A Comparison of Generic and Disease-Specific Health-Related Quality of Life Measures in Hemophilia Patients: An Online Study

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Abstract

Healthcare costs are constantly rising all over the world and healthcare technologies that can reduce costs and enhance health outcomes can potentially provide a solution to this global problem. Health outcomes research is performed nationally and internationally to evaluate the outcomes of new health interventions, technologies, and pharmaceuticals along with their cost and burden for society. Comparing the positive or negative effects of health technologies and medications is important for healthcare policy making and reimbursement strategies. One of the important methods to evaluate health outcomes is measurement of health related quality of life.

Health Related Quality of Life (HRQoL) is a concept that has important uses in research and comprehensive care of patients with chronic illnesses. HRQoL can be measured by using a classification system consisting of a set of attributes with multiple levels per attribute. One approach to evaluate HRQoL uses questionnaires which derive preference-based measures of health utility, based on a measurement system that allows patients to describe impacts on their health and assigns a utility score between 0 (death) and 1 (perfect health) to those descriptions. These questionnaires are called Multi Attribute Utility Instruments (MAUIs) and are the most widely used method to measure health utilities.

HRQoL can be measured with generic or disease-specific instruments. Generic instruments are those that are broadly applicable across types and severities of disease, across different health interventions, and across demographic and cultural subgroups. They are designed to summarize all concepts of HRQoL that apply to many different impairments, illnesses, patients and populations. Disease-specific measures are those that are designed to assess specific diagnostic groups or patient populations. These measures are particularly useful when there they are focused on clinically important changes.

It has been argued that generic instruments are insensitive to the health burdens imposed by hemophilia, and to precisely measure HRQoL of patients with a specific disease, we should use a targeted or a disease-specific instrument.

Disease-specific HRQoL utility assessments can be used for conducting Cost Utility Analysis (CUA) to allocate resources amongst patients with the same disease. On the other hand, in order to run CUA studies for resource allocation purposes across different diseases, we are dependent on generic utility measures.

The purpose of this study was to determine if a generic HRQoL assessment provides relevant utility values in hemophilia patients. We measured HRQoL of hemophilia patients using the EQ-5D-5L (a generic MAUI) and Haemo-QoL-A (a disease –specific descriptive health profile). Significant correlations were found between the utility scores measured by the generic tool EQ-5D-5L and the HRQoL scores measured by Haemo QoL A. Overall, the association between Haemo-QoL-A and EQ-5D-5L was stronger between the total scores as opposed to the domain scores. Associations with Haemo-QoL-A were strongest with the EQ-5D-5L utility scores that were generated using the direct conversion method as opposed to cross-walk valuations based on the extension of the older 3-level EQ-5D-3L utility scores.

It can be concluded that the utility scores associated with EQ-5D-5L are sufficiently correlated (correlation coefficient equal or greater than 0.7) with the HRQoL scores and thus, EQ-5D-5L can be used in hemophilia patient population for calculating the utilities required for resource allocation purposes.

Keywords: Health Related Quality of Life (HRQoL), Hemophilia, Cost Utility Analysis (CUA), Euro QoL (EQ-5D-5L), Quality Adjusted Life Years (QALY) and Haemo-Qol-A

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Chapter 1 – Introduction and Literature Review

Health Related Quality of Life (HRQoL) is a concept that has important uses in research and comprehensive care of the patients with chronic illnesses (Drotar, 1998). The inclusion of HRQoL in medical research plays an important role to address the patients' perspectives of their health conditions and the available treatments (Bullinger et al, 2009). HRQoL can be measured by standardized and validated Multi Attribute Utility Instruments (MAUI) that describe health states using a classification system consisting of a set of attributes with multiple levels per attribute (Torrence, 1996). According to McCaffrey et al (2016), generic MAUIs have two main elements: a set of items with multiple response categories covering different dimensions of HRQoL (descriptive system), and a MAUI developer-created scoring algorithm indicating the strength of preference for the health states defined by the instrument (quality weights). Development of the scoring algorithm associated with a MAUI is usually done by one of the two main methods: Time Trade Off (TTO) and Standard Gamble. Although there are different methods to design TTO studies all MAUI development studies that use TTO method to value health utility share the core element of trading length of life for quality of life (Attema et al, 2013). Standard gamble method is also based on the subjects' preference for measurement of individuals' preferences under uncertainty and to express the outcome of different therapeutic choices in utility values (Gafni, 1994).

As a generic HRQoL measure, a MAUI is directly applicable to policy and resource allocation because the scoring algorithm converts the vector of attribute scores into a single number called a utility, usually scored from 0= death to 1=optimal HRQoL.

With MAUIs, utilities can be measured over a patient population and multiplied by patient survival to create Quality-Adjusted Life Years (QALYs). Health utility is typically measured using generic quality of life measurement tools such as the EuroQol-5D-5L (EQ-5D-5L).

Generics vs. Disease Specific HRQoL Measurement

The comparison between the generic and the disease-specific HRQoL measures has been discussed in the literature for several decades. The generic measures are designed to be applicable to persons with a variety of health conditions including the general population which consists mainly of people with no disease or defined health conditions. Disease-specific measures on the other hand are designed for a defined clinical population with a focus on the most relevant health issues of that group (Bullinger et al, 2009). In a study of the generic and disease-specific tools, Patrick and Deyo (1989) emphasized research opportunities for both generic and disease-specific research. They also reviewed the technical requirements associated with each application along with the advantages and disadvantages of generic and disease-specific measurement tools. According to Patrick and Deyo (1989), although the advantages and disadvantages of generic and disease-specific measures primarily depend on the specific objective and application of the measurement in clinical research, practice, or policy analysis, and the technical requirements of validity, reliability, and generalizability apply to all of the tools.

Since the content validity depends on the extent to which and empirical measurement reflects the full domain relevant to a particular situation, disease-specific measures are expected to have better content validity compared to generic measures. Construct validity on the other hand refers to the extent to which results from a given instrument relate to other measures in a manner consistent with theoretical hypotheses. In other words, it means that an instrument measures what it purports to measure, and therefore relationships between that instrument and measures of other concepts and variables are consistent with expectations based on theory. Studying the correlation between the generic and disease-specific measures and their application for different disease types/severities helps in studying the construct validity of the measurement tools. Internal consistency is usually measured in both generic and disease-specific tools to study the reliability of them. The reliability of the disease-specific measures is expected to be lower than the generic ones because the specific questions about the diseases features are expected to vary more compared to the general questions asked in generic tools. In order to study the generalizability of the tools it is required to look at the comparability across the different diseases, conditions, and populations. This is an important advantage of the generic measurement tool that may be administered to different populations with different diseases. Wells et al (2011) also studied generic and disease-specific measurement tools and summarized the advantages associated with each tool. Aligned with the previous work of Patrick and Deyo, Wells notes that while generic measures have broad application across different types and severity of diseases, disease-specific measures are specifically designed to assess particular diseases or patient populations. Coons et al (2000) compared 7 different generic HRQoL measurement tools and studied validity, reliability and cultural and language adaptation associated with each measurement tool. They concluded that the choice will depend on a variety of factors including the characteristics of the population (e.g. age, health status, and language/culture) and the environment in which the measurement is undertaken (e.g. clinical trial, routine physician visit).

Generic HRQoL measures have been subject to criticism too. Papaionnou et al (2011) studied three generic HRQoL measurement tools in schizophrenia patient population and raised doubts about the use of generic measures of health in patients with schizophrenia. They reviewed thirty three studies that provided data on the validity of the generic instruments and they found the evidence for convergent validity and responsiveness mixed, with studies presenting contradictory results.

Choosing the appropriate HRQoL measurement tools is important in conducting research. Although validity, reliability, and generalizability are essential requirements for all HRQoL tools, there are other features that impact the selection of an appropriate tool for a particular application. Chen et al. (2005) state that the HRQoL tools in routine general practice need to be simple, fast to complete, easy to score, and provide data useful to clinicians. Also, they suggest a few other qualifications in the process of choosing HRQoL measurement tools. They recommend using tools with relevant domains that have been tested before in the relevant population, tools whose floor and ceiling effects have been evaluated. They also looked at the advantages and disadvantages of generic versus disease-specific tools. According to their study, the advantages of generic instruments include being applicable to all persons irrespective of their type or number of illness. In contrast, the disease-specific measures are more specific and sensitive. In terms of disadvantages, the generic tools may not be sensitive to some problems unique to a specific disease while disease-specific tools make comparison between different patient groups difficult. Furthermore, the results of disease specific instruments are difficult to interpret in persons with multiple diseases.

Table 1: Summary of the advantages and disadvantages of generic and disease-specific HRQoL measurement tools

	Advantages	**Disadvantages**
Generic HRQoL Measures	Broad application across different types and severity of diseases	Not sensitive to some problems unique to a specific disease
	Being applicable to all persons irrespective of their type or number of illnesses	Contradictory results in convergent validity and responsiveness of generic HRQoL tools in certain diseases e.g Schizophrenia
Disease-Specific HRQoL Measures	More specific and sensitive	Make comparison between different patient groups difficult
	Designed to assess particular diseases or patient populations	Difficult to interpret in persons with multiple diseases

Hemophilia-Specific HRQoL Measurement

Choosing an appropriate generic HRQoL tool for the hemophilia patient population is not an exception from the selection criteria discussed above. It has been argued that generic tools are insensitive to the health burdens imposed by hemophilia. The need for disease-specific QoL measures for hemophilia has been addressed in the literature (Whitehead and Ali (2010). According to Gringeri and Von Mackensen (2008), if we want to precisely measure HRQoL of patients with a specific disease, we should use a targeted or a disease-specific questionnaire. Moreover, disease-specific HRQoL can be used for conducting Cost Utility Analysis (CUA) to allocate resources amongst patients with the same disease. On the other hand, in order to run CUA studies for resource allocation purposes across different diseases, we are dependent on generic utility measures such as EQ-5D-5L. The relationship between hemophilia-specific HRQoL measures and generic utility measures has not been established. We hypothesized that the generic HRQoL measure, EQ-5D-5L, and a rigorously validated disease-specific measure, the Haemo-QoL-A, would be strongly correlated ($r > 0.70$, corresponding to approximately 50% shared variance). If the hypothesis is confirmed, this will establish that the EQ-5D-5L can be confidently used in CUA studies associated with adult hemophilia population. Because there are currently several EQ-5D-5L utility value sets, for this study we used the following set as our standard (euroqol.org, 2017), and as an exploratory aim, compared agreement between the leading crosswalk and direct evaluation value sets (Feng et al, 2016). The purpose of this study is to determine if a generic HRQoL assessment provides relevant utility values in hemophilia patients. We measured HRQoL of hemophilia patients using EQ-5D-5L (a generic tool) and Haemo-QoL-A (a disease –specific tool). Patient participation in the study was voluntary and the recruitment done through a patient support group. Rare Patient Voice, a patient support group, sent the link to participate in the study, or the hard copy of the questionnaires to the hemophilia patients registered at this group. According to Rare Patient Voice management, there are 292 hemophilia patients registered in this group and they are broadly distributed across the US. The study received completed study questionnaires from 153 hemophilia patients. The responses were analyzed using Excel and SPSS software and the results are discussed in detail.

