it was hypothesized that adults with hemophilia with higher levels of perceived social support will have a higher HRQOL. Third, the use of adaptive coping strategies will be associated with better HRQOL among adults with hemophilia. Fourth, the impact of disability on HRQOL will be partially mediated by the perceived social support and the coping strategies adopted by adults with hemophilia. Fifth, at higher levels of self-efficacy, the impact of maladaptive coping strategies on HRQOL will be diminished. Sixth, at higher levels of self-efficacy, the impact of adaptive coping strategies on HRQOL will be enhanced among adults with hemophilia. Last, at higher levels of self-efficacy, the impact of perceived social support on HRQOL will be enhanced among adults with hemophilia.

METHODS

Study Design

A prospective, cross-sectional design was employed by the current study. An Internet-based survey designed using Qualtrics (Qualtrics Inc., Provo, UT) was self-administered to adults with hemophilia. The study received approval under the exempt status from the University of Mississippi Institutional Review Board.

Study Sample

The study population for the current study included adult patients (≥ 18 years) with hemophilia A or B. Female patients as well as patients with other blood coagulation disorders were excluded from the study sample. The internet-based survey for the current study was administered to adults with hemophilia enrolled with a patient panel called Rare Patient Voice as well as through a private Facebook community of hemophilia patients called Hemo Friends. Considering hemophilia is a rare disease, patients were also recruited with the assistance from the University of Mississippi Medical Center Hemophilia Treatment Center in Jackson, MS.

Study procedures

An email explaining the nature and purpose of the study was sent out to all potential respondents. Participants were assured about the anonymity and confidentiality of their responses. It was also emphasized that participation in the study was voluntary. The email also contained a URL link to the study survey. The survey was active for 3 months from October 31,

2015 to February 1, 2016. \$10 Amazon gift cards were provided to all respondents as a token of appreciation.

Sample Size

The sample size requirements for the current study were based on the analysis technique used to address the study objectives. The current study used structural equation modeling (SEM) in order to assess the direct and indirect relationships among the study variables and identify predictors of HRQOL among adults with hemophilia. Kline (2005) recommends that a sample size of greater than 200 is considered to be acceptable for SEM. Based on this recommendation, a minimum sample size of 200 adults with hemophilia was needed for this study.

Study Measures

SF-12 Health Survey Version 2 (SF-12v2). The SF-12v2 is a shorter version of the Short-Form 36 Health Survey. It provides information on eight subdomains of HRQOL namely general health (GH, one item), physical functioning (PF, two items), social functioning (SF, one item), role physical (RP, two items), bodily pain (BP, one item), vitality (VT, one item), role emotional (RE, two items), and mental health (MH, two items). These subdomains can be further aggregated into the physical component summary (PCS) and the mental component summary (MCS) scores (Ware, Kosinski, & Keller, 1996). The PCS and MCS scores are calculated using the Optum Scoring Software with higher scores indicating better HRQOL. However, for the purposes of this study we extracted latent variables (i.e., Latent Physical Factor and Latent Mental Factor) instead of using PCS and MCS scores.

Health Assessment Questionnaire - Disability Index (HAQ-DI). The Stanford Arthritis Center Health Assessment Questionnaire (HAQ) was used to obtain a measure of the hemophilia-related

disability of the study participants (Bruce & Fries, 2005). This scale has been previously used to assess disability among adults with hemophilia (Santavirta et al., 2010). The HAQ disability-index questionnaire includes 2 to 3 questions (20 items totally) about each of the 8 areas of activity of daily living (ADL) namely rising, dressing and toilet, eating, walking, hygiene, reach, grip, and miscellaneous activities. Each item is scored on a 4-point scale labeled as 0 = “no difficulty,” 1 = “some difficulty,” 2 = “much difficulty or with assistance,” and 3 = “unable to perform.” The highest item score under each area of ADL determines the score for that area unless the respondent requires aid from another individual or an assistive device. Activities that require assistance from another individual or the use of an assistive device receives a score of 2. The scores for each ADL area are summed and divided by 8 in order to obtain a functional disability index. The HAQ-DI usually takes about 5 minutes to complete. The HAQ-DI has been previously validated among patients with arthritis (Bruce & Fries, 2003).

Multidimensional Scale of Perceived Social Support (MSPSS). Patients’ perceived social support received from family, friends and significant others will be measured by using the MSPSS (Zimet, Dahlem, Zimet, & Farley, 1988). The instrument consists of 12-items measured on a seven point linear numeric scale from 1 = ‘very strongly agree’ to 7 = ‘very strongly disagree’. An overall social support score is calculated by taking the mean of the 12 items with higher scores indicating greater perceived social support by PWH. This scale has been previously validated in patients with psychiatric/psychological problems (Eker & Arkar, 1995).

Brief Coping Orientation to Problem Experiences (Brief COPE). The coping style of adults with hemophilia will be assessed using the 28-item Brief COPE. This instrument can broadly help assess the use of adaptive and maladaptive coping strategies. The adaptive coping domain includes 16 items related to acceptance, active coping, humor, planning, positive reframing, use

of emotional support, and use of instrumental support. Maladaptive coping includes 12 items related to behavioral disengagement, denial, self-blame, self-distraction, substance abuse, and venting (Meyer, 2001). Responses to items are assessed using a 4-point linear numeric scale with end points labeled as 1 = “I haven’t been doing this at all” to 4 = “I have been doing this a lot”. Items related to substance abuse were not included considering the sensitivity of these items. Scores for items within each coping domain are summed in order to obtain a total adaptive and maladaptive coping score with higher scores indicating greater use of a particular coping strategy.

Generalized Self-Efficacy Scale (GSES). The GSES is a 10-item measure which was used to assess self-efficacy among adults with hemophilia. Responses on the GSES are assessed using on a 4-point linear numeric scale with endpoints ranging from 1 = “I totally disagree” to 4 = “I totally agree”. Scores for the GSES items are summed to obtain a total self-efficacy score from 10 to 40. Higher scores indicate greater general self-efficacy (Jensen & Karoly, 1991, 1992).

The concepts of general self-efficacy and hemophilia-specific self-efficacy were considered to be related although self-efficacy is considered to be a task-specific concept. Such an approach to assessing self-efficacy is supported by literature in other disease states (Jensen, Turner, & Romano, 1992).

Demographic and Health Information. The following variables were used as covariates in all analyses: age, race/ethnicity (Caucasian, African American, Asian, Hispanic, American Indian, Native Hawaiian, other), education status (less than high school, high school, college degree, master’s degree, doctoral degree, professional degree, other), occupation status (employed full-time, employed part-time, self-employed, retired, seeking work, student, other), marital status (single, married, divorced, separated, widowed, not married but living with a partner, other), type

of hemophilia (hemophilia A or B), disease severity (mild, moderate, severe), number of bleeds experienced in the last month, treatment regimen (prophylaxis, on-demand), hemophilia-related comorbidities (HIV, HCV infection).

Statistical Analysis

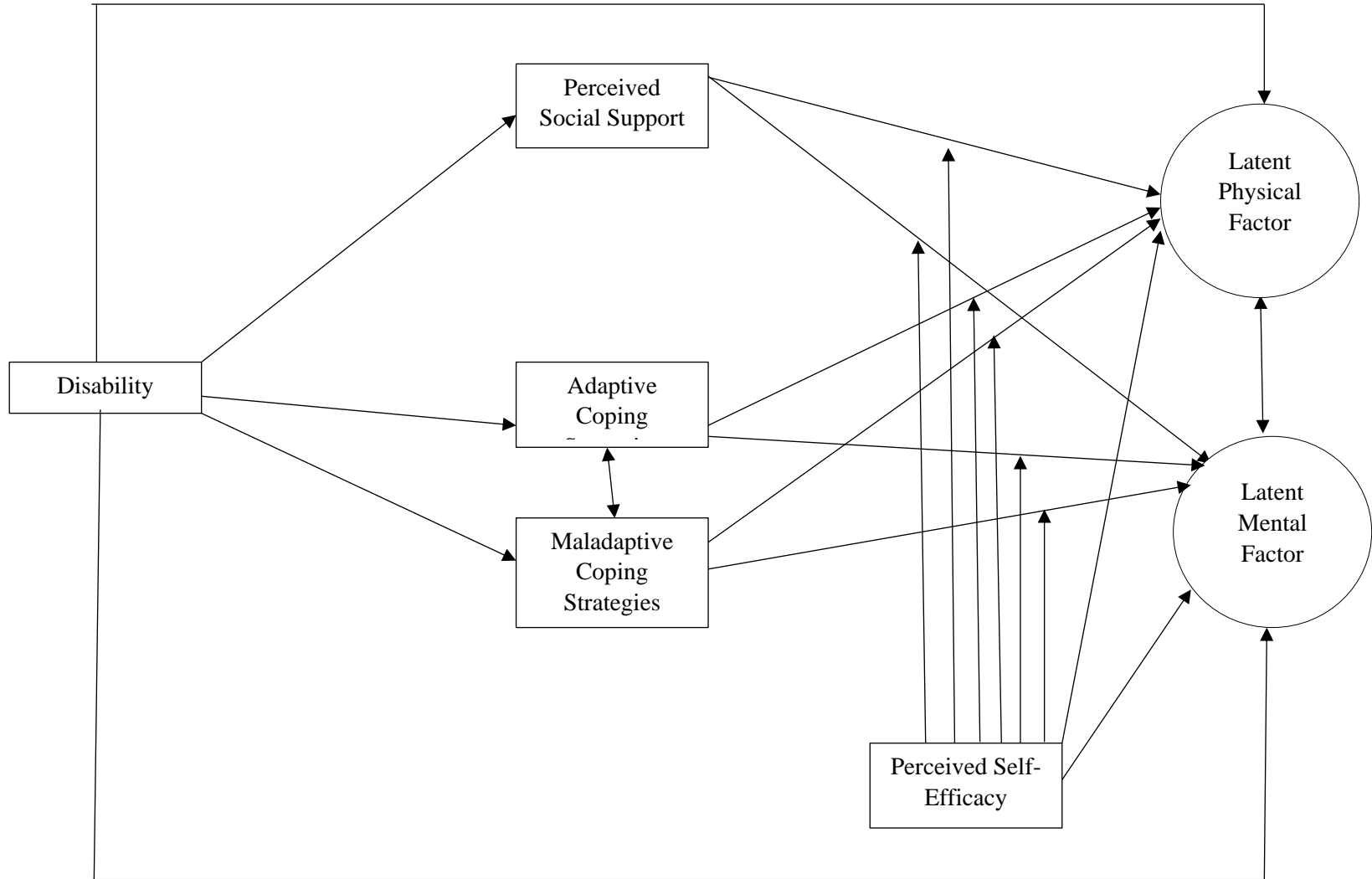
Descriptive statistics were used to summarize the study variables. Means and percentages were reported for the continuous variables. Frequencies and proportions were reported for summarizing the categorical variables. Correlations were assessed between the study variables using Pearson's correlation coefficient. Differences in group proportions for categorical variables were calculated using chi-square (χ^2) tests. Internal consistency reliability was examined for all scales by calculating the Cronbach's alpha (α). An α -value ≥ 0.70 was considered to be an indication of adequate internal consistency reliability. Summated scales were also created for the analyses.

