University of Alberta

Construct Validity of the Health Utilities Index Mark 2and Mark 3 and the Memphis Immunosuppressant-related Quality of Life Survey in Adults with Type 1 Diabetes

by

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List of Abbreviations

ADDQOL – Audit of Diabetes Dependent Quality of Life

HFS – Hypoglycemia Fear Survey

HRQL – health-related quality of life

HUI – Health Utilities Index

IRQOL – Immunosuppressant-related Quality of Life

IT – Islet transplantation

RAND-36 – RAND-36 Health Status Inventory

SF-36 – Short Form- 36

Chapter 1: Introduction

1.1 Statement of Problem

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action, or both. Insulin allows your body to properly use and store fuel from glucose for energy. The long-term effects of hyperglycemia are associated with damage and dysfunction of major organs, particularly the heart, eyes, nerves, kidneys, and blood vessels. Diabetes mellitus can, for the majority, be classified into type 1 and type 2 diabetes. Other types of diabetes, such as gestational diabetes, pancreatic disease and genetic disorders, may also occur, but are temporary or rare.

Type 1 diabetes (formerly known as insulin-dependent diabetes) is primarily a result of pancreatic beta cell destruction, usually leading to absolute insulin deficiency. Type 1 diabetes can be a result of an autoimmune disorder, genetic predisposition or idiopathic cause. Onset usually occurs during childhood or adolescence. Standard treatment for type 1 diabetes includes insulin injection therapy, and in severe cases, pancreas or experimental islet transplantation.

Type 2 diabetes (formerly known as non-insulin dependent diabetes) is a result of relative insulin deficiency, an insulin secretory defect and/or insulin resistance. Type 2 diabetes can be a result of obesity, sedentary lifestyle, other co-morbidities and/or genetic predisposition. Onset is usually middle to late adulthood (i.e., 40-65 yrs). Standard treatment for type 2 diabetes includes diet, exercise, oral antidiabetics, and in severe cases, insulin therapy (CDA, 2003).

The morbidity burden of diabetes can be associated with impairment on many dimensions of health-related quality of life (HRQL), including social, cognitive, role and

physical functioning, emotional well-being, general perceptions of health, and pain (CDA, 2003; Ahroni et al., 1994; Wandell et al., 1997; Aalto et al., 1996; Gafvels et al., 1991; Anderson et al., 2001; Bourdel-Marchasson et al., 1997). Self-reported HRQL is an important outcome to assess in diabetes, in part because clinical measures, such as glycosolated hemoglobin (A1c), may fail to capture the overall impact of the disease on the person's overall health and functional status (Maddigan et al., 2004).

While a number of studies have used specific or generic health profiles to assess HRQL in type 1 diabetes, past research exploring preference-based measures in diabetes is limited, particularly using the Health Utilities Index Mark 2 (HUI2) and the Health Utilities Index Mark 3 (HUI3) (Torrance et al., 1995; Feeny et al., 2002). In reviewing the literature, no studies were identified which employed the HUI2 and/or HUI3 in type 1 diabetes.

Johnson and colleagues are currently evaluating HRQL outcomes in patients with type 1 diabetes mellitus undergoing islet transplantation (IT) through the University of Alberta. Islet transplantation aims to free or reduce patients' insulin requirements, while gaining greater glycemic control. The Edmonton Protocol involves a glucocorticoid-free immunosuppressive therapy regimen because glucocorticoid agents are associated with increased adverse post-transplant effects, in particular, derangements of glycemic control. HRQL assessments include a battery of generic measures (i.e., HUI 2 and 3, RAND-36) and specific measures. One of the specific HRQL measures employed in the evaluation of IT is the Memphis Immunosuppressant-related quality of life (IRQOL) survey (Winsett et al, 1999). The IRQOL is a post-transplant specific HRQL measure designed to assess the HRQL burden associated with immunosuppressant therapy. In order to effectively

evaluate the Edmonton Protocol's glucocorticoid-free immunosuppressant regime, it is important that the IRQOL is able to distinguish the specific HRQL burden (if present) associated with immunosuppression.

1.2. Research Questions

- To what extent do the HUI2 and HUI3 detect HRQL burdens associated with type 1 diabetes and its complications?
- In adults with type 1 diabetes, is the Memphis IRQOL specific for immunosuppressant-related quality of life, or does it perform more like a generic health profile?

1.3. Study Objectives

This study will serve three purposes. The first purpose of the study is to access cross-sectional construct validity of the HUI2 and HUI3 in adults with type 1 diabetes.