Background and Significance of the Study

Hemophilia is a rare, X-linked, recessive congenital bleeding disorder caused by a deficiency or complete absence of coagulation factor VIII (FVIII) in hemophilia A, or factor IX (FIX) in hemophilia B. The incidence of Hemophilia is 1:10,000 of total births or 1:5,000 of male births (Knight, 2005), and represents around 400 hemophilia births in the United States each year. Based upon the coagulation level in plasma, hemophilia is classified as severe (factor level <1 IU/dl, <1% of normal) – representing approximately 60% of cases, moderate (factor level = 1-5 IU/dl, 1-5% of normal) – representing approximately 15% of cases, and mild (factor level = 6-49 IU/dl, 6-49% of normal) – representing approximately 25% of cases (National Hemophilia Foundation, 2016).

Severe and moderate patients need to be treated. They may bleed spontaneously or after minor injuries. These bleedings result in advanced degenerative joint damage over time and may require joint replacements (Knight, 2005). Treatment of hemophilia is based on replacement of the missing clotting factor and the administration of the factor can be through on-demand or prophylaxis treatment. However, the dose, frequency, and type of replacement vary depending not only to the severity of the disease and the patient status, but also on availability of the factor concentrates, reimbursement and the distribution system in the country/state in which the treatment is being given (Bullinger et al, 2009).

Hemophilia impacts the quality of life of patients through disability, pain, caregiving issues, and exposure to HIV virus and other blood-borne diseases (Escobar, 2010). About 50-80% of the treatment cost in hemophilia is related to the costs associated with coagulation factors (Knight, 2005). Since coagulation factors are expensive products and may be covered by health reimbursement systems, CUA studies are important to justify expenditures. Cost-utility analysis is useful to determine the priorities of resource allocation for hemophilia treatment (Colombo et al, 2011). Baseline HRQoL in hemophilia patients assessed with MAUIs, can be converted into QALYs for use in these cost-utility studies.

Specific Aims

The overall objective of this study was to evaluate the performance of the EQ-5D-5L in covering the health problems relevant to hemophilia. The specific aims of the study were to:

1. Evaluate the reliability of Haemo-QoL-A in hemophilia patients. Cronbach's α, which measures the internal consistency of items hypothesized to measure a single construct using the average inter-item correlations (Fayers and Machin, 2007), will be used to measure the reliability of the Haemo-QoL-A, overall and within domains.
2. To assess the construct validity of EQ-5D-5L in measuring HRQoL in US patients with hemophilia.

a. Construct validity is defined as the degree to which an instrument measures the construct that it is designed to measure (Fayers and Machin, 2007). For this study, responses on the Haemo-QOL-A were considered patients' "true" HRQoL, and the EQ-5D-5L results will be compared to this criterion in two ways: by assessing concurrent validity (measured by correlations between comparable domains assess by the questionnaires), and known group differences. Known group comparisons are tests of validity and a form of sensitivity or responsiveness assessment (Fayers and Machin, 2007).

b. Evaluate correlations between the total HRQoL score obtained from the total Haemo-QoL-A and the scores associated with total score and each domain of EQ-5D-5L.

c. Examine floor and ceiling effects in EQ-5D-5L to ensure that the instrument covers the full range of severity and allowed for discrimination among the subjects.

d. Evaluating the Content Validity of EQ-5D-5L relative to Haemo-QoL-A. Responses to the Haemo QoL questions that are expected to have similar responses in EQ-5D-5L will be tabulated and compared using correlation coefficients. Content validity will be supported if the Haemo-QoL-A answers correlate with the EQ-5D-5L questions that measure the similar concept with at least 25% shared variance.

3. Compare the two approaches of valuing the EQ-5D-5L (crosswalk approach and direct measurement approach) on aims 1-2.

Utility values described by HRQoL instruments are either directly measured using a valuation technique such as time trade off or standard gamble, or estimated using a mapping function from known utility values defined by another HRQoL instrument (Luo, 2015). EQ-5D-5L crosswalk value set is mapped from the known EQ-5D-3L values.

The first complete value set of EQ-5D-5L was created with the direct technique of time trade off by Feng et al (2016) in Canada. Agreement between the two valuation methods will be assessed. The aim is to determine if the utility score obtained from one approach correlates with more strongly with Haemo-QoL-A domain scores and have larger between group effect sizes compared to the other approach and if the floor and ceiling effects are smaller with one approach or the other. We evaluated the difference between the total health scores obtained from crosswalk approach and direct reference approach using ANOVA.

Chapter 2 – Research Design and Methodology

The high cost of hemophilia treatment is an economic burden and cost-utility studies help to identify cost effective treatments that provide better health outcomes. HRQoL tools that measure health utilities are essential for cost utility studies. The generic HRQoL measure, EQ-5D is widely used for CUA, and has been previously used in several cost utility studies in hemophilia. The instrument was initially designed in 1990 with 5 domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and each domain had only 3 response levels of no problems, some problems, and extreme problems. The newer version of the instrument, EQ-5D-5L, was released in 2009 with the same domains and with 5 response levels (euroqol.com, 2017). The validity of EQ-5D-5L for hemophilia studies needs to be established and therefore, the EQ-5D-5L is chosen for this study.

The need for development of a valid disease-specific HRQoL measure in hemophilia has been emphasized by Fischer et al (2003) and later by Remor et al (2004). Rentz et al (2008) worked on development and validation of Heamo-QoL-A as disease-specific HRQoL measures designed to address problems relevant to hemophilia and reflect the multi-dimensional nature of the disease. The Haemo-QoL-A is used for this study because it has been shown to have discriminatory power for disease severity and its validity has been evaluated in independent research studies (Rentz, 2008).

Sample and Inclusion Criteria:

The target population for this study is adult Hemophilia A patients registered in Rare Patient Voice patient support group. Hemophilia patients are almost entirely male individuals. Hemophilia A is characterized by deficiency in factor VIII clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing (Konkle et al, 2011). Inclusion criteria are: Diagnosis of Hemophilia A (mild, moderate, and severe cases are included), ability to read and write English, 18 years of age or older.

Sample Size

The sample size was based on Rare Patient Voice data. According to Rare Patient Voice (2017) the total number of the Hemophilia patients registered in this patient support group was 292 patients who are broadly distributed across USA and based on their experience, 100 patients were expected to participate in the study. The number includes mild, moderate, and severe hemophilia cases. Severe hemophilia patients represent 60% of total hemophilia cases (National Hemophilia Foundation, 2016). We assumed that the severity distribution amongst patients in the Rare Patient Voice database was similar to national rates. We expected that about 30-35% of hemophilia patients (mild, moderate and severe cases) will participate in this study.

Patient Recruitment

The patients were recruited by Rare Patient Voice. The patients were completely anonymous to the researchers. The link for the study questionnaires were sent to the registered hemophilia patients by Rare Patient Voice via the Qualtrics platform. Rare Patient Voice is a patient support group that is specialized in healthcare market research and provides patients and caregivers with rare diseases an opportunity to voice their opinions through surveys and interviews to improve medical products and services. (rarepatientvoice.com, 2017).153 patients completed the questionnaires. The researchers could only access the questionnaire results stored in Qualtrics.

The patients were informed about the study in an email from the Rare Patient Voice team (Appendix 1), and interested patients were instructed to access the link to the Qualtrics website to complete the study questionnaires.

Missing items for the Heamo-QoL- A were handled in accordance with the Scoring Manual for Haemo-QoL-A (Appendix 2). For the subscale analyses, if < 50% of the scale items were missing, the mean scale score of the items present were used to impute a score for the missing items. If > 50% of the items were missing, no scale score was calculated, the subscale score was considered missing. If a subscale score is missing, the Haemo-QoL-A total score cannot be calculated. There was no missing data for the EQ-5D-5L.

HRQoL Measures

Generic Measure

We used EQ-5D-5L as a generic MAUI and a patient-reported outcomes (PRO) instrument to determine the quality of life in hemophilia patients. Using PRO as the instrument to measure HRQoL provided us with some advantages. The first advantage was that we received the reports directly from the patients and captured their perspective about how they function or feel in relation to their current health status. Second, the results were without any interpretation by physicians or pharmaceutical manufacturers or third party payers. The patient reported outcomes and the importance of including the patients' opinions in decision making process has been discussed in the recent literature. It is emphasized in some available literature that encouraging patients to take responsibility for their health was the best way to ensure health system sustainability (Smith et al, 2009). Xu et al (2017) used EQ-5D-5L to study the relationship between shared decision-making and health-related quality of life. They found direct relationship between HRQoL and shared decision-making. According to their study, the patients partially involved in decision-making had higher HRQoL scores than the other involvement groups, even when adjusting for demographic, socioeconomic and health-related factors.

EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal (Health Policy, 1990). EQ-5D-5L is applicable to a wide range of health conditions and treatments and is known as a tool suited for use in clinics and in face-to-face interviews. It provides a simple descriptive profile and a single index value for health status that can be used in clinical and economic evaluation of health care. The EQ-5D-5L descriptive system comprises the 5 domains of mobility, self-care, usual activities, pain/discomfort, and anxiety depression. Responses are recorded at 5 levels (no problems, slight problems, moderate problems, severe problems, unable/extreme problems) for each dimension. The instrument has been developed from the older version EQ-5D-3L that also has the same domains but it describes the problems in each domain into 3 levels (no problems, some/moderate problems, and unable/extreme problems) rather than 5 levels in newer EQ-5D-5L.

According to euroqol.com (2017) the EQ-5D-5L was introduced to improve sensitivity and to reduce the ceiling effects compared to the older version EQ-5D-3L which had only three response levels.

There is also a Visual Analogue Scale (EQ VAS) designed in the tool that records the respondents' self-rated health on a vertical, visual analogue scale ranging from the "Best Imaginable" or score 100 to the "Worst Imaginable" health state or score 0. (Euroqol.com, 2015).

The EQ-5D-5L is short and written in straight forward language (Table 2).

Table 2: Example of an EQ-5D-5L questionnaire completed by two patients (Patient ID#1001 and Patient ID#1002)

Variable Name	**Self-Care**	**Activity**	**Mobility**	**Pain**	**Anxiety**	**Sate**	**EQ-VAS**
Variable Description	1 = No Problems 2 = Slight Problems 3 = Moderate Problems 4 = Severe Problems 5 = Unable to 9 = Missing Value	1 = No Problems 2 = Slight Problems 3 = Moderate Problems 4 = Severe Problems 5 = Unable to 9 = Missing Value	1 = No Problems 2 = Slight Problems 3 = Moderate Problems 4 = Severe Problems 5 = Unable to 9 = Missing Value	1 = No Pain 2 = Slight Pain 3 = Moderate Pain 4 = Severe Pain 5 = Extreme Pain 9 = Missing Value	1 = Not Anxious 2 = Slightly Anxious 3 = Moderately Anxious 4 = Severely Anxious 5 = Extremely Anxious 9 = Missing Value	5 Digit Code from EQ-5D-5L	999 - Missing Value
Patient ID# 1001	1	1	1	1	1	11111	100
Patient ID# 1002	3	3	3	3	3	33333	50

A health utility value index is used to convert each patient's five digit EQ-5D-5L code to a single health state between 0 and 1 at which 1 is perfect health and 0 is death.

Every set of the 5 digits represents a unique health state. The actual utility value of each 5 digit score (for example for 11111 and 33333) is based on the valuation index set.