SEM was used to test the aforementioned theoretical relationships. A robust weighted least squares (i.e., WLSMV) estimator was used to in order to account for the ordinal nature of the SF-12 items (Muthén, 1984). The assumption of multivariate normality and linearity were tested by assessing the absolute skewness and kurtosis indices (Kline, 2005). The proposed theoretical relationships were tested using a single model (Figure 4.1). This model tested the mediating role of perceived social support and coping in the disability and HRQOL relationship. Additionally, the model tested the moderating impact of self-efficacy on the social support and HRQOL relationship as well as the coping and HRQOL relationship. The moderated mediation approach suggested by Hayes (2013) was employed for conducting the analysis for the SEM model. HRQOL as measured on the SF-12v2 was used as a latent variable and operationalized using the latent mental factor (LMF) and the latent physical factor (LPF). The GH, PF, RP, and

BP sub-domain items were allowed to load onto a LPF. The RE, MH, VT, and SF sub-domain items were allowed to load onto a LMF. The residuals for each of the two PF, RP, RE, and MH items were allowed to be correlated. The LPF and LMF were also correlated. Disability, perceived social support, adaptive coping, maladaptive coping, and self-efficacy were treated as measured variables in the SEM models. For testing the moderating effect of self-efficacy, interaction terms were created for social support, adaptive coping, and maladaptive coping with self-efficacy.

Model fit for the model was assessed using the following five fit statistics. The χ^2 statistic, the root mean square error of approximation (RMSEA), the Tucker Lewis Index (TLI), the comparative fit index (CFI), and the weighted root mean square residual (WRMR). It has been suggested that for a well-fitting model, the RMSEA, TLI, CFI and WRMR must be ≤ 0.08 , ≥ 0.92 , ≥ 0.93 , and ≥ 1.00 respectively (Bagozzi & Yi, 2012; Newsom, 2015). Non-significant paths were eliminated and parameters were added to arrive at the best-fitting model based on the underlying theory in addition to the standardized residuals and modification indices. All analyses were carried out using Mplus version 7.31 (Muthen & Muthen, Los Angeles, CA).

Figure 0.1: Hypothesized model for the study



RESULTS

Descriptive statistics

The study sample included 218 adults with hemophilia. Responses from 21 adults with hemophilia were excluded due to $\geq 15\%$ missing data on study measures mentioned in Figure 4.1. The mean age of the study sample was 35.45 (± 12.3) years. The majority of the patients included in the study were white (68.5%), males (79.5%) diagnosed with hemophilia A (77.6%). Most of the respondents had a college degree (58.4%), were employed/self-employed full time (47%), and had private health insurance (51.6%). The study sample included an even distribution of adults with hemophilia from all four census regions of the country. Details related to the demographic and clinical characteristics of patients with hemophilia enrolled in the study can be found in Table 4.1.

Table 0.1: Demographic and clinical characteristics the study sample (N = 219)

Characteristics	N (%)
<u>Diagnosis</u>	
Hemophilia A	170 (77.6)
Hemophilia B	49 (22.4)
<u>Gender</u>	
Male	174 (79.5)
Female	24 (11.0)
Age, mean (sd)	35.45 (\pm 12.3)
<u>Race/Ethnicity</u>	
White/Caucasian	150 (68.5)
Other*	47 (21.5)
<u>Marital Status</u>	
Never Married	66 (30.1)
Married	98 (44.7)
Other†	34 (20.1)
<u>Education level</u>	
Less than high school	9 (4.1)
High school or technical school	30 (13.7)
College degree	128 (58.4)
Masters degree	17 (7.8)
Doctoral degree	6 (2.7)
Professional degree	8 (3.7)
<u>Employment Status</u>	
Employed/self-employed full time	103 (47.0)
Employed part-time	23 (10.5)
On disability	16 (7.3)
Other‡	56 (25.6)
<u>Region of the country</u>	
Northeast	46 (21.0)
Midwest	40 (18.3)
South	54 (24.7)
West	58 (26.5)
<u>Health Insurance</u>	
Public	61 (27.9)
Private	113 (51.6)
Both	6 (2.7)
None	18 (8.2)
<u>Disease severity</u>	
Mild (5%-40% clotting factor activity)	42 (19.2)
Moderate (1%-5% clotting factor activity)	25 (11.4)
Severe (>1% clotting factor activity)	127 (58.0)
Not sure	3 (1.4)

<u>Symptom Severity</u>	
No symptoms	31 (14.2)
Mild symptoms	67 (30.6)
Moderate symptoms	61 (27.9)
Severe symptoms	39 (17.8)
<u>Treatment Regimen</u>	
Always received on prophylaxis therapy	121 (55.3)
Received both prophylaxis and on-demand therapy	31 (14.2)
Always received on on-demand therapy	45 (20.5)
Number of bleeding episodes in the past year, mean (sd)	11.69 (\pm 19.1)
<u>Hemophilia-related surgery</u>	
Yes	73 (33.3)
No	124 (56.6)
Number of hemophilia-related surgeries in the past year, mean (sd)	3.64 (\pm 3.9)
<u>Comorbidities</u>	
Hepatitis C	80 (36.5)
HIV ^v	26 (11.9)
Depression	84 (38.4)
Inhibitors to clotting factor	41 (18.7)
<u>Annual number of hemophilia-related visits, mean (sd)</u>	
Hemophilia Treatment Center (HTC)	2.23 (\pm 3.1)
Hematologist outside a HTC	0.83 (\pm 1.8)
Primary Care Practitioner	2.42 (\pm 4.2)
SD standard deviation	
*Other includes American Indian/Alaskan Native, Asian/Indian Asian, Native Hawaiian/Other Pacific Islander, Hispanic, etc.	
†Other includes divorced, separated, widowed, and not married, living with partner	
‡Other includes retired, home-maker, student, seeking work, etc.	
^v HIV - Human Immuno Deficiency Virus.	

The mean PCS and MCS summary scale scores for the study sample were 43.68 (\pm 10.19) and 46.48 (\pm 10.09). Kurtosis and skewness coefficients were calculated in order to check for multivariate normality. Absolute values of the skew index and kurtosis index for all study variables were found to be less than 3.0 and less than 10.0 respectively. Therefore the data were

considered to be normally distributed (Kline, 2005). Descriptive statistics for all study measures have been reported in Table 4.2 below.