The second purpose will be to evaluate the IRQOL as a measure of HRQL. As per our experience in HRQL assessments of IT patients, we hypothesize that this measure will perform similar to the generic health measures employed. The HUI3 and RAND-36 will be used as benchmark generic measures for comparisons.

Third, we will establish local norms for the battery of generic HRQL measures (HUI2, HUI3, RAND-36) in patients who have type 1 diabetes. This will allow us to compare HRQL differences between adults with type 1 diabetes who have undergone either islet or whole pancreas transplants with those who are currently using standard insulin therapy.

Chapter 2: Background/ Literature Review

2.1. Diabetes

Diabetes is a common chronic disease and with its rapidly increasing prevalence, diabetes mellitus has become a large public health issue. Recent Canadian data available (from the National Diabetes Surveillance Strategy [NDSS]) indicates that in 1998-99, the physician-diagnosed prevalence of diabetes in adults (people $\geq$ 20 years) was 4.8%. Other sources indicate this prevalence to be as high as 8%, while as many as one-third of cases may be yet undiagnosed (Hux et al., 2003). Prevalence estimates of diabetes between 1995-1999 show a relative 31% increase, although incidence rates remain steady (Hux et al., 2003). This suggests that while there are a growing number of individuals with diabetes, it is primarily due to persons living longer with the diabetes, rather than an increase in individuals developing diabetes. With this prevalence expected to increase by 35% over the next 25 years, the health and economic burden of diabetes posses a significant public health problem (Dawson et al., 2002).

Diabetes mellitus can, for the majority, be classified into type 1 and type 2 diabetes. Although type 2 diabetes accounts for approximately 90% of the cases of diabetes, type 1 diabetes is nonetheless a global health issue (CDA, 2003). The worldwide incidence of type 1 diabetes varies from 0.1/100,000 per year (China) to 36.8/100,000 per year (Sardinia) (Karvonen et al., 2000). This demonstrates a > 350-fold global variation in incidence of type 1 diabetes. This incidence is reported to be increasing in virtually all global populations (Bailes, 2002). In Alberta, there were 175 new cases of type 1 diabetes reported between 1990-1994. These cases result in an incidence density of 27.82/100,000/year (Karvonen et al., 2000). This translates to mean that 27.82 people out of 100,000 were diagnosed with type 1 diabetes in Alberta each

year. The risk of type 1 diabetes increases between the ages of 10-14 years, then dramatically decreases after age 14 (Bailes, 2002). For type 1 diabetes, incidence density may be a more useful measurement of incidence as the risk of type 1 diabetes changes for an individual over time (Bailes, 2002).

Diabetes mellitus can result in acute and long term complications. While acute complications, such as diabetic ketoacidosis and hyperosmolar nonketotic coma, can lead to hospital admissions, it is the long term microvascular and macrovascular complications that account for the majority of the morbidity and mortality associated with diabetes (Booth et al., 2003; DCCT, 1993). Cardiovascular disease (CVD) accounts for approximately 70% of all deaths amoung individuals with diabetes, which can be up to three to five times higher than that of the general population (Booth et al., 2003). For individuals with a duration of diabetes of twenty-five years or greater, prevalence estimates of complications are estimated at 10-30% for cardiovascular and/or peripheral vascular disease, 25-45% for nephropathy, 50% for neuropathy, and 50-70% for some degree of retinopathy (Hux et al, 2003; Oliver et al., 2003; Ruhrmann et al., 2003; Bailes et al., 2002; Orchard et al., 1990; Bakris, 2001).

As the development and progression of complications is associated with a longer duration of diabetes, those with type 1 diabetes tend to show complications earlier in life than those with type 2 diabetes. For this reason, prevalence estimates of long term complications in those with type 1 diabetes tend to be two to three times greater than those with type 2 diabetes (Orchard et al., 1990). Despite the burden of complications, evidence has shown these complications can be reduced by tight glycemic control and

intensive treatment regimens aimed at lowering glycosolated hemoglobin A1c levels below 7% (CDA, 2003; DCCT, 1993; UKPDS, 1999).

2.2. Health-related quality of life (HRQL) burden of diabetes

Diabetes places a substantial burden on individuals with the disease and their families. This burden arises not only from diabetes itself, but also its treatment, the complications, and possible co-morbidities associated with diabetes. Diabetic complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, stroke, and peripheral vascular disease result in significant morbidity and mortality (Ahroni et al., 1994). The morbidity burden of diabetes can be associated with impairment on many dimensions of health-related quality of life (HRQL), including social, cognitive, role and physical functioning, emotional well-being, general perceptions of health, and pain (Wandell et al., 1997).