There are two main valuation techniques to convert the health scores to the health states. According to Luo et al (2015) the health state values can either be measured using a direct valuation technique such as Time Trade Off (TTO), or they can be estimated using a mapping function from a known set of utility values defined by another HRQoL measure. The available EQ-5D-5L "crosswalk" value set for United States in Euro-QoL website (2017) was created from the currently available EQ-5D-3L value set using the mapping technique.(Euroqol.org, 2017) According to euroqol.com (2017) "crosswalk was based on a response mapping approach that estimated the relationship between responses to the EQ-5D-3L ('3L') and EQ-5D-5L ('5L') descriptive systems, and subsequently established a link to the 3L value sets." Xie et al (2016) set up a country specific EQ-5D-5L value set for Canada using the direct method of TTO with a sample of 1209 patients and classified these patients into 86 health states.

Disease-Specific Measure

Haemo-QoL-A is a hemophilia-specific HRQoL descriptive health profile designed for adult hemophilia patients. It was designed for adults 18 years of age and older and includes 41 items in 6 domains of physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns. Rentz et al (2008) evaluated the content validity of the Haemo-QoL-A by examining its correlations with a generic HRQoL measure, Health Assessment Questionnaire – Functional Disability Index

(HAQ-FDI) and the Overall Treatment Effect (OTE) scale in a sample of 221 patients. Using Cronbach's α at baseline and week 4 of their study they found the Haemo-QoL-A to be a reliable measures of HRQoL for hemophilia patients. Rentz 's study reported a Cronbach's α of 0.95 for the total overall score of the Haemo-QoL-A, which indicates high reliability, since a Cronbach's α of ≥0.70 is generally considered sufficient instrument reliability for comparing groups.

Responses to Haemo-QoL-A questions are recorded in 6 levels on a frequency scale: none of the time, a little of the time, some of the time, a good bit of the time, most of the time, and all of the time. Responses are then coded to provide overall and domain-specific health scores. Domain scores are calculated by taking the mean of the items in each domain and transforming them to 0 (none or absent) to 100 (very severe) scale. The scoring manual of Haemo-QoL-A is provided in Appendix 2.

Young et al (2012) also validated Haemo-QoL-A in a Canadian French speaking population by examining its correlation with the generic SF36 in a sample of 22 adult men with hemophilia, 19 boys with hemophilia and 19 parents. The Haemo-QoL-A had good test retest reproducibility that exceeded 0.78 in all domains and a generally good concurrent validity with total and subscale scores across the different domains with SF-36 (Rentz et al, 2008). This tool also can discriminate adult hemophilia patients by severity of disease and by treatment protocols (On demand vs. prophylaxis). Because the Haemo-QoL-A has discriminatory power for disease severity and its validity has been evaluated in independent research studies, it was selected for this dissertation.

Informed Consent

The study subjects are adult patients over 18 years of age. The IRB approved this dissertation project as an exempt study since the questionnaire did not include sensitive questions that these individuals wouldn't encounter in their everyday life, and the patients' identities would not be revealed to the researcher. Choosing to access the Qualtrics link to the study questionnaires was voluntary, and there was no separate consent form.

Study Setting and Procedures:

The study was implemented in 3 steps:

Step 1: Patient Recruitment. The patients in the Rare Voice hemophilia support group were notified about the study and given access to the study questionnaires via a link to the study's Qualtrics website.

Step 2: Interested patients completed the study questionnaire via the link to the Qualtrics online platform.

Step 3: Data were exported from Qualtrics to the investigator for analysis.

Data Collection

The study questionnaire consisted of the EQ-5D-5L, the EQ-5D VAS, the Haemo-QoL-A HRQoL descriptive health profile, a qualitative item - "name the most important determinant of your quality of life", and two additional health questions: factor level and disease severity. The questionnaires were self-administered. No data was required in respect with the treatment protocol used by participants.

Qualtrics online platform provided easy and reliable access for the participants (qualtrics.com, 2017).

Data Analysis

1. Validity: We used statistical analysis to study the validity of EQ-5D-5L in measuring HRQoL in hemophilia patient population.
    a) Construct validity was studied to find if the different measures of HRQoL for Hemophilia patients in the two measurement tools are in fact related. Construct Validity is defined as the degree to which an instrument measures the construct that it is designed to measure (Fayers and Machin, 2007). Construct validity is determined in a number ways such as concurrent validity and known-groups validation. In this study the concurrent criterion validity and known group differences will be examined using Pearson's Correlation Coefficient, floor and ceiling effects, and ANOVA methods.
    b) The concurrent validity will be supported if EQ-5D-5L score is strongly correlated (> 0.70) with the domains of Haemo-QoL-A, physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns. Rentz et al (2008) arbitrarily chose correlation coefficient threshold of > 0.4 for demonstrating construct validity. Criterion validity determines the agreement to a true value (Fayers and Machin, 2007). In this study, Haemo-QoL-A is considered the criterion or true HRQoL state. The correlation among EQ-5D-5L average

scores and utility scores with overall HRQoL score and the scores of each Haemo-QoL-A domain were studied. The construct validity of EQ-5D-5L for use in the hemophilia patient population will be supported if the correlation coefficient value between utility scores and total Haemo-QoL-A scores is greater than 0.4. The two measurement tools will be considered strongly correlated if the correlation coefficient value is equal or greater than 0.7. According to Mukaka (2012) a correlation coefficient value between 0.5 and 0.7 is considered evidence that two instruments used in medical research are moderately correlated, and a value between 0.3 and 0.5 is considered evidence that the instruments are weakly correlated. Any value lower than 0.3 is considered negligible.

We hypothesized that the correlation between the utility score calculated with both direct and crosswalk methods for the EQ-5D-5L and the total score of the Haemo-QoL-A will be moderate to strong. We also hypothesized that the similar domains in each instrument will be moderately to strongly correlated.

c) Floor and ceiling effect: In order to study the full range of scores associated with Haemo-QoL-A and EQ-5D-5L items, and make sure that the items discriminated well at very low and at very high levels of the traits being measured we looked at the proportion of the responders who chose the highest possible score (ceiling effect) and the proportion of the responders who chose the lowest possible score (floor effect). According to Petrillo et al (2015) at least 5% but not more than 40% selecting the extreme categories is considered acceptable in patient-reported outcomes (PRO) studies. We propose to use 20% as the threshold as for floor and ceiling effect to study if the instrument is able to discriminate among the disease severity levels, cover the full range of severity in patients, and allow for discrimination between the subjects (Fayers and Machin, 2007). Floor effect will be considered present if 20% of the responders select the worst score. Ceiling Effect will be considered present if 20% of the responders select the highest score.

Known-group validation is used based on the assumption that the greater the severity of hemophilia, the worse patients' HRQoL. Therefore, the instruments should be sensitive to differences in the HRQoL reported by patients with mild, moderate, and severe hemophilia. As another method to evaluate the construct validity of EQ-5D-5L to be used for hemophilia patients we looked at the ability of EQ-5D-5L domain scores and utility scores and Haemo-QoL-A domains scores and total score to discriminate hemophilia patients based on the severity of the disease (mild, moderate, and severe). We use ANOVA methods to compare the utility scores measured by EQ-5D-5L. ANOVA model included severity - mild, moderate, and severe hemophilia disease states - as the independent variable and HRQoL subscales, total score, and EQ-VAS total score as dependent variables. The objective is to find out if the HRQoL utility scores can discriminate the patients with Mild, Moderate, and Severe hemophilia. We studied the P value of ANOVAs, and the relative validity of the two measures was compared based on the magnitude of the ratio of their F-statistics (Rentz et al, 2008).

   d) Content Validity of EQ-5D-5L relative to Haemo-QoL-A was evaluated by studying the correlation between the mean scores of each EQ-5D-5L domains and the mean scores associated with the questions that should have similar answers on the Haemo-QoL-A. All 41 questions of the Haemo-QoL-A were reviewed and the questions that were expected to have similar answers with any of the five EQ-5D-5L questions were identified and the correlation between the mean scores of each set of questions with the average score of the corresponding question in EQ-5D-5L instrument was calculated. See Appendix 3.

2. Internal Consistency Reliability associated with Haemo-QoL-A scores was obtained for each domain: physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns. Internal consistency is based on the correlations between the different items in the same test. It measures whether several items that propose to measure the same general construct produce similar scores. Since we are trying to evaluate and compare the different items that measure the domains of HRQoL in Hemophilia patients we use Cronbach's α as our method for measuring internal consistency within each domain and overall.

   The resulting α coefficient of reliability ranges from 0 to 1. According to Goforth (2015) If all of the scale items are entirely independent from one another (i.e., are not correlated or share no covariance), then $\alpha = 0$; and, if all of the items have high covariance, then α will approach 1 as the number of items in the scale approaches infinity. As a result, the higher α coefficient is indicative of a higher probably to measure the same underlying concept. Although there is no standard threshold for Cronbach's α to be considered for evaluating internal consistency, it is generally accepted that a Cronbach's α value greater than 0.7 is usually acceptable and a Cronbach's α value lower than 0.5 is considered unacceptable. Rentz et al (2008) considered Cronbach's α greater than 0.7 sufficient for group-level internal comparisons in their study of Haemo-QoL-A.

3. The crosswalk value set and direct value set will be used in order to convert the value scores of the hemophilia patient sample to utilities. The distributions of the value-based and mapped EQ-5D-5L utilities will be compared. Luo et al (2015) have shown that direct method utility scores are generally higher than the crosswalk scores, and hence may increase the possibility of ceiling effect in this method. However, in their study the magnitude of the effect was small and the corresponding 90% CI fell within the pre-specified equivalence margin. The mean scores associated with each conversion method and the standard deviations of the two conversion approaches will be compared for the entire hemophilia sample. We will use scatter plot and comparison to the 45 degree line of perfect agreement to compare the results associated with each approach. We set the x axis and y axis of the scatter plot to the range of 0 to 1 for the 45 degree line to serve as the identify line in our analysis. The equivalence of the two approaches will be assessed by comparing 90% confidence interval (CIs) of the differences with the

predefined equivalence margin of 0.05. This is consistent with the previous research (Luo, 2015).

We use Time Trade off-Derived Canada EQ-5D-5L Value set to convert the obtained score to utilities. The validity of this method has been evaluated and confirmed by Xie et al (2016). We will also use the US crosswalk Value Set that was developed by the EQ5D team to convert the scores to utilities and we will compare the results with the Canada Value Set. The strength of the correlation between each utility conversion method and Haemo-QoL-A scores determines if one method provides better correlation and hence, be preferred to be used in hemophilia patient population. We will use correlation coefficients to find out which conversion method yields scores that are more strongly correlated to Haemo-QoL-A and EQ5D VAS results.

Excel Data Analysis tool pack (XLSTAT) was used in order to analyze the data and provide the statistical information. XLSTAT is a user-friendly statistical software for Microsoft Excel. It is the most complete and widely used data analysis add-on for Excel.

Impacts of Findings and Relevance to Social and Administrative Pharmacy:

Comparison between a disease-specific instrument validated to describe hemophilia patient HRQoL and a widely used generic instrument that provides health utilities will establish if we can confidently use this generic HRQoL tool for administrative and social evaluations for hemophilia patients. An important administrative consideration with respect to hemophilia is the economic burden of disease and resource allocation. Cost-utility studies that include QALY evaluations show the overall HRQoL and the cost associated with improvement. An important advantage of using valid and reliable generic HRQoL tools is the ability to compare the cost and burden of hemophilia with the cost and burden of the other diseases and to facilitate resource allocation decisions along with the priority setting among the different diseases. As a result, these methods are used in determining outcome based resource allocation policies. Our study contributes in this social and economic context by evaluating the pragmatic validity of a generic measure that can potentially be used in future cost-utility studies.