Table 0.2: Descriptive statistics for the variables in the study model

Measure	N	Mean (SD)	Possible Range	Minimum	Maximum	Skewness		Kurtosis	
						Statistic	Std. Error	Statistic	Std. Error
HAQ-DI	198	0.563 (0.64)	0 to 3	0.00	3.00	1.306	0.166	1.104	0.330
Self-Efficacy	198	32.952 (5.80)	10 to 40	11.00	40.00	-1.292	0.167	2.338	0.333
Social Support	198	5.632 (1.19)	1 to 7	1.50	7.00	-1.062	0.169	0.754	0.336
Adaptive Coping	198	38.589 (10.04)	16 to 64	16.00	56.00	-0.525	0.173	0.002	0.344
Maladaptive Coping	198	20.788 (7.84)	10 to 40	10.00	40.00	0.629	0.173	-0.241	0.344
Physical Component Score	219	43.68 (10.19)	0 to 100	16.95	67.63	-0.620	0.164	0.613	0.327
Mental Component Score	219	46.48 (10.09)	0 to 100	15.75	68.91	-0.719	0.164	1.230	0.327

Note: HAQ-DI, Health Assessment Questionnaire Disability Index

Bivariate Analysis

Bivariate correlations between study variables were computed using the Pearson's correlation coefficient. Statistically significant correlations were seen between all variables in the SEM model and PCS and MCS summary score among adults with hemophilia except for the correlation between social support and PCS. All bivariate correlations have been reported in Table 4.3 below.

Table 0.3: Correlations among study variables

	HAQDI	Social Support	Self-Efficacy	Adaptive Coping	Maladaptive Coping	PCS	MCS
HAQDI	1	-	-	-	-	-	-
Social Support	-.143*	1	-	-	-	-	-
Self-Efficacy	-.320**	.335**	1	-	-	-	-
Adaptive Coping	.194**	.207**	.032	1	-	-	-
Maladaptive Coping	.294**	-.092	-.117	.597**	1	-	-
PCS	-.542**	.130	.217**	-.160*	-.181*	1	-
MCS	-.287**	.310**	.327**	-.147*	-.438**	.122	1

Note: HAQ-DI, Health Assessment Questionnaire Disability Index; PCS, Physical Component Score; MCS, Mental Component Score
 *. Correlation is significant at the 0.05 level (2-tailed).
 **. Correlation is significant at the 0.01 level (2-tailed).

Psychosocial predictors of HRQOL

Based on the hypothesized relationships, a structural equation model was tested. This model tested the mediating role of social support and coping in the relationship between disability and HRQOL. Additionally, model also tested the moderating effect of self-efficacy on the relationship between social support and HRQOL as well as coping and HRQOL (Figure 4.1). This model had a poor fit (Chi-square [df] = 459.153 [193]; RMSEA [90% CI] = 0.168 [0.148-0.188]; CFI = 0.320; TLI = 0.154; WRMR = 1.602). All the interaction terms testing the moderating role of self-efficacy were not statistically significant at $\alpha = 0.05$. Overall we were not able to obtain a model with acceptable fit to identify psychosocial predictors of HRQOL among adults with hemophilia by employing the hypothesized moderated mediation approach.

In the context of the stress-appraisal-coping framework, previous studies have also examined the role of self-efficacy as a mediator of the relationship between social support or coping and the adaptational outcome of interest (i.e., physical functioning, medication adherence) among patients with HIV and osteoarthritis (DiIorio et al., 2009; EunSeok, Erlen, Judith A, Kim, Sereika, & Caruthers, 2008; McKnight et al., 2010). Therefore, as a post-hoc analysis, the role of self-efficacy as mediator of the relationship between social support and HRQOL as well as coping and HRQOL instead of its moderating effect was tested. The serial mediator model which was tested has been shown in Figure 4.2. This model had an acceptable fit as indicated by the model fit indices (Chi-square [df] = 321.645 [140]; RMSEA [90% CI] = 0.082 [0.070-0.094]; CFI = 0.930; TLI = 0.909; WRMR = 1.084). The model fit statistics for both study models have been presented in table 4.4. The final model explained 65.3% of the variance in the LPF and 60.3% of the variance in the LMF.

Figure 0.2: Final study model based on structural equation modeling

Goodness of fit statistics for the following model (Chi-square [df] = 321.645 [140]; RMSEA [90% CI] = 0.082 [0.070-0.094]; CFI = 0.930; TLI = 0.909; WRMR = 1.084). Only significant standardized relationships have been shown in the figure below. Non-significant paths and item loadings of the SF-12v2 items on the two latent factors have not been shown.

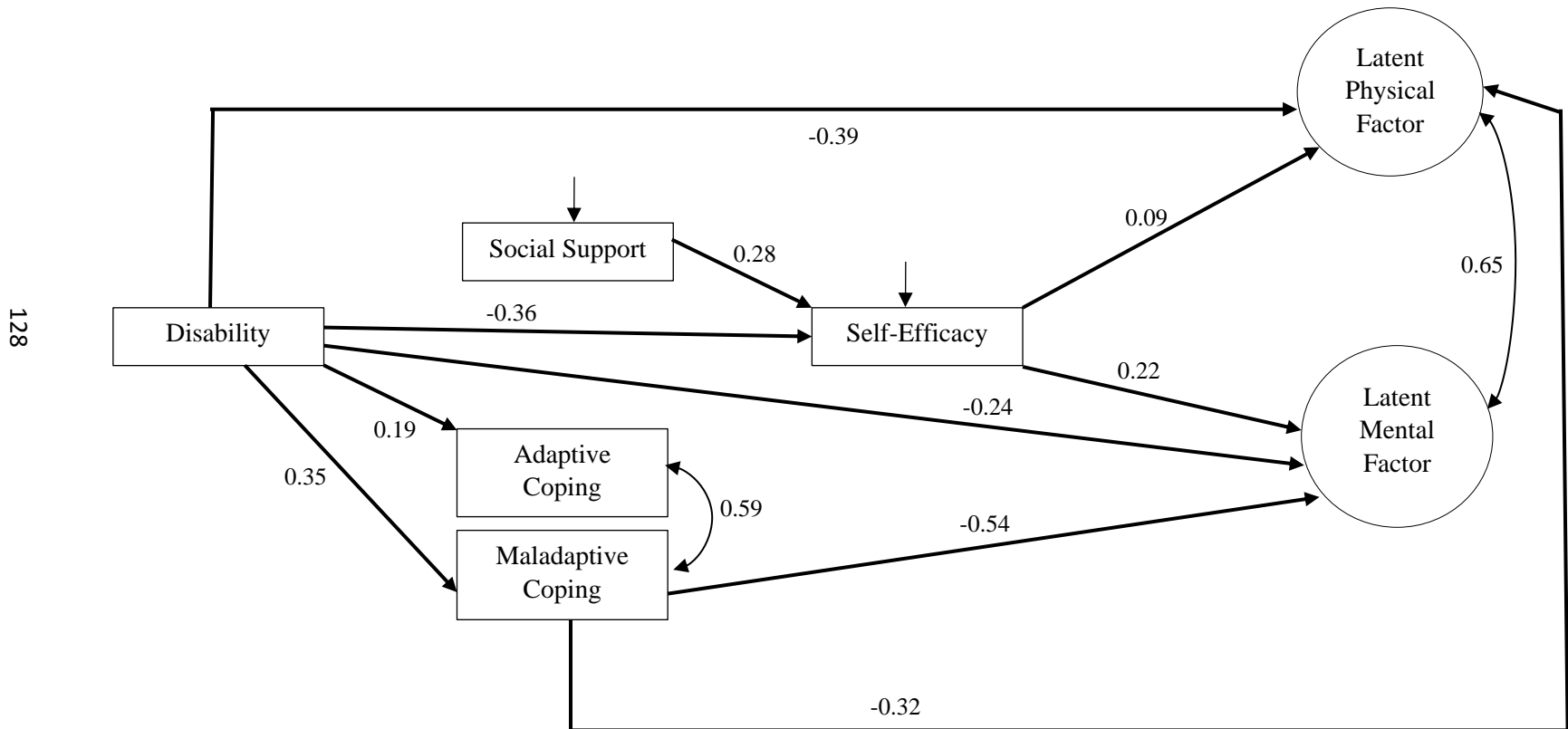


Table 0.4: Summary of fit indices for the models examining psychosocial predictors of health-related quality of life among adults with hemophilia

Fit Statistics	Model 1	Model 2
Chi-square (<i>df</i>)	459.153 (193)	321.365 (140)
CFI	0.320	0.930
TLI	0.154	0.909
RMSEA (90% <i>CI</i>)	0.168 (0.148 - 0.188)	0.082 (0.070 - 0.094)
WRMR	1.602	1.084
Model 1 - Testing the role of self-efficacy as a moderator in the stress-appraisal-coping framework; Model 2 - Testing the role of self-efficacy as a mediator in the stress-appraisal-coping framework. Note: <i>df</i> , degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation; WRMR, Weighted Root Mean Square Residual; CI, Confidence Interval.		

The significant direct and indirect effects of the study variables for model 2 have been reported in table 4.5 below. The indirect effects in the model were tested for statistical significance using the Sobel test and bias-corrected bootstrap confidence intervals with 500 draws. As hypothesized all study variables had a direct effect on the LPF and LMF except social support and adaptive coping. Disability as measured on the HAQ-DI had a significant direct effect on the LPF (standardized indirect effect = -0.390) as well as on the LMF (standardized indirect effect = -0.244). Maladaptive coping had a significant negative impact on the LPF (standardized indirect effect = -0.316) and even worse impact on the LMF (standardized indirect effect = -0.536). Self-efficacy had a significant positive effect on the LPF (standardized indirect effect = 0.091) and LMF (standardized indirect effect = 0.221).