Self-reported HRQL is an important outcome to assess in diabetes, in part because clinical measures, such as glycosolated hemoglobin (A1c), may fail to capture the overall impact of the disease on the person's overall health and functional status (Maddigan et al., 2004). Also, the assessment of HRQL is an essential element of health care evaluation, not only in terms of appraising the effect of the treatment on the well-being of patients, but also to facilitate the development of clinical and public policy guidelines and the conduct of economic analyses (Guyatt et al., 1993).

2.3. Health-related quality of life measures

When measuring HRQL in any condition, it is essential that the instruments used are valid in the population under study. Construct validity can be defined as the extent to which an instrument measures the property it is intended to measure (Hays et al., 1993).

Construct validation cannot be proven definitively, it is a result of a continuing process and accumulation of evidence. This continuing process of validation involves testing pre-determined hypotheses about the performance of the instrument's components and theoretical relationships of the scale scores (McDowell and Newell., 1996). Although one single study cannot prove validity, the accumulation of multiple studies contributes to the understanding of the measures capabilities and limitations, in specific populations/situations.

The three main types of evidence used to indicate construct validity are: correlational evidence, factorial evidence, and group differences or discriminant evidence (McDowell and Newell., 1996). Correlational evidence involves formulating hypotheses about how the measurement will (or will not) correlate with other methods/measures that have or will measure the same concept. Factorial validity is used to generate evidence of the internal structure and how well the items measure common themes. Factor analysis can also indicate the association amoung several measurements. Discriminant evidence involves testing whether the measure can distinguish between subgroups of individuals, expected to differ in HRQL (McDowell and Newell., 1996).

HRQL measures can be broadly classified into specific and generic measures. Both specific and generic measures of HRQL have been used to study HRQL in individuals with diabetes.

2.3.1. Specific measures

Specific HRQL measures are designed to be used within a certain disease-state, defined population/subgroup or for evaluation of a particular treatment. The majority of specific measures are disease-specific and have the advantage of focusing on issues of

particular concern to patients with the disease (Luscombe, 2000). Also, they may be better able to identify functional impairments arising for the illness under study and may be more sensitive to small changes in health resulting from treatment than generic HRQL measures (MacKeigan et al., 1992). For these reasons, patients and clinicians often tend to prefer specific measures, as items seem clinically sensible. Disadvantages of disease specific measures are that they may not permit broad comparisons between disease states and they may miss the effects of co-morbidities or treatment side effects. For these reasons, disease specific measures may less informative for resource allocation decision makers and third party payers.

Some examples of disease specific measures include the Audit of Diabetes-Dependent Quality of Life (ADDQOL) (Bradley et al., 1999), the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (Townsend et al., 1991) and the Erectile Function -Visual Analogue Scale (EF-VAS) (Torrance et al., 2004).

2.3.2. Generic Measures

Generic HRQL measures are intended for general use, irrespective of disease state, population or treatment. These measures can also be used in healthy people in the general population and in patient populations. Generic measures of HRQL have an advantage over disease-specific measures in that they permit comparisons of the impact of various diseases on multiple dimensions of HRQL and allow comparisons across conditions or populations. This may provide useful data for policy and resource allocation decisions (MacKeigan et al., 1992). Additionally, generic HRQL measures may be expected to distinguish between varying degrees of states within a condition; however, may not be expected to distinguish between treatment effects as well as specific measures

can. Generic measures can be classified into health status profiles and preference-based measures (Guyatt et al., 1993).

2.3.2.1. Health Status Profile Measures

Health status profile measures reflect an individual's current health status on multiple dimensions or domains and assign a score to each dimension, but do not necessarily create on overall aggregate score to reflect overall HRQL.

Profile measures are often derived from psychometric or clinimetric approaches and include key generic health concepts and capture morbidity associated with various health states. However, the scales are not anchored at dead, and therefore they do not include mortality. An example of a health status profile measure is the Short-Form-36 (SF-36), which includes the domains of physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, and role limitations due to emotional problems, mental health and health transition. Each of these domains are scored on a scale of 0 to 100, with higher scores representing better functioning on that particular domain (Ware, 2000). Summary scores representing physical (Physical Composite Score-PCS) and mental (Mental Composite Score-MCS) health are also generated.

2.3.2.1.1. Norm-based scoring in health profile measures

Some profile measures utilize a norm-based scoring algorithm where each scale is scored to have a standardized mean and standard deviation, relative to the general population scores/norms. The T-score is one example of a norm-based score where the mean is 50.0 and the standard deviation is 10.0. Z-scores could also be used in norm-based scoring, where the mean is 0.0 and the standard deviation is 1.0.