Chapter 3 – Study Results

Study Subjects

A total of 156 persons (142 men and 14 women) responded to the Rare Patient Voice study invitation and completed a survey. Six patients skipped one item and one patient skipped two item on the Haemo-QoL-A, and all these questionnaires could be fully scored. Three patients did not meet age eligibility criteria, two were under 18 years old and one did not report their age. These patients were excluded, leaving a final sample for analysis of 153 patients (139 male and 14 female) who completed online questionnaires for the EQ-5D-5L, EQ-VAS, and Haemo-QoL-A on Qualtrics online platform. A summary of the demographic data is shown in Table 3:

Table 3: Clinical and Demographic Information

Clinical and Demographic information		
		Total (n=153)
Age	Mean (SD)	37.1 (1.2)
	Median	33
	Range	18-73
Gender	Male (%)	139 (91%)
	Female (%)	14 (9%)
Hemophilia Severity	Severe [FVIII:C < 1%]	97 (64%)
	Moderate [FVIII:C 1-5%]	34 (22%)
	Mild [FVIII:C > 5%]	21 (14%)

Internal Consistency Analysis (Aim 1)

Cronbach's α was used to assess the internal consistency reliability of the Haemo-QoL-A, overall and for each subscale: physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns.

Table 4 shows the results associated with determining Cronbach's α for each of the domains of Haemo-QoL-A.

Table 4: Internal Consistency Reliability Assessed by Cronbach's α (n=153)

Haemo-QoL-A Domain	Number of Items	Cronbach's α
Physical Functioning	9	0.88
Role Functioning	11	0.92
Worry	5	0.87
Consequences of Bleeding	7	0.88
Emotional Impact	6	0.86
Treatment Concern	3	0.74
Total Haemo-QoL-A Score	41	0.97

Internal consistency is considered good to excellent if Cronbach's α is between 0.75-0.95 (Rentz et al, 2008). Internal consistency in our study was good to excellent in all domains of Haemo-QoL-A except from Treatment Concerns domain (Cronbach's α of 0.74). This is consistent with the previous study done by Rentz et al (2008) on Haemo QoL A.

The results show high reliability for the total Haemo-QoL-A and in each domain (Cronbach's α >0.7) with a range of 0.74 to 0.9. Although Cronbach's α is between 0.75-0.95 indicates good to excellent internal consistency, Rentz et al (2008) also used

Cronbach's α of 0.7 as the threshold for adequate reliability for an instrument to compare groups. It is notable that Treatment Concerns, the smallest subscale consisting of only 3 items, shows sufficient internal consistency (Cronbach's α of 0.74). Overall, Haemo-QoL-A shows very good internal consistency reliability in each domain and in total Haemo-QoL-A score.

Convergent Validity (Aim 2)

We conducted a convergent validity analysis to investigate the construct validity of the EQ-5D-5L for use in the hemophilia patient population. Since the Haemo-QoL-A was specifically designed to describe HRQoL in hemophilia patients, the degree of correlation between Haemo-QoL-A and EQ-5D-5L scores was expected to reflect how well the EQ-5D-5L evaluates HRQoL in hemophilia patients.

Table 5 shows the correlation between each domain of the EQ-5D-5L and Haemo-QoL-A along with the correlation between the total score obtained from Haemo-QoL-A and utilities for the EQ-5D-5L calculated from schedules devised by Cross Walk and Direct methods of utility calculation. The correlation between the EQ-VAS score and Haemo-QoL-A total score is also shown in the table.

Table 5: Pearson Correlations between EQ-5D-5L and Haemo-QoL-A – overall, domain and utility scores

	EQ-5D-5L Domains Scores					**EQ-5D-5L Utilities**		
Haemo Qol A Domains Scores	**Mobility (1-5)**	**Self-Care (1-5)**	**Usual Activities (1-5)**	**Pain (1-5)**	**Anxiety/ Depression (1-5)**	**Overall Score Cross Walk (0-1)**	**Overall Score Direct (0-1)**	**EQ VAS (0-100)**
Physical Functioning (0-5)	0.73	0.53	0.74	0.71	0.38	0.73	0.75	NA
Role Functioning (0-5)	0.51	0.53	0.62	0.58	0.47	0.67	0.69	
Worry (0-5)	0.52	0.48	0.58	0.50	0.51	0.64	0.67	
Consequences of Bleeding (0-5)	0.35	0.41	0.43	0.38	0.38	0.46	0.50	
Emotional Impact (0-5)	0.40	0.43	0.59	0.41	0.55	0.60	0.60	
Treatment Concern (0-5)	0.32	0.26	0.34	0.33	0.37	0.43	0.43	
Haemo QoL A Total (0-30)	0.56	0.52	0.65	0.57	0.53	0.70	0.72	0.56

Note: EQ-5D-5L scores were recoded to align with the Haemo-QoL-A so that a higher number represents better quality of life on both instruments. Convergent validity is supported when the items that are expected to be related show a stronger correlation.

The strongest correlations between the items were observed between EQ-5D-5L Usual Activities, Mobility, and Pain domains with Physical Functioning domain in Haemo-QoL-A. It was hypothesized that a strong correlation would exist between these domains as physical functioning may impact, or be impacted by, mobility, usual activities, and pain. The weakest correlation is seen between Treatment Concerns in the Haemo-QoL-A and all five domains of EQ-5D-5L. Our study results indicate that the EQ-5D-5L ratings do not reflect the treatment concerns of hemophilia patients.

To establish the construct validity of the EQ-5D-5L in hemophilia patients we expected to find strong correlation between this instrument and the Haemo-QoL-A. We used correlation coefficients to quantify the relationship between the two instruments.

According to Hays and Hayashi (1990), item convergence is supported with an item correlation coefficient of 0.4 or above with the scale it is hypothesized to correlate. Rentz (2008) also used a correlation coefficient threshold of 0.4 to determine the correlation between Haemo-QoL-A and SF-36 as a generic HRQoL measurement tool. Using this criterion, the construct validity of the EQ-5D-5L utility scores for assessing the HRQoL of hemophilia patients is supported for every domain including treatment concerns.

Similar domains in EQ-5D-5L and Haemo-QoL-A were expected to have moderate to strong correlations:

- Physical functioning and mobility are expected to be strongly correlated.
- Role functioning and Usual Activities are expected to be strongly correlated.
- Emotional impact or Worry and Anxiety/Depression are also expected to be strongly correlated.
- Consequences of Bleeding and Pain are also expected to be strongly correlated.

Also, it was expected to find a weak correlation between certain domains:

- Treatment Concerns and Mobility are not expected to be strongly correlated.

In addition, the total score obtained from Haemo-QoL-A is expected to be strongly correlated with utility scores obtained by using EQ-5D-5L.

Correlations between the domain scores of EQ-5D-5L and Haemo-QoL-A shows that in four similar domains there is a strong correlation of 0.7 ($P<0.01$ in all cases). EQ-5D-5L domains of mobility, usual activities, and pain have strong correlations with the Haemo-QoL-A physical functioning domain. However, the correlation between role functioning, worry, and emotional impact is within the moderate correlation range (R =

0.4 – 0.7). Consequences of bleeding domain is weakly related with mobility, pain, and anxiety/depression. Lastly, the treatment concern domain is weakly correlated with all EQ-5D-5L domains which suggests that unlike the Haemo-QoL-A, EQ-5D-5L may not reflect the impact of treatment concerns on the HRQoL of hemophilia patients.

Correlations between Haemo-QoL-A total scores and EQ-5D-5L utility scores utility scores calculated with Cross Walk and Direct methods are strong and statistically significant (P<0.01 for both Cross Walk and Direct methods). EQ VAS scores are moderately correlated (R = 0.56, P<0.01) with Haemo-QoL-A total scores.

Floor and Ceiling Effects (Aim 2)

Table 6 shows the percentage of the responses at the lowest score and the percentage of the responses at the highest score to assess floor and ceiling effects in this study.

Table 6: Haemo-QoL-A Mean HRQoL Score Distributional Characteristics, Floor and Ceiling Effects (n=153)

Haemo-QoL-A Domains Transformed Scores (0-100)	Mean	SD	Median	Floor (%)	Ceiling (%)
Physical Functioning	63.86	20.95	64.44	8.42%	23.97%
Role Functioning	72.62	19.78	76.36	5.29%	36.66%
Worry	69.36	26.92	76.00	9.93%	39.61%
Consequences of Bleeding	72.18	19.78	74.29	3.64%	34.17%
Emotional Impact	70.96	21.65	76.67	4.03%	32.79%
Treatment Concern	69.28	22.46	73.33	6.32%	32.46%
Total Haemo-QoL-A	69.71	18.58	75.02	6.14%	32.82%

Note: The higher scores mean better HRQoL or less impairment. The Ceiling% represent the percentage of the cases with the best HRQoL or the lowest impairment. The Floor% represent the worst HRQoL or the highest impairment.

The ceiling effect occurs when a high the proportion of subjects that choose the maximum score. The floor effect occurs when a high proportion of the study subjects choose the minimum possible score. In our analysis of Haemo-QoL-A, the lowest possible item score –which represents the worse HRQoL - was seen in 3.6 - 9.9% of subjects and the highest item score – which represents the better HRQoL - was seen in 23.9–31.6% of subjects. No items demonstrated high floor or ceiling effects (i.e. 60% of subjects with the lowest and highest score respectively). In other words, more patients report a better HRQoL.

Table 7 also shows floor and ceiling effects in the original 1-5 rating EQ-5D-5L responses.

Table 7: EQ-5D-5L Mean HRQoL Score Distributional Characteristics, Floor and Ceiling Effects (n=153)

EQ-5D-5L Domain Ratings (1-5)	**Mean**	**SD**	**Median**	**Ceiling (%)**	**Floor (%)**
Mobility	2.19	1.02	2	1.96%	29.41%
Self-Care	1.29	0.58	1	0.00%	77.12%
Usual Activities	1.88	0.88	2	0.00%	41.18%
Pain	2.61	0.93	3	4.58%	8.50%
Anxiety/Depression	1.99	1.08	2	3.27%	40.52%
Total EQ-5D-5L	1.99	1.01	2	1.96%	39.35%

Note: The higher scores mean worse HRQoL or more impairment. The Ceiling% represent the percentage of the cases with the worst HRQoL or the highest impairment. The Floor% represent the best HRQoL or the lowest impairment.

The percentage of the lowest and the highest value responses for each of the 5 EQ-5D-5L questions – which represents each domain of the instrument - were calculated to determine the floor and ceiling effects. The highest score in EQ-5D-5L represents the lowest quality of life and the lowest score represents the best quality of life. In the ceiling analysis, 0% to 4.58% of the participants reported the maximum domain scores, the worst HRQoL in EQ-5D-5L. In the floor effect analysis, 8.5% to 77.12% of the participants reported the minimum possible score that represents the best HRQoL. In other words, more patients reported the better HRQoL.This inconsistent with the floor and ceiling effect observed in Haemo-QoL-A.

Ceiling effect was observed in one item (Self Care) where more than 60% of all the subjects were with the highest score.

In Table 8 floor and ceiling effects of the severe hemophilia cases in the research are shown. When we just look at the severe hemophilia cases, the high ceiling effect disappears for the EQ-5D-5L.