The impact of disability on LPF was mediated by self-efficacy (standardized indirect effect = -0.032) and maladaptive coping (standardized indirect effect = -0.109). Self-efficacy (standardized indirect effect = -0.079) and maladaptive coping (standardized indirect effect = -

0.185) also mediated the impact of disability on LMF. The effect of social support on LMF was also mediated by self-efficacy (standardized indirect effect = 0.063).

Table 0.5: Unstandardized path coefficients for the study model examining psychosocial predictors of health-related quality of life among adults with hemophilia

Path	Estimate (SE)^y	<i>p</i>-value*
<u>Direct Paths</u>		
Disability→Social Support	-0.089 (0.067)	0.184
Disability→Adaptive Coping	0.194 (0.060)	0.001
Disability→Maladaptive Coping	0.345 (0.072)	<0.0001
Disability→Self-Efficacy	-0.356 (0.052)	<0.0001
Disability→Latent Physical Factor	-0.390 (0.074)	<0.0001
Disability→Latent Mental Factor	-0.244 (0.084)	0.001
Social Support→Self-Efficacy	0.283 (0.065)	<0.0001
Social Support→Latent Physical Factor	0.001 (0.057)	0.988
Social Support→Latent Mental Factor	0.118 (0.070)	0.128
Adaptive Coping→Self-Efficacy	0.055 (0.115)	0.636
Adaptive Coping→Latent Physical Factor	0.030 (0.063)	0.651
Adaptive Coping→Latent Mental Factor	0.096 (0.091)	0.319
Maladaptive Coping→Self-Efficacy	-0.023 (0.106)	0.832
Maladaptive Coping→Latent Physical Factor	-0.316 (0.079)	<0.0001
Maladaptive Coping→Latent Mental Factor	-0.536 (0.089)	<0.0001
Self-Efficacy→Latent Physical Factor	0.091 (0.049)	0.046
Self-Efficacy→Latent Mental Factor	0.221 (0.060)	0.001
<u>Indirect Paths</u>		
Disability→Self-Efficacy→Latent Physical Factor	-0.032 (0.019)	0.039
Disability→Maladaptive Coping→Latent Physical Factor	-0.109 (0.035)	0.002
Disability→Self-Efficacy→Latent Mental Factor	-0.079 (0.024)	0.004
Disability→Maladaptive Coping→Latent Mental Factor	-0.185 (0.053)	0.005
Social Support→Self-Efficacy→Latent Mental Factor	0.063 (0.022)	0.004
Note: SE, Standard Error		
^y Parameter estimates are obtained from bias corrected bootstrap estimates		

* p -values and standard errors are obtained from Sobel test

Covariance between residual terms of adaptive coping and maldaptive coping as well as adaptive coping and social support have been omitted from the table for simplicity, but were estimated in the model.

DISCUSSION

Although several previous studies have examined predictors of HRQOL among patients with hemophilia, the majority of these studies have focused on the role of clinical (i.e., disease severity, presence of comorbidities such as hepatitis C, HIV, or inhibitors to clotting factor) and socio-demographic factors (i.e., age) (Miners et al., 1999; Szucs, Öffner and Schramm, 1996). However, these studies have generally overlooked the role of psychosocial variables such as social support, coping strategies, and self-efficacy. These factors have been identified as key determinants of HRQOL among patients with other diseases (Luszczynska et al., 2007a; McKnight et al., 2010). The current study sought to identify psychosocial predictors of HRQOL by employing Lazarus and Folkman's cognitive behavioral model of stress, appraisal, and coping. The relationships between constructs such as disability, social support, coping strategies adopted, patient self-efficacy, and HRQOL (operationalized as the LPF and the LMF) were examined in the current study using a structural equation modeling.

Results from the SEM analysis suggested a direct as well as an indirect effect of disability on HRQOL among adults with hemophilia. As hypothesized, disability had a significant negative direct effect on the LPF and the LMF. A study by Santavirta and colleagues suggested disability had a significant negative impact on the physical activity level and psychosocial well-being assessed using the Rand 36-item Health Survey v1.0 among adults with hemophilia in Sweden (Santavirta et al., 2010). The detrimental impact of disability on physical and psychosocial functioning has also been reported among adults with hemophilia in the

Netherlands (Triemstra et al., 1998). With respect to the individual domains of HRQOL, the current study suggested that the negative impact of disability on physical HRQOL was much greater than its impact on mental HRQOL. Patients with hemophilia suffer from repeated bleeding into joints and large muscle groups of the body. This can lead to long term impairments in mobility, reduction in the range of joint motion and eventually impact physical HRQOL (Aznar et al., 2009; Mackensen, 2007). Although hemophilia does impact the mental well-being of patients as well, this is to a much lesser extent. In fact some studies in the literature have suggested the mental HRQOL of adults with hemophilia was similar to the general healthy population (Aznar et al., 2009; Lindvall et al., 2012; Molho et al., 2000; Poon et al., 2014). Considering these limitations placed by hemophilia on the physical, mental, and social aspects of the lives of patients, it is reasonable to expect a negative relationship between disability and the physical and mental HRQOL of the study population.

The impact of coping on HRQOL among adults with hemophilia has not been assessed extensively in the existing literature. The findings from the current study suggested that maladaptive coping had a significant negative impact on the physical and mental HRQOL of adults with hemophilia. A study by Binnema et al. (2014) among severe hemophilia patients in the Netherlands suggested that patients' use of maladaptive coping was associated with poor socio-psychological health, lesser participation in daily activities, and reduced social interaction. Santavirta and colleagues found that Swedish patients with bleeding disorders used maladaptive coping strategies like distraction and catastrophizing more often than adaptive coping strategies such as reinterpreting pain and the use of maladaptive coping strategies was significantly associated with poor psychosocial well-being (Santavirta et al., 2010). A similar finding was reported by Klein and colleagues among hemophilia patients with HIV (Klein et al., 1994). In

the current study, maladaptive coping also mediated the relationship between disability and physical as well as mental HRQOL. These results suggest that an increase in hemophilia-related disability may lead to a greater adoption of maladaptive coping strategies which in turn would be associated with lower physical and mental HRQOL. Santavirta and colleagues (2010) reported a similar finding where coping was found to mediate the relationship between disease severity and psychosocial well-being among adults with hemophilia. Overall, the impact of disability on HRQOL may be alleviated with the restricted use of maladaptive coping strategies. Clinicians as well as caregivers of adults with hemophilia must encourage patients to develop better coping mechanisms which could help in the long-term management of their symptoms and possibly improve their HRQOL.

A positive direct effect of self-efficacy on physical as well as mental HRQOL was observed in this study. Self-efficacy has been found to predict better functional status among patients with arthritis (Maly, Costigan, & Olney, 2006; Marks & Allegrante, 2005) and sickle cell disease (Clay & Telfair, 2007). Similarly, a study among adult hemophilia patients reported that higher self-efficacy scores were significantly correlated with higher HRQOL (Lock et al., 2014). Additionally as hypothesized, we also found that self-efficacy mediated the effect of disability on physical and mental HRQOL. In the context of the stress, appraisal, coping framework employed by the current study, self-efficacy served as an important concept in the self-appraisal process which can favorably impact self-reported outcomes of the adaptational process (HRQOL in this case) more so than other objectively measured outcomes (McKnight et al., 2010). Family members and clinicians should therefore target improving positive strengths such as self-efficacy among adults with hemophilia. Interventions designed to improve self-efficacy could result in long-term functional and psychosocial benefits in this patient population

and diminish the negative impact of disease severity, pain, and disability on patient HRQOL. No support was found for the moderating role of self-efficacy in the current study.

Finally, the study results suggested that social support did not have a direct impact on the physical or mental HRQOL. Also, we did not find any support for the hypothesis that social support will mediate the relationship between disability and HRQOL. Triemstra and colleagues (1998) reported a similar finding among Dutch hemophilia patients where social support was not found to be a mediator of the relationship between disability and well-being. However, a significant indirect effect of social support on mental HRQOL through self-efficacy was observed among adults with hemophilia in the current study. A core tenet of the social cognitive theory is social support which is important for the development of self-efficacy beliefs (Bandura, 1994). Social support in the form of emotional support (encouragement, affirmation), informational support (providing advice and guidance to boost one's positive mood), and instrumental help from people who are close to the patient may positively affect self-efficacy beliefs. According to Bandura's social cognitive theory, social support can have an enabling effect on self-efficacy. Individuals receiving adequate social support are likely to harbor stronger self-efficacy beliefs. These in turn will positively impact health-related outcomes such as HRQOL. Therefore the benefits of receiving adequate social support on HRQOL may be partially mediated by self-efficacy. Such a relationship has been found to exist among patients with HIV, where social support impacted medication adherence to HAART therapy indirectly via self-efficacy (Cha, Erlen, Kim, Sereika, & Caruthers, 2008; Luszczynska et al., 2007a; Simoni, Frick, & Huang, 2006).