Although an overall score is not generated in a norm-based scoring system, profile measures and norm-based scoring allow for possible detection of the different effects on different dimensions on HRQL. This can be useful when evaluating a medical intervention, which may not have equal effects on all domains of an individual's health state. The various effects on measure dimensions can then be made across disease groups or populations, irrespective of the raw scoring of the scale (i.e., number of items or response options). Norm-based scoring is also intended to aid in the interpretation of health status of a sample by having a "built-in" reference. For example, a sample mean of 40.0 on a T-score would indicate the sample is 1.0 standard deviation below the mean of the reference population. It is important to note that norm-based scoring assumes the data is normally distributed, which may not always be the case.

The RAND-36 and Short Form-36 (SF-36) are examples of health profile measures that utilize norm-based scoring system. The RAND-36 (or the related SF-36) has been frequently applied in the assessment of health status in diabetes (DCCT Research Group, 1996; Jacobson et al., 1994; Johnson et al., 1996; Maddigan et al., 2004). The RAND-36 includes two summary scores (i.e., a physical and mental health composite score) and eight scale scores. The RAND-36 summary scores are T-score norm-based; therefore, interpretation of these scores is based on a general US population mean of 50.0, with a standard deviation of 10.0.

The RAND-36 differs from the SF-36 in its scoring method and overall development of the composite scores (Hays, 1998). The SF-36 is a simple summation method, where essentially all items contribute equally to the overall scale and are assumed to have interval properties. In contrast, the RAND-36 utilizes an item response

theory (IRT) model, where the expected score of a respondent on a particular item is a function of both the item difficulty and respondent's ability (Hays, 1998). Therefore, the RAND-36 offers the theoretical advantage of providing an estimate (based on the respondent's answers) of how much each response should contribute to the overall score.

The methodology used to derive the composite scores for the RAND-36 differs from the SF-36 in several ways. First, the factor analysis applied to the physical and mental health factors of the RAND-36 are based on common, not total variance, as in the SF-36. Second, the domain scores used for composite score construction of the RAND-36 are only those associated with either physical or mental health. In contrast, the SF-36 uses all domain scores in the construction of both the physical and mental composite scores. In the SF-36, mental domains have a negative effect and physical domains have a positive effect on the physical composite scores and vice versa for the mental composite score. Lastly, the RAND-36 uses an oblique rotation, rather than the orthogonal rotation employed in the SF-36. This allows the overall physical and mental health factors of the RAND-36 to correlate whereas, the SF-36 would result in independent uncorrelated composite scores (Hays, 1998). For these reasons, it is felt that the RAND-36 provides a more rational and clinically sound scoring system for HRQL. Recent evidence suggests that the different scoring approaches will affect the validity of the summary scores, as represented by the RAND-12 and SF-12 (Johnson et al., 2004).

Increased attention to these differences have called into question the validation of the SF-36 summary scores (Simon et al., 1998; Taft et al., 2001). A recent study by Johnson and Maddigan comparing the RAND-12 and SF-12 (shortened, validated versions of the RAND-36 and SF-36, respectively) in type 2 diabetes observed

differences in the discriminative performance of the two measures/scoring systems (Johnson et al., 2004). Here, the SF-12 summary scores (i.e., PCS and MCS) did not find statistically significant differences between known subgroups of individuals, whereas the RAND-12 summary scores (i.e., PHC-12 and MHC-12) did find statistically significant differences (Johnson et al., 2004). This research supports the finding that the RAND scoring system may be more sensitive to differences in HRQL than the SF scoring system, in type 2 diabetes.

2.3.2.2. Preference based measures

Preference-based measures offer advantages over profile measures. First, preference measures include the state of "dead", anchored at a value of "0". Thus, they capture both morbidity and mortality. In addition, some preference-based measures allow for negative utility values that reflect health states worse than dead. Profile measures are not anchored at death so that they only include morbidity associated with health states. Preference-based measures also allow an overall score to be obtained, which allows for comparison between overall, or net, effects of a disease and intervention. The comparison of burden across disease states using preference-based measures may provide useful data for policy and resource allocation decisions (Wandell et al., 1997). An overall score also provides information about the overall positive or negative effect of an intervention/disease. Profile measures generally do not provide an overall aggregate HRQL score. There are notable exceptions (e.g., Sickness Impact Profile (SIP)), but again, mortality is typically not integrated into profiles. Lastly, interpretation of preference-based measures is not based on population norms and/or sample distribution, which is important in cases where the sample is not normally distributed. As noted

previously, profile measures, which utilize norm-based scoring, assume a normal distribution in their interpretation.