Table 8: EQ-5D-5L Mean HRQoL Score Distributional Characteristics for Severe Hemophilia Patients, Floor Effect and Ceiling Effect (n=97)

EQ-5D-5L Domains Transformed Scores (0-100)	**Floor (%)**	**Ceiling (%)**
Mobility	1.96%	13.73%
Self-Care	0.00%	47.71%
Usual Activities	0.00%	23.53%
Pain	3.92%	5.23%
Anxiety/Depression	2.61%	30.07%
Total EQ-5D-5L	1.70%	24.05%

We looked at floor and ceiling effect to make sure that the instrument covers the full range of severity and allowed for discrimination among the patients. In the literature there are different floor and ceiling effect thresholds considered to be acceptable for different patient-reported outcomes measurement tools. Rentz et al (2008) determined 60% as the threshold for high floor and ceiling effect to assess Haemo-QoL-A.

In the analysis of EQ-5D-5L in severe hemophilia cases, the lowest possible item score was seen in 0.0 – 3.9% of subjects and the highest possible item score was seen in 5.2–47.7% of subjects. Study of floor and ceiling effect in severe hemophilia cases, the proportion of the maximum scores (ceiling effect) was lower in comparison with the total number of mild, moderate, and severe cases.

Known Group Validation (Aim 2)

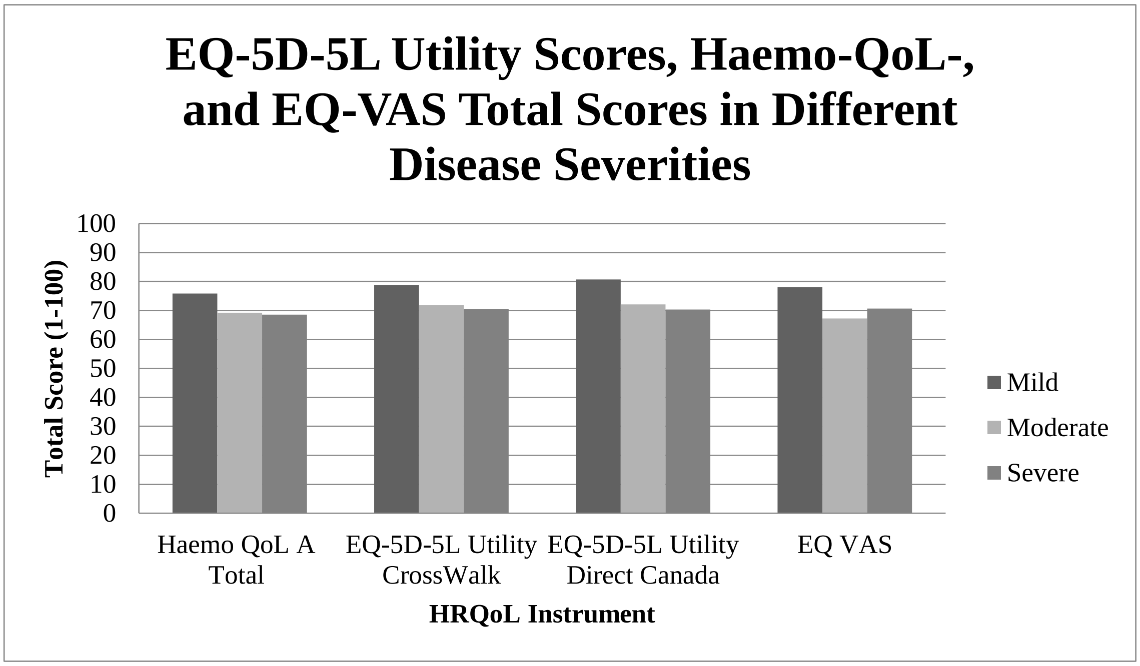
In order to evaluate the construct validity of the EQ-5D-5L relative to the Haemo-QoL-A in hemophilia patients we compared HRQoL scores across hemophilia severity subgroups. We looked at the average scores in each domain of EQ-5D-5L, the average utility scores calculated with direct conversion method and crosswalk conversion method, and Haemo-QoL-A average total scores separately to find out if the average scores are significantly different for mild, moderate, and severe hemophilia cases. We also looked at the average scores in each domain of EQ-5D-5L and Haemo-QoL-A in mild, moderate, and severe hemophilia patients groups to study the discrimination pattern in each domain for each disease severity.

We transformed EQ-5D-5L responses on to a 1 to 100 scale in order to align the scores with Haemo-QoL-A results and have higher scores indicate better quality of life.

Mean Haemo-QoL-A total scores, utility scores of EQ-5D-5L calculated with cross walk method and direct methods, and EQ-VAS scores for each hemophilia severity group are shown in figures below. ANOVA was used to compare reported levels HRQoL across disease severity groups and evaluate how well each measurement tool the discriminated between severity groups.

Figure 1 shows the EQ-5D-5L utility scores obtained with the direct method and crosswalk method and converted to 1-100 scale along with the total Haemo-QoL-A score and EQ-VAS score in severe, moderate, and mild hemophilia subjects.

Figure 1: Comparison of the mean total scores for Haemo-QoL-A, EQ-5D-5L crosswalk



values, EQ-5D-5L Direct values, and EQ-5D-VAS in patients with Mild, Moderate, and Severe Hemophilia

In Table 9 the researcher analyzed total scores of the EQ-5D-5D and Haemo-QoL-A using ANOVA to determine the association of each domain with the severity of hemophilia.

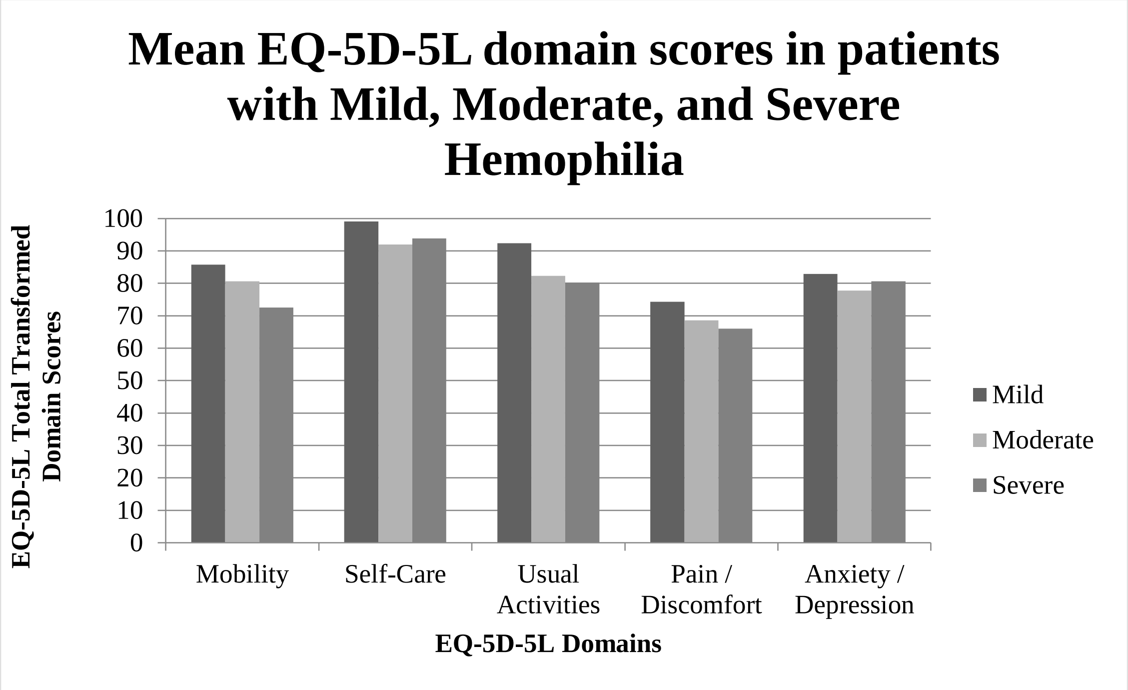
Table 9: ANOVA analysis of Haemo-QoL-A total score and EQ-5D-5L utility scores calculated by Cross Walk and Direct methods (n=153)

	F	*P-Value*	*F-Critical*
EQ-5D-5L Cross Walk	2.11	0.12	3.06
EQ-5D-5L Direct Canada	2.63	0.08	3.06
EQ-VAS	1.78	0.17	3.06
Haemo-QoL-A	1.33	0.27	3.06

ANOVA showed that the direct conversion EQ-5D-5L utilities have the highest F-statistic to discriminate among the disease severities, but none of the instruments significantly distinguished amongst the 3 severity groups.

Figure 2 shows the scores associated with each domain of EQ-5D-5L converted to 1-100 scale and separated by the disease severity of the subjects.

Figure 2: Mean EQ-5D-5L adjusted scores in each domain for patients with Mild, Moderate, and Severe Hemophilia



The mean adjusted domain scores (1-100) based on 1-5 problem rating in each domain of EQ-5D-5L and Haemo QoL A evaluated to determine if the instruments can discriminate the subjects with mild, moderate, and severe hemophilia.

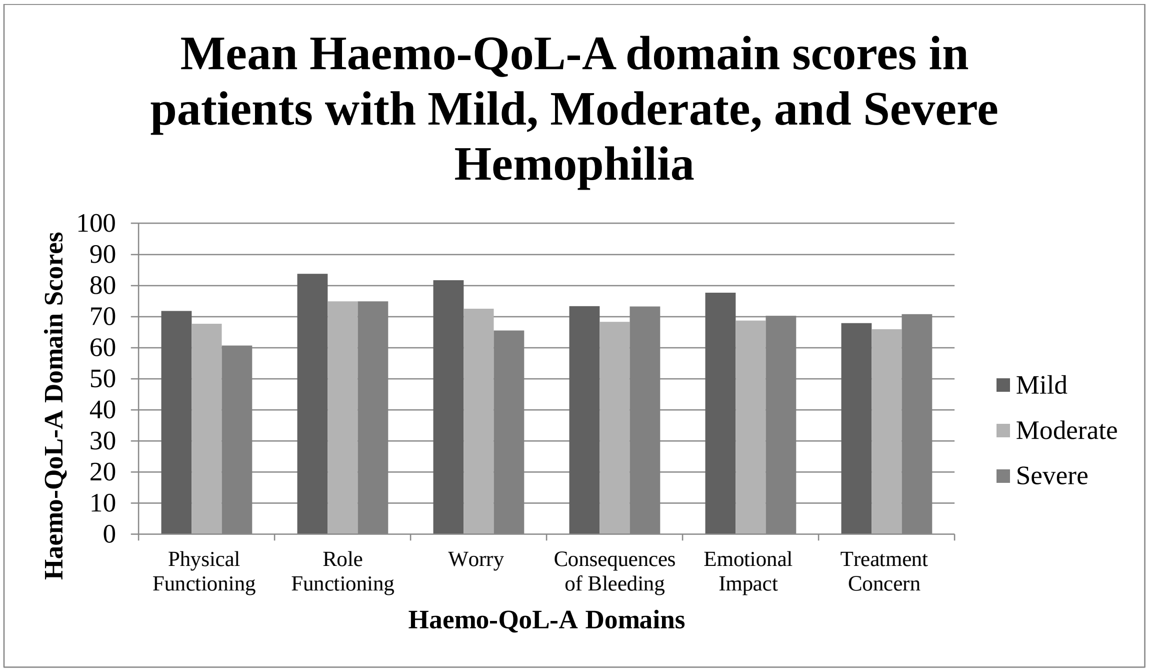
Table 10 shows that average EQ-5D-5L adjusted domain scores differed among disease severity groups and it is statistically significant in Mobility and Usual Care domains. Mobility and Usual Activities are the domains that are strongly associated with the disease severity (F>3.06, P<0.01).