Overall, the results of this study have both practical and theoretical implications. From a practical perspective, our results can be used to design interventions to improve social support,

increase the use of adaptive and restrict the use of maladaptive coping strategies, and develop stronger self-efficacy beliefs among adults with hemophilia. Such interventions could potentially improve functional status, psychosocial well-being and the overall HRQOL in this patient population. From a theoretical perspective we found that the Lazarus and Folkman's cognitive behavioral model of stress, appraisal, and coping worked well in trying to explain the nature of the relationship between disability, resulting from hemophilia, and HRQOL. This was the first US based study to use an SEM based approach toward identifying psychosocial predictors of HRQOL among adults with hemophilia. The information from this study can help researchers modify their understanding of HRQOL among hemophilia patients. In the future, it would be very important to consider the role of psychosocial variables such as social support, coping, and self-efficacy while designing studies in which HRQOL is a key outcome parameter. Excluding such important determinants may lead to biased estimates and an incorrect understanding of HRQOL among patients with hemophilia and other bleeding disorders.

A few limitations must be considered while interpreting the results of this study. First, the cross-sectional nature of the study precludes us from drawing any causal inferences despite the findings of the study which support the proposed theoretical model. The proposed causality of the model is based on plausible and theoretical arguments which must be tested using longitudinal studies in the future. The study employed a national convenience sample of hemophilia patients. This may limit the generalizability of the study results. To the best of our knowledge, this is the first US based study to employ such a large sample size of hemophilia patients. We recruited patients through multiple sources including online patient panels, private patient communities on social media websites as well as at hemophilia treatment centers in order to improve study generalizability. However, future studies should try to employ probability

sampling based strategies to recruit rare disease patients. Future studies must also try to assess the role of psychological variables such as depression and anxiety in the relationship between disability and HRQOL among hemophilia patients. These variables have been shown to be key predictors of patient well-being in previous studies (Triemstra et al., 1998).

The current study builds on existing literature among adults with hemophilia. The current study employed the stress, appraisal, and coping framework to identify psychosocial predictors of HRQOL among adults with hemophilia. Study results revealed the key role played by variables such as maladaptive coping, self-efficacy, and social support in influencing the HRQOL of adults with hemophilia. It was found that maladaptive coping had a negative influence on both physical and mental HRQOL. Maladaptive coping also mediated the relationship between disability and HRQOL. Stakeholders must encourage the restricted use of maladaptive coping strategies in order to minimize its detrimental impact on HRQOL. Self-efficacy had a significant direct positive relationship with HRQOL. Self-efficacy also mediated the impact of disability on HRQOL and intensified the beneficial impact of social support on HRQOL. Caregivers, policy makers, and clinicians must pay heed to these modifiable psychosocial variables in providing care to adults with hemophilia in order to maximize the benefit which patients may receive from treatment and improve their HRQOL.

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LIST OF APPENDICES

Appendix A: Cover Letter

Dear Sir/Madam,

We are conducting an online survey to gather information on the experiences of individuals with hemophilia. The survey will assess the disease burden and quality of life among individuals with hemophilia. This study is being conducted by researchers at the University of Mississippi - School of Pharmacy. This study is part of a Ph.D. student's research project. We would appreciate it very much if you could take a few minutes to complete the online survey. Your response is very important in helping us achieve accurate estimates of the impact of hemophilia on quality of life and assess the burden of this disease.

Adult (18 years of age and older) patients with hemophilia A or B are eligible to participate in this study. The survey should take no longer than 15-20 minutes to complete. Upon completion of the survey, a \$10 Amazon gift card will be emailed to you as a token of our appreciation for your participation. In addition, upon the completion of the study an executive summary of the study findings will be made available to you. You will be asked to provide an email ID upon the completion of the survey so that the research team can send you the gift card and the summary of the study results. Your email ID will not be linked with your response or used for any other purpose.

We THANK YOU in advance for your time and contribution in providing us with this valuable information. If you have any questions or need more information about this project, please contact Ruchit Shah in the Department of Pharmacy Administration at the University of Mississippi at **662-801-1520**.

Click on the following link or Copy and Paste it in your internet browser to complete the survey:

http://uofmississippi.qualtrics.com/SE/?SID=SV_51PhfEFYJwLo9o1

Sincerely,

Ruchit Shah, MS
Ph.D. Candidate
Pharmacy Administration
The University of Mississippi
School of Pharmacy

John P. Bentley, Ph.D.
Professor
Pharmacy Administration
The University of Mississippi
School of Pharmacy

Appendix B: Study Survey

Thank you for your willingness to participate in this survey.

GENERAL INSTRUCTIONS: For each of the following questions please check the most appropriate response. Please note that there are no right or wrong answers to any of the following questions.

1. Are you 18 years of age or older?

- Yes
- No

2. Which of the following conditions do you suffer from?

- Hemophilia A
- Hemophilia B
- Other (please specify) _____

If you answered 'NO' on No. 1 or 'OTHER (please specify) on No. 2:

Unfortunately, this study focuses on adult patients with Hemophilia A or B. **Please *do not* proceed with this survey.** Thank you for your time.

**PLEASE COMPLETE QUESTIONS ON FRONT AND BACK OF THE FOLLOWING
PAGES**

Section I Part A - Your Health and Well-Being

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. For each of the following questions, please select the option that best describes your answer.

1. In general, would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Climbing several flights of stairs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Were limited in the kind of work or other activities	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

4. During the past 4 weeks, how much of the time 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)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Did work or other activities less carefully than usual	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

6. 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. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Did you have a lot of energy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Have you felt downhearted and depressed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

7. 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.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

SECTION I: PART B – Your Ability to Function in Daily Life

INSTRUCTIONS: In this section we are interested in learning about your ability to function in daily life. Please select the response which best describes your usual abilities OVER THE PAST WEEK:

Dressing and Grooming

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Dress yourself, including shoelaces and buttons?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Shampoo your hair?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Arising

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Stand up from a straight chair?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Get in and out of bed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Eating

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Cut your own meat?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Lift a full cup or glass to your mouth?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Open a new milk carton?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Walking

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Walk outdoors on flat ground?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Climb up five steps?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please check any AIDS OR DEVICES that you usually use for any of the above activities:
(Please check all that apply)

- Devices used for dressing (button hook, zipper pull, etc.)
- Built up or special utensils
- Crutches
- Cane
- Wheelchair
- Special or built up chair
- Walker
- No, I don't use any aids or devices

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:
(Please check all that apply)

- Dressing and grooming
- Arising
- Eating
- Walking
- No, I don't need help from another person

SECTION I: PART B – Your Ability to Function in Daily Life (continued)

Please select the response which best describes your usual abilities OVER THE PAST WEEK:

Hygiene

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Wash and dry your body?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Take a tub bath?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Get on and off the toilet?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Reach

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Bend down to pick up clothing from the floor?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Grip

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Open car doors?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Open previously opened jars?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Turn faucets on and off?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Activities

Are you able to:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
a. Run errands and shop?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Get in and out of a car?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Do chores such as vacuuming or yard work?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please check any AIDS OR DEVICES that you usually use for any of the above activities:
(Please check all that apply)

- Raised toilet seat
- Bathtub bar
- Long-handled appliances for reach
- Bathtub seat
- Long-handled appliances in the bathroom
- Jar opener (for jars previously opened)
- No, I don't use any aids or devices

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:
(Please check all that apply)

- Hygiene
- Reach
- Gripping and opening things
- Errands and chores
- No, I don't need help from another person

Your Activities: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

- Completely
- Mostly
- Moderately
- A little
- Not at all

Your PAIN: How much pain have you had IN THE PAST WEEK? On a scale of 0 to 100 (where zero represents “no pain” and 100 represents “severe pain”), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents “very well” and 100 represents “very poor health”), please record the number below.

SECTION I: PART C – Your Self-Efficacy

INSTRUCTIONS: Below are ten statements about yourself which may or may not be true. Please indicate your agreement with each item by selecting the appropriate option. Please be open and honest in your responding.

	Not at all true	Hardly true	Moderately true	Exactly true
a. I can always manage to solve difficult problems if I try hard enough.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. If someone opposes me, I can find the means and ways to get what I want.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. It is easy for me to stick to my aims and accomplish my goals.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. I am confident that I could deal efficiently with unexpected events.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e. Thanks to my resourcefulness, I know how to handle unforeseen situations.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f. I can solve most problems if I invest the necessary effort.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g. I can remain calm when facing difficulties because I can rely on my coping abilities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h. When I am confronted with a problem, I can usually find several solutions.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i. If I am in trouble, I can usually think of a solution.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
j. I can usually handle whatever comes my way.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART D – Your Social Support

INSTRUCTIONS: We are interested in how you feel about the following statements. Read each statement carefully. Please indicate your level of agreement with each statement.

	Very strongly disagree	Strongly disagree	Mildly disagree	Neutral	Mildly agree	Strongly agree	Very strongly agree
a. There is a special person who is around when I am in need.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. There is a special person with whom I can share my joys and sorrows.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. My family really tries to help me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. I get the emotional help and support I need from my family.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e. I have a special person who is real source of comfort to me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f. My friends really try to help me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART D – Your Social Support (continued)

Please indicate your level of agreement with each statement.

	Very strongly disagree	Strongly disagree	Mildly disagree	Neutral	Mildly agree	Strongly agree	Very strongly agree
g. I can count on my friends when things go wrong.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h. I can talk about my problems with my family.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i. I have friends with whom I can share my joys and sorrows.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
j. There is a special person in my life who cares about my feelings.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
k. My family is willing to help me make decisions.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
l. I can talk about my problems with my friends.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART E – Your Coping Strategies

INSTRUCTIONS: These items deal with ways you've been coping with the challenges of having hemophilia. There are many ways to try to deal with problems. These items ask what you've been doing to cope with this one. Different people deal with things in different ways, but we are interested in how you've tried to deal with it. Each item says something about a particular way of coping. We want to know to what extent you've been doing what the item says. Don't answer on the basis of whether it seems to be

working or not - just whether or not you're doing it. Use the response choices provided below. Please select your response for each question. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
a. I've been turning to work or other activities to take my mind off things.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. I've been concentrating my efforts on doing something about the situation I'm in.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. I've been saying to myself "this isn't real".	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. I've been getting emotional support from others.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e. I've been giving up trying to deal with it.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f. I've been taking action to try to make the situation better.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g. I've been refusing to believe that it has happened.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h. I've been saying things to let my unpleasant feelings escape.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART E – Your Coping Strategies (continued)

INSTRUCTIONS: Use the response choices provided below. Please select your response for each question. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
i. I've been getting help and advice from other people.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
j. I've been trying to see it in a different light, to make it seem more positive.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
k. I've been criticizing myself.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
l. I've been trying to come up with a strategy about what to do.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
m. I've been getting comfort and understanding from someone.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
n. I've been giving up the attempt to cope.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
o. I've been looking for something good in what is happening.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
p. I've been making jokes about it.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
q. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
r. I've been accepting the reality of the fact that it has happened.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART E – Your Coping Strategies (continued)

INSTRUCTIONS: Use the response choices provided below. Please select your response for each question. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
s. I've been expressing my negative feelings.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
t. I've been trying to find comfort in my religion or spiritual beliefs.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
u. I've been trying to get advice or help from other people about what to do.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
v. I've been learning to live with it.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
w. I've been thinking hard about what steps to take.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
x. I've been blaming myself for things that happened.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
y. I've been praying or meditating.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
z. I've been making fun of the situation.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SECTION I: PART F – Your Symptom Severity

1. When thinking about all of the hemophilia-related symptoms that you may have experienced during the past 4 weeks, please indicate the one option that best describes how your symptoms overall have been.

- No symptoms
- Mild symptoms
- Moderate symptoms
- Severe symptoms

Section II: Information about you and your clinical condition

INSTRUCTIONS: Please answer the following questions to help us better understand your responses.

1. Are you:

- Male
- Female

2. What is your current age?

_____ years

3. Which of the following best describes your race or ethnicity?

- African American/Black
- American Indian/Alaska Native
- Asian
- Hispanic
- Native Hawaiian/Other Pacific Islander
- White/Caucasian
- Other (please specify) _____

4. Which of the following describes your current marital status?

- Never Married
- Married
- Divorced
- Separated
- Widowed
- Not married, living with partner

5. What is the highest level of education you have completed?

- Less than high school
- High school/GED
- Some college
- 2 year college degree
- 4 year college degree
- Professional degree
- Masters' degree
- Doctoral degree

6. Which of the following describes your main occupation?

- Employed/Self-employed full time
- Employed part-time
- Retired
- Home-maker
- Student
- Seeking work
- Other (please specify) _____

7. Please indicate the region of the country in which you reside.

- Northeast
- Midwest
- South
- West

8. Do you currently have health insurance?

- Yes
- No **[If you selected this, SKIP No. 9, and GO TO No. 10]**

9. What type of health insurance do you currently have?

- Public insurance (e.g. Medicare, Medicaid, VA)
- Private insurance
- Other (please specify) _____

10. Please indicate your level of disease severity based on your normal blood clotting factor activity level.

- Mild (clotting factor level between 6% - 40%)
- Moderate (clotting factor level between 1% - 5%)
- Severe (clotting factor level less than 1%)
- Not sure

11. Please indicate the number of bleeds you experienced in the last twelve months.

12. Which of the following best describes the type of treatment you currently receive.

- Currently on prophylaxis therapy only
- Received prophylaxis therapy previously but currently on on-demand therapy only
- Never received prophylaxis therapy and currently on on-demand therapy only
- Others (please specify) _____

13. Have you ever undergone an orthopedic surgery for the treatment of joint damage due to hemophilia?

- Yes
- No [If you selected this, SKIP No. 14, and GO TO No. 15]

14. Please indicate the number of orthopedic surgeries you have undergone for the treatment of joint damage due to hemophilia.

15. Please indicate whether you currently have or have ever had each of the following conditions.

a. Hepatitis C

- Never been infected with Hepatitis C
- Infected with Hepatitis C in the past but not infected currently
- Currently infected with Hepatitis C
- Decline to answer

b. HIV

- Never been infected with HIV
- Currently infected with HIV
- Decline to answer

c. Depression

- Never been diagnosed with depression
- Previously diagnosed with depression but do not have it currently
- Currently diagnosed with depression
- Decline to answer

d. Inhibitors to blood clotting factor

- Never developed inhibitors to blood clotting factor
- Developed inhibitors to blood clotting factor in the past but not currently
- Currently have inhibitors to blood clotting factor
- Decline to answer

16. Please indicate the number of times you have visited each of the following for hemophilia-related treatment (e.g. for clotting factor infusions, regular check-ups) in the last twelve months.

- _____ Hemophilia Treatment Center (HTC)
- _____ Hematologist outside a HTC
- _____ Primary Care Practitioner/ General practitioner
- _____ Other (please specify)

Thank you for your participation in this research study!

Appendix C: IRB Approval Notice

IRB Exempt Approval of 16x-105

5 messages

irb@olemiss.edu <irb@olemiss.edu>

Thu, Oct 22, 2015 at 2:48 PM

To: "rmshah@go.olemiss.edu" <rmshah@go.olemiss.edu>, John Bentley <phjpb@olemiss.edu>

Cc: Donna West <dswest@olemiss.edu>

Mr. Shah:

This is to inform you that your application to conduct research with human participants, "Measuring and understanding health-related quality of life among adult patients with hemophilia" (Protocol #16x-105), has been approved as Exempt under 45 CFR 46.101(b)(#2).

Please remember that all of The University of Mississippi's human participant research activities, regardless of whether the research is subject to federal regulations, must be guided by the ethical principles in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.

It is especially important for you to keep these points in mind:

- You must protect the rights and welfare of human research participants.
- Any changes to your approved protocol must be reviewed and approved before initiating those changes.
- You must report promptly to the IRB any injuries or other unanticipated problems involving risks to participants or others.

If you have any questions, please feel free to contact the IRB at irb@olemiss.edu.

Jennifer Caldwell, PhD

Senior Research Compliance Specialist, Research Integrity and Compliance

The University of Mississippi

212 Barr

P.O. Box 1848

University, MS 38677-1848

U.S.A.

CHAPTER V: SUMMARY AND FUTURE RESEARCH

STUDY SUMMARY

Hemophilia is a rare X-linked chronic genetic blood coagulation disorder among males that is caused by a deficiency of clotting factors VIII or IX. It impacts about 400,000 people across the world and about 20,000 in the United States (US) (National Hemophilia Foundation, 2014).

Patients with hemophilia experience bleeding into joints and muscles which in severe cases can lead to chronic pain, reduce the range of joint motion and eventually progress to chronic arthritis (Dolan et al., 2009). Also, patients with hemophilia often suffer from comorbidities such as infections due to hepatitis C virus (HCV), human immunodeficiency virus (HIV), or tolerance to clotting factors in the form of an inhibitor (Franchini & Mannucci, 2009).

For a patient living with hemophilia, merely treating and preventing bleeding episodes and other physical symptoms using clotting factor concentrates is not enough. Patients with hemophilia must be careful about participating in activities such as contact sports because immediate bleeding may ensue. Long-term impairments in mobility and impact on functional status due to reduced range of joint motion may also limit the activities in which patients can participate. This can impact social participation and peer integration (Aznar, Magallón, Querol, Gorina, & Tusell, 2009; Mackensen, 2007). Patients can be impacted by employment and occupational disabilities as well. Also, the disease can impact the mental well-being of patients within whom signs of depression, anxiety and psychological distress are common (Ghanizadeh & Baligh-Jahromi, 2009). Thus the physical, mental and social consequences of the disease serve to reduce the HRQOL of patients. Therefore HRQOL assessment is now recognized as an important health

outcomes endpoint which can help decide and optimize treatment options among patients with hemophilia (Fischer, van der Bom, & van den Berg, 2003). A key consideration in HRQOL assessment is the use of an appropriate instrument. One of the most commonly used measures of HRQOL is the SF-12 Health Survey version 2 (SF-12v2).