Table 10: ANOVA Results of EQ-5D-5L domains adjusted scores 1-100 (n=153)

EQ-5D-5L ANOVA Analysis	**F**	**P-Value**	**F-Crit**
Mobility	5.14	0.01	3.06
Self-Care	2.53	0.08	3.06
Usual Activities	3.86	0.02	3.06
Pain	1.78	0.17	3.06
Anxiety/Depression	0.41	0.67	3.06

Figure 3 shows the scores associated with each domain of Haemo-QoL-A separated by the disease severity of the subjects.

Figure 3: Mean Haemo-QoL-A domain scores for patients with Mild, Moderate, and Severe Hemophilia.



As shown in Table 11, Haemo-QoL-A domain scores differed significantly across disease severity groups for Physical Functioning and Worry (P=0.04 and 0.03, respectively). The differences across groups in Role Functioning scores approached significance (P=0.05).

Table 11: ANOVA analysis of Haemo-QoL-A domains scores

Haemo-QoL-A Domains ANOVA Analysis	**F**	**P-Value**	**F-Crit**
Physical Functioning	3.31	0.04	3.06
Role Functioning	2.98	0.05	3.06
Worry	3.56	0.03	3.06
Consequences of Bleeding	0.86	0.43	3.06
Emotional Impact	1.27	0.28	3.06
Treatment Concern	0.65	0.52	3.06

The scores associated with each domain of Haemo-QoL-A show a difference between the known groups of mild, moderate and severe hemophilia patients. In physical functioning, role functioning, and worry domains we observed statistically significant differences among the severity types. However, the differences were not statistically significant in three other domains – consequences of bleeding, emotional impact, and treatment concerns based on the ANOVA results.

Content Validity (Aim 2)

In order to study the content validity of EQ-5D-5L for hemophilia patients we looked at the relationship between responses to individual Haemo-QoL-A questions and particular EQ-5D-5L domain responses. We selected Haemo-QoL-A questions hypothesized to be related to a particular domain of EQ-5D-5L and correlated the responses. EQ-5D-5L responses were transformed so that higher values reflect a better quality of life in both instruments:

Table 12: Correlation between EQ-5D-5L domain questions and the related questions in Haemo-QoL-A

EQ-5D-5L Domain	Number of Related Questions in Haemo-QoL-A	Correlation with Related Questions in Haemo-QoL-A	P-Value
Mobility	3	0.79	<0.01
Self-Care	0	N/A	N/A
Usual Activities	6	0.69	<0.01
Pain/Discomfort	2	0.64	<0.01
Anxiety/Depression	6	0.61	<0.01

We chose Haemo-QoL-A questions that we thought may be related to the same domain question in EQ-5D-5L and looked at the correlation between the mean score of the selected Haemo-QoL-A questions with the average score of the related question in EQ-5D-5L. A strong correlation between the selected questions suggests that EQ-5D-5L domains adequately measure the quality of life in hemophilia patients and may demonstrate the content validity of EQ-5D-5L for hemophilia patients. Results show that the conceptually similar questions between the Haemo-QoL-A and EQ-5D-5L are strongly related. There was no question in haemo-QoL-A that directly relates to self-care domain in EQ-5D-5L that asks the subjects about the problem with washing or dressing. The strongest correlation was observed in mobility domain ($R=0.79$, $P<0.01$) followed by usual activities domain ($R=0.69$, $P<0.01$). All other domains show moderate to strong correlation with correlations ranging from 0.61 – 0.79.

Moderate to strong correlations between the selected questions related to EQ-5D-5L domains is suggestive of the relevant subscale for hemophilia patients is adequately being measured in each domain of EQ-5D-5L.

Comparison of EQ-5D-5L Cross Walk and Direct Reference Approaches (Aim 3)

We looked at the impact of the source of utilities for EQ-5D-5L disease stages on the relationship between EQ-5D-5L and Haemo-QoL-A. Table 13 shows the correlations between the EQ-5D-5L utilities scored from a crosswalk mapping function based on the older 3-level EQ-5D, utilities based on TTO direct valuations of the EQ-5D-5L conducted in Canada, the Haemo-QoL-A and EQ-VAS.

Table 13: Correlations between the Haemo QoL A, EQ-5D-5L Crosswalk Utilities, EQ-5D-5L Direct Utilities, and EQ-VAS in a Hemophilia Patient Sample (N=153).

Total Score Correlation	**Haemo-QoL-A**	**EQ-5D-5L Cross Walk**	**EQ-5D-5L Direct**
Haemo-QoL-A			
EQ5D5L CrossWalk	0.70		
EQ5D5L Direct	0.72	0.95	
EQ VAS	0.56	0.55	0.58

As expected, the Direct and Cross Walk utilities were very highly correlated with each other, with a correlation of 0.95 which is close to perfect. Direct utility scores had slightly stronger correlations with the Haemo-QoL-A total score and EQ-VAS than the Cross Walk utilities did. These findings suggests that the direct method values for may be preferable to the Cross Walk values for converting EQ-5D-5L scores to utility scores for hemophilia patients.

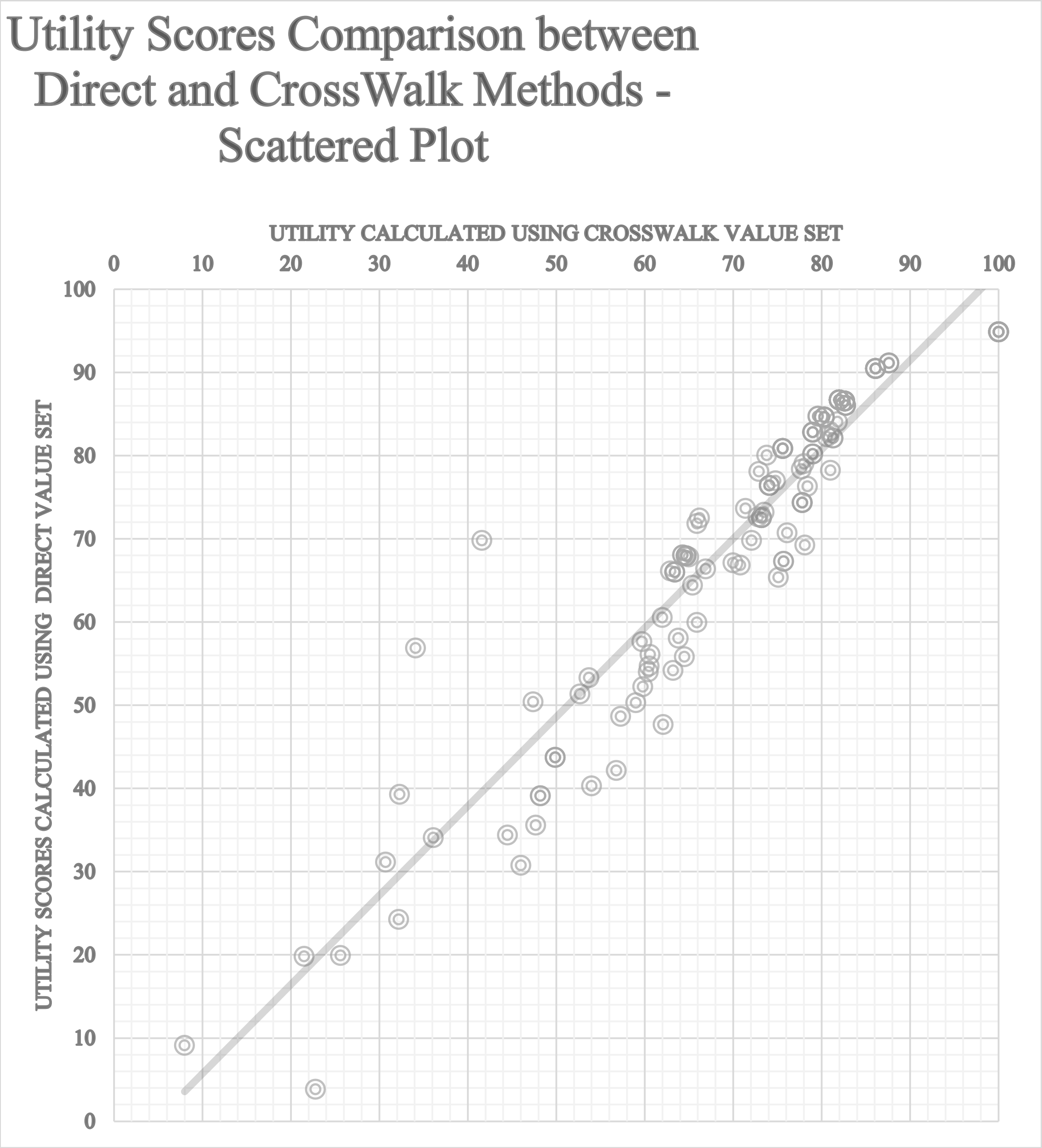
EQ-VAS is moderately correlated with the utility scores in cross walk (R= 0.55) and direct (R=0.58) methods. EQ-VAS is also moderately correlated with Haemo-QoL-A total score (R=0.56). Average utility values were very similar between the direct and crosswalk methods in all disease severity subgroups.

Table 14: The comparison of the utility index scores in crosswalk and direct valuation methods.

Characteristic	**Direct Valuation Method Utility Score**	**Standard Deviation**	**Crosswalk Method Utility Score**	**Standard Deviation**	**Difference (90% CI)**
All Patients	0.722	0.190	0.720	0.168	0.0018 (0.0254 to 0.0225)
Mild	0.726	0.192	0.725	0.170	0.0006 (0.0266 to 0.0235)
Moderate	0.722	0.190	0.720	0.168	0.0018 (0.0254 to 0.0225)
Severe	0.722	0.191	0.720	0.169	0.0016 (0.0256 to 0.0226)

We also used a scattered plot to look at the shape of the relationship between the utility scores calculated by Cross Walk and Direct methods.

Figure 4: Scattered Plot of the Utility Scores Obtained from Direct Reference Method and the Cross Walk Method of Converting ED-5D-5L Scores to Utility Scores



Study of the shape of the distribution of utility scores calculated with cross walk and direct methods demonstrates the agreement between the utility scores calculated using crosswalk method and the utility scores calculated with the direct method (Figure 4).

Quality Question Analysis

We asked the participants about the most significant thing that impacts their quality of life. The answers are presented in the table below. Some of the participants mentioned more than one factor as the most significant thing that impacts their quality of life:

Table 15: Most significant concerns of hemophilia patients

Most Significant Concern	Answer Count	%
Pain/Joint damage	81	50%
Hemophilia Treatment/resources Concerns	18	11%
Social Life/family/school/work	16	10%
Money/Financial concerns/Insurance	11	7%
Physical activity/Ability to run/Walk	11	7%
Feeling alone/Anxiety/depression	7	4%
Age	6	4%
Good education and fewer problems	5	3%
Internal Bleeding/Bleeding	2	1%
Adherence to treatment	1	1%
Weight	1	1%
Inhibitors	1	1%
Lack of sleep	1	1%
Becoming blind due to Hemophilia	1	1%

The number of answers is greater than the total number of 153 participants because some of the participants mentioned more than one factor as the most significant thing that impacts their quality of life.

Results show that joint damage and pain is the most significant concern in this patient population and accounts for 50% of the answers. This is suggestive of the correlation between the Haemo-QoL-A total score and EQ-5D-5L pain domain (r=0.57, P<0.01). No other concern is as clearly reflected in the correlations between the specific domains of Haemo-QoL-A and EQ-5D-5L but hemophilia treatment and the social life, as the main concern of 11% and 10% of the participants respectively, may be consistent with the correlation between anxiety/depression domain in EQ-5D-5L and Haemo-QoL-A total score.