Study 1

A good HRQOL tool should have the ability to discriminate between individuals based on their health status (Guyatt, Feeny, & Patrick, 1993). Therefore it is recommended that the psychometric properties of a HRQOL measure must be established in terms of its validity, reliability, and responsiveness before its use in a particular population (Patrick & Deyo, 1989). Psychometric assessments provide evidence about the appropriateness of use of measures of HRQOL in a particular group of patients. The SF-12 has been previously used to assess HRQOL among patients with hemophilia (Duncan, Kronenberger, Roberson, & Shapiro, 2012; Poon, Pope, & Tarlov, 2013). However, its psychometric properties in this population had not been assessed. This study provides evidence about the acceptable psychometric properties of the SF-12v2 among adults with hemophilia in the US. The SF-12v2 was found to be a valid and reliable generic measure of HRQOL among adults with hemophilia. The scale demonstrated adequate factorial, convergent, discriminant, and known-groups validity. The scale was found to have adequate internal consistency reliability and no evidence of the presence of a floor or ceiling effect was found. Overall, the results provide basis for the future use of the SF-12v2 among adults with hemophilia and incorporating the HRQOL information obtained from these studies into health policy and clinical decision making.

Study 2

When testing HRQOL differences between groups of patients using a well-established measure of HRQOL, it is also fundamental that members of different groups assign the same meaning to questionnaire items. If it can be shown that patient characteristics (such as age, gender, type of disease, disease severity) do not affect the psychometric properties of the observed indicators (i.e., questionnaire items), then the assumption of measurement invariance is not violated. If the assumption of measurement invariance holds, then the observed differences in HRQOL among groups defining the study population are true differences in HRQOL and not measurement artifacts. In the context of the current study, the assumption of measurement invariance was said to be met if specific characteristics such as age, disease severity, and treatment regime did not influence observed responses to the items on the SF-12v2. The study results indicated that the SF-12v2 was invariant with respect to age of the study participants. The presence of DIF was seen with respect to item 9 while comparing hemophilia patients across different severity levels. This item has shown DIF effects among other patient populations as well as in the general US population. Finally, findings for the invariance analysis across hemophilia treatment regimens lend support to the interpretation of “approximate invariance”. Although HRQOL comparisons across hemophilia patients on different treatment regimens can be carried out, these results must be interpreted with caution. Overall, the SF-12v2 was largely invariant with respect to age, symptom severity, and treatment regimen among a sample of adults with hemophilia.

Study 3

While previous studies have emphasized on clinical and socio-demographic determinants, this was the first US-based study which critically shifted focus to an assessment of psychosocial

predictors of HRQOL among patients with hemophilia. An adapted version of the Lazarus and Folkman's cognitive-behavioral model of stress, appraisal, and coping was employed in order to help us examine the interplay between the patient's use of resources (i.e., social support, coping strategies, and self-efficacy) and adaptational health outcomes such as HRQOL. Study results revealed the key role played by variables such as maladaptive coping, self-efficacy, and social support in influencing the HRQOL of adults with hemophilia. Knowledge about these psychosocial factors will not only assist healthcare providers and caregivers in improving care provided to individuals with hemophilia, but will also enable patients to better understand and self-manage their disease condition. Such assessments can assist both clinicians and healthcare policymakers in designing programs aimed at increasing the level of social support provided, fostering the use of adaptive coping strategies, and overall ensuring better health among these patients.

This dissertation is a significant addition to the literature concerning HRQOL among patients with hemophilia. The findings of the psychometric evaluation of the SF-12v2 pave the way for future use of this instrument in studies concerning HRQOL among adults with hemophilia. The fact that the SF-12v2 was found to be invariant with respect to age, symptom severity, and treatment regimen among a sample of adults with hemophilia is a key for future studies which may want to carry out HRQOL comparisons across subgroups of hemophilia patients. Researchers would confidently be able to draw conclusions from such studies because the observed differences among these patient subgroups would be true differences in HRQOL and not measurement artifacts. Finally, by examining the role of modifiable psychosocial variables (social support, coping, and self-efficacy) in predicting the HRQOL of adults with

hemophilia, this dissertation highlighted the need for inclusion of these parameters into disease management and treatment decisions.

DIRECTIONS FOR FUTURE RESEARCH

The findings from this dissertation project provides different avenues for future research.

Study 1

Future studies should adopt a longitudinal design in order to explore the predictive validity and test-retest reliability of the SF-12v2 among adults with hemophilia. A longitudinal design may be useful in assessing any response shift in the HRQOL of adults with hemophilia over a period of time. Future studies should also consider using a disease-specific HRQOL measure to ascertain the convergent and discriminant validity of the SF-12v2 in this patient population.

Study 2

Future research should focus on determining whether hemophilia patients interpret items on the SF-12v2 equivalently over a longer period of time (i.e., longitudinal measurement invariance). Also, considering the DIF effect on item 9 seen in this study and in the existing literature, future studies should consider either revising or completely removing this item from the HRQOL measure.

Study 3

Future studies should test the study model using a longitudinal design in order to determine whether the direction and causality of the hypothesized relationships in the current study. Also, in order to improve the generalizability of the study results to all US adults with hemophilia,

future studies should consider adopting a probability sampling based technique to recruit patients into the study. Future studies must also try to assess the role of psychological variables such as depression and anxiety, other appraisal variables (hopelessness, uncertainty, family hardiness) in the relationship between disability and HRQOL among hemophilia patients. Researchers must also try to assess the burden of hemophilia on the HRQOL of caregivers of hemophilia patients. It may be interesting to examine the relationship between the physical and mental HRQOL of patients and caregivers of patients with hemophilia.

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Patrick, D. L., & Deyo, R. a. (1989). Generic and disease-specific measures in assessing health status and quality of life. *Medical Care*, 27, S217–S232.

Poon, J.-L., Pope, A. M., & Tarlov, A. R. (2013). *Burden of illness in hemophilia A: taking the patient's perspective (Doctoral Dissertation)*. Available from Proquest Dissertations & Theses database. 3609983 *Eds Disability in America Toward a national agenda for prevention National Academies Press*.

VITA

RUCHITBHAI SHAH

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ACADEMIC EXPERIENCE:

June 2013 – Current (Expected completion – June 2016)

The University of Mississippi.

- Doctoral Candidate, Department of Pharmacy Administration.
- **Dissertation Title** – Measuring and understanding health-related quality of life among adult patients with hemophilia.

August 2011 – May 2013

The University of Mississippi.

- Masters of Science (M.S.) in Pharmacy Administration.
- **Thesis Title** – Community pharmacists' attitudes toward an expanded class of non-prescription drugs.

Relevant Coursework:

- Research methods, Primary and Secondary data techniques, Data management.
- General linear models, Multivariate data analysis, Structural equation modeling, Longitudinal data analysis, Statistical mediation and moderation analysis, Introductory econometrics.
- Drug development and Marketing, Consumer behavior, Marketing theory.
- Pharmacoeconomics, Health economics, Pharmacoepidemiology, US healthcare system.

August 2007 – May 2011

Bombay College of Pharmacy, University of Mumbai.

- Bachelor of Pharmacy (B.Pharm).
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PROFESSIONAL EXPERIENCE:

June – August 2015

Health Economics and Outcomes Research Intern, Pharmerit International

- Assisted in developing an early economic model for a new launch Respiratory Syncytial Virus product for an ex-US market.
- Assessed of the impact of treatment switching on healthcare resource utilization and cost among patients with major depressive disorder using Truven Health MarketScan data.
- Assisted in developing a statistical analysis plan for the patient reported outcomes (PRO) measures included in a phase III clinical trial for a new launch pancreatic cancer product.

June – August 2013

Health Economics Intern, Global Market Access (GMAx), Biogen Idec

- Developed a budget impact model for a new launch multiple sclerosis (MS) product for an ex-US payer.
- Assisted in developing a patient-reported measure to assess mobility impairment among MS patients.
- Reviewed MS patient registries across the world.

January 2013 – Present

Data Manager and Research Analyst – Mississippi Medicaid Drug Utilization Review (MS-DUR)

- Current responsibilities include conducting research projects on an ad-hoc basis to influence MS-DUR board policy decisions.
- Running weekly claims data adjustment routines in order to generate research files from raw data files received from MS-DUR.
- Designing monthly educational interventions for physicians and pharmacists to monitor patient adherence on cardiovascular drugs, assess monthly dose of prescribed opioids, and ensure the implementation of any preferred drug list changes by MS-DUR.
- Generating monthly resource utilization reports and yearly exceptions monitoring reports for submission to CMS and the MS-DUR board.

August 2011 – August 2012

Research Assistant, Delta Health Patient Care Management Project (HRSA Grant - U1FRH07411-3)

- Responsibilities included data entry, analyses of pre and post medication therapy management (MTM) data.

August 2012 – January 2013

Graduate Teaching Assistant, Pharmacy Law (PHAD 491) course

- Responsibilities included grading assignments, creating, proctoring and grading tests, and conducting exam review sessions.
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RESEARCH EXPERIENCE:

Doctoral Dissertation Project – Measuring and understanding health-related quality of life among adult patients with hemophilia.

- Evaluating the psychometric properties and assessing measurement invariance of the SF-12 among hemophilia patients.
- Examining psychosocial predictors of health-related quality of life among hemophilia patients in the US.
 - Data collection assistance provided by Rare Patient Voice (online panel of hemophilia patients), hemophilia treatment centers in Jackson, MS and Memphis, TN.

Master's Thesis Project – Community pharmacists' attitudes toward an expanded nonprescription drug class: A national survey.