The results show that Haemo-QoL-A domain consequences of bleeding and treatment factors – that may be related to treatment and resources concerns in the qualitative survey- are moderately correlated with utility scores calculated with cross walk and direct methods (r = 0.43 - 0.50). But the correlation between emotional impact and worry domain scores in Heamo-QoL-A and the utility scores of EQ-5D-5L (for both cross walk and direct methods) is stronger and ranges from 0.60 to 0.69. This finding suggests that utility scores associated with EQ-5D-5L may be impacted by the emotional concerns and worry of the hemophilia patients.

Chapter 4 – Discussion

Reliability of EQ-5D-5L (Aim 1)

Internal consistency is among the various types of reliability for HRQOL measures. Internal consistency refers to the homogeneity of items, that is, the extent to which the items of a domain or scale measure the same concept or construct. Cronbach α is the most widely used statistical test to assess internal consistency (Lin et al, 2013). The minimum level of reliability depends on the type of analysis. In general, reliabilities in the 0.50–0.70 range are acceptable for making comparisons between groups (Lin et al, 2013). Internal consistency has been used to evaluate the reliability of other hemophilia specific HRQoL measures. Varaklioti et al (2014) used Cronbach α to study the reliability of Haem-A-QoL which is another hemophilia specific HRQoL measurement tool and used the 0.70 standard for the group level comparison. Their results show Cronbach α value of 0.872 for the total HRQoL score.

Ferreira et al (2013) also used Cronbach α to evaluate the reliability of Heam-A-QoL in hemophilia patients with the total Cronbach α value of 0.90 for the total HRQoL score. The results of our study in evaluating the internal consistency of Haemo-QoL-A show Cronbach α of 0.97 for the total HRQoL score which is suggestive of ab acceptable internal consistency of the instrument in hemophilia patient population.

Construct Validity of EQ-5D-5L in Hemophilia Patient Population (Aim 2)

Our study confirms the construct validity of EQ-5D-5L in hemophilia population, and is consistent with previous and recent studies in evaluating HRQoL with PROs in hemophilia patient population. Szentes et al (2018) found a good correlation between

EQ-5D-5L and the disease-specific King's Brief Interstitial Lung Disease questionnaire (K-BILD) in a German population with evaluating the correlation between the two instruments.

Pederson et al (2018) studied the validity and reliability of the Norwegian version of Stroke-Specific Quality of Life (SS-QOL) scale and looked at the correlation between this disease-specific QoL measure and EQ-5D-3L as the generic utility based QoL measurement tool. Our study is also designed to study the validation and reliability of EQ-5D-5L in hemophilia patient population by looking at the correlation between hemophilia disease-specific QoL measure and the generic measure.

However, depending on the different domains associated with each generic PRO tool the correlation strength may vary among the different domains. Some studies that were performed to compare the disease-specific HRQoL measurement tools with generic HRQoL tools did not focus on each domain in the instrument and instead, just studied the total scores. Dickerson et al (2018) studied the longitudinal construct validity of generic quality of life measures including EQ-5D-3L and looked at the correlation between them and the disease specific Quality of Life in Depression Scale (QLDS) in order to assessment of change in depression outcomes in teens. They did not look at the scores associated with each domain of the measurement tools they studied.

In general, the similar domains in generic PROs that exhibit the concepts such as pain and mobility are more strongly correlated with the similar domains in disease-specific tools. As a result, the relevant functioning and health domains is an important consideration in choosing the appropriate generic instrument for hemophilia population.

The maximum score values represent the best HRQoL in Haemo-QoL-A and ceiling effect is observed for this measurement tool. In contrast, in EQ-5D-5L a floor effect was observed because of the high proportion of the participants who chose the lowest possible score. However, Study of floor and ceiling effect in Haemo-QoL-A and EQ-5D-5L shows the same trend in which a high proportion of the participants reported the best HRQoL score in both instruments.

Mapping (Crosswalk) Utility Conversion Method vs. Direct Utility Conversion Method (Aim 3)

We compared EQ-5D-5L utility values derived from direct valuation or mapping approaches. Luo et al (2015) also compared the utility-based EQ-5D-5L index scores derived from the mapping and direct valuation approaches for the EQ-5D-5L instrument in 269 breast cancer patient population. He regards mapping as a ‘second-best’ approach to deriving utility values, although it is accepted by NICE as a legitimate approach to generating utility values for CUA. Similar to our study, Luo studied the correlation between the utility scores and the disease-specific scores associated with Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire as a disease-specific tool. According Luo’s finding, the valuation-derived index scores were generally higher than the mapping-derived index score in patients with similar characteristics. However, the magnitude of the difference was small and the corresponding 90 % CI fell within the pre-specified equivalence margin for most of the patient groups. The same pattern was observed in our study. We also observed slightly higher utility scores obtained with direct valuation method in hemophilia patient population with all disease severities.

Our study is among the very few studies that directly compare EQ-5D-5L utility scores obtained from mapping and direct valuation approaches and it shows similar results with same study done on a different patient population. Our study confirms the strong correlation between the utility scores obtained from both approaches and the total HRQoL scores obtained from the disease-specific tools. We suggest that this pattern may be consistent along the other patients' populations and other diseases. It means that we expect to see the same correlation between the utility scores obtained from both approaches and the disease-specific HRQoL scores. Besides we expect to see slightly higher utility values when we use the direct valuation method for calculating the utility scores with a slightly stronger correlation between the disease-specific HRQoL score and the utility scores calculated with direct valuation approach.

We recommend using the utility scores calculated using the direct method of utility conversion when possible. The direct method provides stronger correlation with hemophilia specific HRQoL scores. However, it is not always possible to use the direct method. There are some countries that do not have a health utility value set that is made by a direct methodology. In these cases, a value set that is made by mapping method (i.e. crosswalk value set) can be used to conduct health utility studies.

Moreover, the reason for use should also be considered in this respect. EQ-5D-5L is a preferred instrument for pharmaceutical economics studies including cost-utility, ICER, and resource allocation and decision-making and is a good choice for our research. We evaluated the correlation between the utility scores calculated with two different methods and the HRQoL scores associated with a disease-specific tool. A demonstrated correlation between EQ-5D-5L and Heamo-QoL-A can ensure us about the appropriateness of EQ-5D-5L for economic studies in hemophilia patient populations.

Hemophilia Disease-Specific Tools vs. Generic Tools

Over the last decades, the focus of hemophilia care and the outcome of factor replacement therapy has become very important in different contexts, including adjusting treatment for individual patients, justification of costs and the evaluation of efficacy and costs of new concentrates. Hemophilia treatment is becoming more effective and more expensive in the same time. Disease-specific measures are helpful for the healthcare providers in evaluating the clinical decisions in hemophilia population. Grongeri and Von Mackensen (2008) listed 6 hemophilia disease-specific tools for measuring HRQoL in children and 5 disease-specific tools to be used for adults. Haemo-QoL-A is a relatively new disease-specific tool that is developed by Anne Rentz. It is relatively short and easy to be answered by the patients and covers all of the relevant areas associated with hemophilia disease.

HRQoL and patient reported outcomes is another context that may provide information for the decision makers in respect with evaluating the different clinical procedures as well as the resource allocation decisions. Although, the patient reported outcomes should be used appropriately to lead to the right conclusions.

The concerns about the content coverage of EQ-5D-5L for a given disease-specific application have been raised before. Lin et al (2013) did a research on the public literature at the time and looked at the content of disease-specific instruments in cancer, coronary artery disease, osteoarthritis, rheumatoid arthritis, obesity, and stroke and concluded that the unique content of some of the disease-specific tools are not covered in EQ5D. They recommended that EQ5D descriptive system should be enhanced. We studied the application of EQ-5D-5L in hemophilia patients that is a patient population that was not studied by Lin. We also used the newer EQ-5D-5L along with the utility index scores obtained from direct and mapping methods and looked at the overall correlation between the two instruments.

We studied a hemophilia-specific specific HRQoL measurement tool, Haemo-QoL-A, and its correlation with a much shorter and easier to fill, generic HRQoL measurement tool, EQ-5D-5L, and looked at the correlation between this two instruments to determine if EQ-5D-5L is reliable, valid, and relevant enough to be used in hemophilia patient population. A summary of all materials and statistical methods that were used for analyzing our results and drawing our conclusions is available on Appendix 4.

Disease-specific HRQoL tools are more comprehensive than the generic ones in covering all of the relevant factors that may impact the quality of life of the patients for that specific disease. They can also be used to calculate the utility scores for that particular disease. But they can only be used for one disease. And the methods of calculating the utilities is different for each disease-specific tool. That’s why the utility scores are not equivalent and comparable with the utility scores obtained from another disease-specific tool. Generic HRQoL tools have the advantage of being able to be applied to all of the diseases with any disease severity or patient status. This is considered an advantage when the resource allocation decisions include different diseases. When the outcomes of the health interventions are determined by the utilities, a uniform method to calculate the utilities in different methods will be helpful. We wanted our study to be simple, easy to use, and be applicable to the patient with different health status, languages, and culture and EQ-5D-5L as a short and easy to fill HRQoL questionnaire could serve this purpose.

Response Burden

An important feature of our research was the feasibility and ease of administration. EQ-5D-5L is a short questionnaire that can easily be distributed among the patients in paper hard copies, through emails, or through the platforms such as Qualtrics. A previous meta-analysis study done by Rolstad et al (2009) shows that the response rates are lower for longer questionnaires. The higher than anticipated response rate to our questionnaires in our study as well as the low missing data rate suggests that a short and simple questionnaire along with an easy and convenient mode of administration result in a high response rate and low missing data. Besides, in our study we tried to demonstrate that a short generic HRQoL measurement tool such as EQ-5D-5L that is appropriate for economic evaluations is a valid tool to be used in hemophilia population. Kaye et al (2012) studied the importance of the patients' involvement in biomedical research as well as the increasing awareness of the value of patient involvement in research. Our study is one of the few studies that leverages the value of the direct hemophilia patient involvement in conducting the research. Besides, we created a concise questionnaire that is preferred by the participants based on the previous studies (Van Geest et al, 2007).

We asked our patients to openly discuss about the important problems in respect with their disease and our research method. Skinner et al (2018) point to the continuously increasing interest of health care agencies, private payers, and policy makers for PROs. According to them, there is a substantial need to improve capacity to collect and interpret relevant PRO data to support implementation of patient-centered research and advocacy to obtain optimal care in hemophilia.

Application of EQ5D and its role in healthcare reimbursement is also being studied in many health systems around the world. Davlin (2013) studied the National Institute of Care Excellence (NICE) case and brought up the question of whether the new health technologies are good value for the money. Since we need cost effectiveness analysis for providing a means of comparing the value of money, we require standardized measures of health outcomes such as QALY.

We tried to include the aforementioned advantages in our research design. The electronic versions of the questionnaires or the link to open them can be easily sent to the smartphones or computers of the participants. Moreover, the participants should only answer the 5 questions instead of filling a long disease-specific questionnaire. The results of our study demonstrates the validity of EQ-5D-5L for hemophilia population.