- Data collection assistance provided by Delta Marketing Dynamics (online panel of community pharmacists).

Burden of hemophilia in the Mississippi Medicaid population

- Examined the prevalence of the disease and associated comorbidities, treatment patterns, costs, healthcare resource use, and characteristics of hemophilia patients in the Mississippi Medicaid administrative claims data.
- Worked as a part of a research team which included hematologists, nurse practitioners, and pharmacy directors from MS-DUR to design an algorithm to identify disease severity among hemophilia patients and validate it using patient electronic health records from hemophilia treatment centers in Jackson, MS and Memphis, TN.

Healthcare utilization and cost burden of melanoma among Medicaid beneficiaries.

- Developed a proposal to submit to CMS, conducted analysis using Medicaid data from 46 states.

Comparative effectiveness of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) among elderly patients with coronary artery disease: A propensity-score matched analysis.

- Performed a literature review, conducted time-to-event analysis to compare clinical outcomes associated with the two surgical procedures using national 5% Medicare sample.
- Compared costs and resource utilization between CABG and PCI using generalized

linear models.

Impact of overweight and obesity on arthritis-attributable burden and health-related quality of life among adults with arthritis.

- Conducted multivariate analysis using Behavioral Risk Factor Surveillance System (BRFSS) data.

Testing of antipsychotic quality measures among children enrolled in the Mississippi Medicaid population.

- Examined the performance of the Mississippi Medicaid program on HEDIS quality measures: use of metabolic monitoring and psychosocial care services, assessment of multiple concurrent antipsychotics, presence of an appropriate primary mental health diagnosis and follow-up visits in children taking antipsychotics.

An examination of stress in school of pharmacy faculty.

- Conducted focus groups which lead to the development of a survey that was administered nationally to school of pharmacy faculty.

PUBLICATIONS:

- **Shah R**, Yang Y. Health and economic burden of obesity in elderly individuals with asthma in the United States. *Population Health Management*, 2014.
- Joshi N, Khanna R, **Shah R**. Relationship between depression and physical activity, disability, burden and health-related quality of life (HRQOL) among patients with arthritis. *Population Health Management*, 2014.
- **Shah R**, Yang Y, Bentley JP, Banahan BF. Comparative effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention among elderly Medicare beneficiaries with diabetes mellitus. (Submitted for peer review – *Current Medical Research and Opinion*)
- Ziemssen T, Phillips G, **Shah R**, Mathias A, Foley C, Coon C, Sen R, Lee A, Agarwal S. Development of the Multiple Sclerosis (MS) Early Mobility Impairment Questionnaire (EMIQ). (Submitted for peer review – *Journal of Neurology*)
- **Shah R**, Holmes E, West-Strum DS, Patel AP. Community pharmacists' attitudes toward an expanded class of non-prescription drugs. (Under preparation – *Research in Social and Administrative Pharmacy*)

PODIUM AND POSTER PRESENTATIONS:

- **Shah R**, Holmes ER, West-Strum DS, Patel AP. Community pharmacists' attitudes toward an expanded class of non-prescription drugs. Presented as a podium at the American Pharmacists' Association annual meeting and exposition, 2014 in Orlando, FL.
- **Shah R**, Nunna S, Banahan BF, Hardwick SP. Use of multiple concurrent antipsychotics among children enrolled in the Mississippi Medicaid program.

Presented as a podium at International Society of Pharmacoeconomics and Outcomes Research (ISPOR), Philadelphia, USA, May 2015.

- **Shah R**, Jackson T. Cost analysis of Febuxostat versus Allopurinol for the prophylaxis of gout flares. ISPOR, Washington DC, June 2012.
- **Shah R**, Holmes ER. Pharmacists' Attitudes, Perceptions, and Opinions about a Behind-the Counter Medication Class: Preliminary Literature Review. Southern Pharmacy Administration and Western Pharmacoeconomic Conference, Austin, TX, June 2012.
- **Shah R**, Banahan BF, Hardwick SP, Clark J. Need for case-mix adjustment in evaluating geographic disparities in medication adherence to oral hypoglycemics. ISPOR, New Orleans, USA, May 2013.
- **Shah R**, Yang Y. Is obesity a significant predictor of asthma, asthma-related costs, and total healthcare costs among elderly individuals in the United States. ISPOR, New Orleans, USA, May 2013.
- Ramachandran S, Jackson T, Dikun JA, **Shah R**, Wamble DE. An analysis of stress in pharmacy school faculty. The American Association of Colleges of Pharmacy Conference, May 2013.
- **Shah R**, Holmes ER, West-Strum DS, Patel AP. Using innovative technologies to increase patient access to medications. Pharmaceutical Marketing Research Group (PMRG), New Jersey, USA, March 2014.
- Ziemssen T, Mathias A, Coon C, Agarwal S, **Shah R**, Philips G. Psychometric Testing of the Early Mobility Impairment Questionnaire for Multiple Sclerosis. European Committee for Treatment and Research in Multiple Sclerosis, Boston, USA, June 2014.
- **Shah R**, Mahabaleshwarkar R, Null KD, Hardwick SP, Clark JP. Utilization of smoking cessation products in the Mississippi Medicaid Fee-for-Service population. ISPOR, Montreal, Canada, June 2014.
- Ramachandran S, Mahabaleshwakar R, **Shah R**, Null KD, Banahan BF, Hardwick SP, Clark JP. Performance of the National Quality Forum Diabetes Adherence Measure in the Mississippi Medicaid Population. ISPOR, Montreal, Canada, May 2014.
- Phillips G, Mathias A, Coon C, Agarwal S, **Shah R**, Ziemssen T. Psychometric analyses to inform item reduction and evaluate sensitivity of the early mobility impairment questionnaire for Multiple Sclerosis. European ISPOR, Amsterdam, NL, November 2014.
- Banahan BF, Nunna S, **Shah R**, Hardwick SP, Clark JP. Antipsychotic quality measures: Metabolic monitoring in children taking antipsychotics. The American Drug Utilization Review Society, Scottsdale, USA, February 2015.
- **Shah R**, Khanna R, Pace P, Banahan BF. Burden of melanoma among adults enrolled in the Medicaid program. ISPOR, Philadelphia, USA, May 2015.
- **Shah R**, Khanna R, Joshi N. Impact of overweight and obesity on arthritis-attributable burden and health-related quality of life among adults with arthritis. ISPOR, Philadelphia, USA, May 2015.

GRANT WRITING EXPERIENCE:

Title: Pharmaceutical Marketing Research Group Student Travel Grant.

Amount: \$2,500

Agency: Pharmaceutical Marketing Research Group

Role: Graduate student

Award dates: March 2013

Status: Funded

Title: Measuring and understanding health-related quality of life among adults with hemophilia.

Amount: \$1,000

Agency: University of Mississippi Graduate School

Role: Principal investigator

Award dates: January 2015

Status: Funded, ongoing

Title: Drug Information Association Student Travel Grant.

Amount: \$1,500

Agency: Drug Information Association

Role: Graduate student

Award dates: May 2015

Status: Funded

Title: Measuring and understanding health-related quality of life among adults with hemophilia.

Amount: \$500

Agency: Phi Kappa Phi Love of Learning award

Role: Principal investigator

Award dates: June 2015

Status: Funded, ongoing

Title: Burden of hemophilia in the national Medicaid population.

Amount: \$250,000

Agency: Novo Nordisk investigator initiated grants

Role: Co-investigator

Award dates: November 2015

Status: Submitted – under review

Title: Health utility and its predictors among mothers of children with hemophilia.

Amount: \$10,000

Agency: Bayer Hemophilia Awards Program – Caregiver award

Role: Co-investigator
Award dates: November 2014
Status: Unfunded

AWARDS:

- Outstanding Student Research Paper of the Year Award – Department of Pharmacy Administration – 2015.
 - Phi Kappa Phi Love of Learning Award – Phi Kappa Phi national - 2015.
 - Drug Information Association travel grant to attend and present a poster at the 50th annual international conference - 2015.
 - Poster finalist award at the 20th ISPOR annual international conference – ‘Impact of overweight and obesity on arthritis-attributable burden and health-related quality of life among adults with arthritis’ – 2015.
 - Pharmaceutical Marketing Research Group travel grant to attend and present a poster at the annual conference – 2014.
 - Phi Kappa Phi honor society inductee – 2013.
 - Rho Chi honor society inductee – 2013.
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TECHNICAL SKILLS:

- Possess a working knowledge of statistical software such as SAS, SPSS, STATA, MPlus and AMOS.
 - Understanding of research employing primary and secondary data techniques.
 - Decision Modeling using TreeAge, Microsoft Excel.
 - Proficient in questionnaire development, conducting focus groups, group interviews, and personal interviews.
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PROFESSIONAL CITIZENSHIP:

- Secretary, Chi chapter of the Rho Chi society, 2014-15.
 - President, UM-ISPOR student chapter, 2014-15.
 - Chair, Survey Committee, ISPOR Student Network, 2014-15.
 - President, Pharmaceutical Marketing Research Group (PMRG) student chapter, 2013-14.
 - Senator, Graduate Student Council, 2011-12.
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