In addition, the ease of use and the feasibility of the study design to be used in hemophilia population may provide an advantage for the health policy makers to gather fast and reliable patient reported outcomes data to be used for resource allocating purposes in developing countries. EQ-5D-5L is available in more than 130 languages and in various modes of administration. There are many publication from the developing countries in which EQ-5D-5L is used for evaluating the HRQoL in hemophilia patients. Cost-utility studies that can be done by using the utility scores calculated from EQ-5D-5L can help the decision makers to allocate the budget for importing the medications. Our study demonstrates the possibility of using a fast and easy to administer tool that is short, valid, and reliable tool such as EQ-5D-5L can also help the decision makers to evaluate the health outcomes associated with hemophilia medications and take patients' preference into account.

One Disease at a Time

As it was discussed earlier in this research, EQ-5D-5L is a HRQoL measurement tool that can be used for all of the diseases. It is a patient-reported outcomes tool that can be used by the patients and providers independent from the disease. One of the big questions about this tool is whether it is applicable to all diseases. When we compare EQ-5D-5L results to Haemo-QoL-A we found that there are specific domains of the disease-specific tool that are not strongly correlated with any of the individual domains of EQ-5D-5L. We speculate that this trend may be consistent with what is observed in other EQ-5D-5L versus the disease-specific tools in other diseases. The reason is that EQ-5D-5L is a short questionnaire that cannot include all the details that may be specific to a particular disease.

However, our results show that when the domain scores are combined together and are converted to the utility scores – either with the mapping method or with the direct method of conversion – the overall utility scores are strongly correlated with the overall scores obtained from the disease-specific tool. The same trend has been observed in many different diseases and in other researches that compared EQ-5D utility scores to the overall HRQoL scores obtained from the disease -specific tools as we cited earlier in this document. (Szentes et al, 2018 – Pederson et al, 2018).

However, the selection of the generic or disease-specific tools for measuring the quality of life or the utilities depends on the study objectives, the study design, and the target population as well. For instance, if the study is designed to compare two or more different diseases or to compare the HRQoL of a patient population to that of the general population it is best to use the generic tools. According to O'Connor (2004) a comprehensive assessment of HRQoL would ideally combine three questionnaires: a disease-specific questionnaire to target the condition, a treatment-specific questionnaire to target the intervention, and a generic questionnaire to allow comparison with population norms and/or other health conditions.

Our study results along with the other findings from the other studies suggest that the correlation between the utility scores in EQ-5D-5L is consistent among the other diseases as well. We believe the comparison between the individual disease-specific tools with EQ-5D-5L may provide confirmatory evidence about the strong correlation between the utility scores and the overall HRQoL scores and provide more evidence for the validity and reliability of EQ-5D-5L in hemophilia patient population. We think it is the best to choose a questionnaire that has a proven track record in research that had been studied in similar objectives and target populations whenever possible.

Study Limitations

The questionnaire link was emailed to the registered hemophilia patients by Rare Patient Voice. The researcher could not verify that the form was filled by the patients or the caregivers. The women participants in this study is 9%. Hemophilia is an X-link recessive disease and most of the hemophilia cases are male patients. However, it is possible that some of the participants have a female gender identity or have participated in the study as caregivers.

Coding of the qualitative data was done by the researcher. Reviewing the coding data by multiple judges could enhance the rigor of the study.

Conclusion

The results of our study demonstrate a relatively strong correlation between the utility scores obtained from EQ-5D-5L and the total scores of Haemo-QoL-A. Moderate to strong correlations also exist between the conceptually related individual domains of each instrument between the domains that measure a similar concept (i.e. mobility and physical functioning).

Overall, the validity of EQ-5D-5L instrument for using in hemophilia population is supported by our study of the correlations between the utility scores obtained from direct and mapping methods with the HRQoL scores obtained from Haemo-QoL-A. The results demonstrate that direct method of converting EQ-5D-5L scores to utility score provided higher correlation with the total Haemo-QoL-A score. The utility scores calculated by cross walk method also show slightly weaker correlation with the disease-specific Haem-A-QoL tool. We conclude that the direct utility index development technique to may be the best option for converting the scores to utilities and is strongly correlated with Haemo-QoL-A scores as a gold standard for evaluating HRQoL in hemophilia patients.

Recommendations

We recommend the use of EQ-5D-5L utility scores calculated with direct method for cost utility studies in hemophilia patient population. The statistical analysis of our results support the content and construct validity of the EQ-5D-5L for hemophilia patients. When hemophilia patients' domain scores were converted to utilities using a schedule from a direct valuation of EQ-5D-5L disease states, correlations between the EQ-5D-5L and hemophilia-specific measures were slightly stronger than when a cross walk derived schedule was used for conversion. Therefore, we recommend other researchers use a direct valuation utility schedule whenever possible with EQ-5D-5L for CUAs with hemophilia patients.

Appendix 1: Rare Patient Voice Email Template

Hi {First Name},

Thanks for being a member of Rare Patient Voice. We have an opportunity for you to take part in a xxx study for Patients. Our project number for this study is ABC_1234.

Project Details:

Web-Based Online Questionnaires about Hemophilia Quality of Life (you must be by a computer or a smart phone with high-speed internet access during the time of the interview)

The questionnaire will approximately take 30 minutes to get completed.

$10 Gift Card Reward will be provided to the participants

Things to Note:

Adult Patient (18+) study only, Caregivers please pass the link along

Unique links, please do not pass along for 2nd use

Want to share this opportunity? Let us know and we can provide a new link

Please use a laptop/computer ONLY. No smartphones or tablets - Preliminary questions are Mobile Friendly!

Save this email to reference if you have any questions about the study!

If you are interested in this study, please click the link below to answer a few questions to see if you qualify.

Study Link: https://umn.qualtrics.com/jfe/form/SV_eDuGkWubj60AEiV

Thanks as always for your participation! Please be aware that by entering this information you are not guaranteed that you will be selected to participate. As always, we do not share any of your contact information without your permission.

Not interested in this study? (Click link below so we do not send you any reminders for this study)

Study Opt Out Link: {Unique Opt Out Link}

We truly appreciate the time you set aside to interact with our company and don’t take it for granted. Receive a $10 gift card for referring others who may want to participate in this or future studies. Invite them to join Rare Patient Voice: www.rarepatientvoice.com/sign-up. They, too, receive a gift card.

Appendix 2: Scoring Manual for Haemo-QoL-A

Items are answered on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time). Higher scores mean better HRQL or less impairment for a particular subscale.

Recoding items

Some items are positively worded and some are negatively worded. Negatively worded items should be reverse scored so that higher scores reflect better quality of life. The item scores of negatively worded items should be subtracted from 5. For example: Question 1 is a negatively worded item so it should be scored:

(5 – Question 1) = Score of reverse scored Question 1.

The positively worded items are the following: 3, 6, 7, 9, 12, 16, 19, 32, and 34. All other items are negative and should be reverse scored.

Scoring

For the Haemo-QoL-A subscales [physical functioning, role functioning, worry, consequences of bleeding, emotional impact (formerly: positive affect), treatment concern], scores are computed by averaging across the items within a subscale. The range of subscale scores is 0 to 5; higher scores mean better HRQL or less impairment for a particular subscale.

To calculate the Haemo-QoL-A total score, sum the value of the individual subscales (do not sum all the individual items). The range of total scores is 0 to 30; higher scores mean better HRQL or less impairment.

For both total and subscale scores, use the formula below to transform raw scores to a 0 to 100 scale. Higher scores will be indicative of better HRQL.

Missing Items

For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the Haemo-QoL-A total score cannot be calculated

Items by subscale:

SAS Variable Name	Number	Scoring
Physical Functioning		
rHQ3	1	Reverse
rHQ4	2	Reverse
HQ5	3	
rHQ7	5	Reverse
HQ8	6	
HQ9	7	
rHQ10	8	Reverse
HQ12	9	
rHQ14	10	Reverse
Role Functioning		
rHQ6	4	Reverse
rHQ21	17	Reverse
rHQ25	21	Reverse
rHQ26	22	Reverse
rHQ31	26	Reverse
rHQ33	28	Reverse

rHQ37	31	Reverse
rHQ39	33	Reverse
rHQ45	36	Reverse
rHQ46	37	Reverse
rHQ48	38	Reverse
Worry		
rHQ28	23	Reverse
rHQ29	24	Reverse
rHQ30	25	Reverse
rHQ32	27	Reverse
rHQ34	29	Reverse
Consequences of Bleeding		
rHQ15	11	Reverse
rHQ17	13	Reverse
rHQ18	14	Reverse
rHQ19	15	Reverse
rHQ22	18	Reverse
rHQ24	20	Reverse
rHQ36	30	Reverse

	Emotional Impact	
HQ16	12	
HQ20	16	
HQ23	19	
HQ38	32	
HQ43	34	
rHQ44	35	Reverse
	Treatment Concern	
rHQ49	39	Reverse
rHQ51	40	Reverse
rHQ52	41	Reverse

Scale	Average the Item Values	Lowest /Highest Possible Raw Scores	Range
Physical functioning	(1+2+3+5+6+7+8+9+10) 9	0, 5	5
Role functioning	(4+17+21+22+26+28+31+ 33+36+37+38) 11	0, 5	5
Worry	(23+24+25+27+29) 5	0, 5	5
Consequences of bleeding	(11+13+14+15+18+20+30) 7	0, 5	5
Emotional impact	(12+16+19+32+34+35) 6	0, 5	5
Treatment concern	(39+40+41) 3	0, 5	5
Haemo-QoL-A Total	Sum of subscales (not individual items)	0, 30	30

Formula for transformation of the Haemo-QoL-A total raw score:

$$\text{Transformed Score} = \frac{\textit{Actual raw}\text{ total score}}{\text{Possible raw score range}} \times 100$$

Appendix 3: Haemo-QoL-A Questions Related to each EQ-5D-5L Domain

EQ-5D-5L Domain	**Questions Expected to have the same answer**	**Question Number**
Mobility	Loss of joint mobility affects how I walk	H1
	It is hard for me to climb the stair	H2
	I am unable to leave the house because of my hemophilia.	H4
Usual Activities	It is easy for me to perform daily activities.	H3
	It is easy for me to lift heavy objects.	H7
	I am able to participate in sports.	H9
	I experience restrictions at work or school.	H25
	My hemophilia treatment interferes with my daily activities.	H37
	I feel I can carry out a normal life like the rest of society.	H34
Pain/Discomfort	I have to adjust my activities because of pain.	H5
	I feel frustrated because I can't do what I want to do.	H21
Anxiety/Depression	My infusions for hemophilia are stressful.	H38
	I feel like a burden to my family.	H26
	I am hopeful about the future.	H12
	I feel less confident than others.	H15
	I enjoy life.	H16
	I feel much older than my years.	H17

Appendix 4: Summary of Aims and Methodologies

Aim No.	Topic	Study Aim	Methods Used
I	Reliability	Internal Consistency of Haemo-QoL-A Domains	Cronbach's α
II	Construct Validity	EQ-5D-5L Overall Scores and Scores in each Domain	Mean Scores, SD, Floor and Ceiling Effect
		Haemo-QoL-A Overall Scores and Scores in each Domain	Mean Scores, SD, Floor and Ceiling Effect
		Correlation Between EQ-5D-5L and Haemo-QoL-A	Correlation Coefficient
		Sensitivity to Disease Severity - Overall and Domain Scores	ANOVA, Mean Scores, SD
III	Content Validity	Correlation between EQ-5D-5L and Haemo-QoL-A Related Questions	Correlation Coefficient
IV	Conversion Method Comparison	Correlation of EQ-5D-5L Overall Scores obtained from Crosswalk and Direct Methods with Haemo-QoL A and EQ-VAS Scores	Correlation Coefficient

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