Preferences for health states can be elicited under direct or indirect approaches. Direct preference-based measures can be based on a visual analogue scale (VAS), time-trade-off (TTO) or standard gamble (SG) to elicit value or utlity scores. Indirect approaches are multiattribute measures which utilize a multi-dimensional health status classification system, to describe an individual's health status, and a preference-based scoring system, to assign an overall index score to that state.

2.3.2.2.1. Direct Preference-based Measures

A VAS has individuals place health states along a line, often anchored at "dead/least preferred" and "healthy/most preferred." VAS scores are a function of an individual's preference for health states, under conditions of certainty. As VAS methods typically don't involve choice, they are less desirable for the elicitation of preferences (Drummond et al., 1997; Torrance, 1986).

TTO elicits preferences under conditions of certainty, where a subject is asked to make a choice between two alternative health states (e.g., an intermediate health state for a lifetime vs. a better health state for a shorter period) (Torrance, 1986). TTO has the advantage over VAS that it involves choice; however, both TTO and VAS do not elicit true utility scores because the element of risk/uncertainty is omitted.

SG is based on von Neumann Morgenstern (vNM) utility theory, a quantitative approach to normative decision making under conditions of uncertainty. SG provides subjects with the option between a certain intermediate health state and an uncertain health state. The uncertain health state is a "lottery" between a better and worse health

state. The probability of occurrence between these health states is varied until the individual becomes indifferent between the two choices (Drummond et al., 1997). Overall, SG has the strongest theoretical foundation for producing utility scores and therefore, preference-based measures based on SG techniques are preferable (Drummond et al., 1997; Torrance, 1986).

2.3.2.2.2. Indirect Preference-based Measures

Indirect preference-based index measures assess multiple domains or dimensions of HRQL/health status and apply a "preference" value to the health state. Typically, the preference-based scoring function would have been previously derived using direct preference elicitation methods (e.g., SG or TTO) from a sample of the general population. Thus, indirect, multiattribute measures usually represent general community preferences for health states.

An overall aggregate score is generated to reflect preferences for alternative health outcomes. The overall aggregate score is derived from the composite/attribute scores. Some examples of indirect, multiattribute preference-based index measures include the Health Utilities Index (HUI) (Feeny et al., 1995), EQ-5D (Essink-Bot et al., 1993; Dolan et al., 1997), and the Quality of Well-Being (QWB) (Kaplan et al., 1997).

The Health Utilities Index Mark 3 (HUI3), for example, uses a SG approach to assign overall utility scores. The HUI3 defines HRQL according to eight attributes/domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. There are five or six levels in each domain, ranging from highly impaired (e.g. blind for vision) to no impairment. Ability to function on each of these domains contributes to overall HRQL as assessed by HUI3 score (Feeny et al., 2002).

2.4. HRQL measures in diabetes

Much research has assessed the ability of disease-specific and generic health profile measures of HRQL to discriminate between subgroups of individuals with diabetes expected to have different levels of HRQL. Diabetes specific measures, such as the Diabetes Quality of Life (DQOL) (Jacobson et al., 1994) the Audit of Diabetes Dependent Quality of Life (ADDQoL) (Bradley et al., 1999) and the Appraisal of Diabetes Scale (ADS) (Carey et al., 1991) have been shown to have evidence for reliability and internal and external validity for measuring diabetes HRQL (Garratt et al., 2002).

Although specific and generic measures offer complementary information, this literature review will concentrate on previous research in generic HRQL measures in diabetes as they are most pertinent to the study objectives. Overall, the vast majority of literature focuses on generic health profile measures in diabetes; however, the literature on preference-based index measures is less extensive.

2.4.1. Generic health status profile measures in diabetes

There is extensive literature of generic health status/HRQL measurement in diabetes. Previous applications of generic health status profile measures in diabetes HRQL have identified several trends. First, increased intensity of treatment (i.e. progressing from diet to oral medications, and finally to insulin) in individuals with type 2 diabetes has been associated with lower levels of HRQL, measured using either disease-specific or generic HRQL instruments (Woodcock et al., 2001; Maddigan et al., 2004). This relationship is likely attributable to the fact that more intense treatment is associated with more advanced disease, but it may also reflect an increased treatment burden.

There is also evidence that the presence and severity of complications is associated with clinical depression and anxiety. These trends have been observed in individuals with type 1 or type 2 diabetes on a variety of generic measures, including the Medical Outcomes Study 36 Item Short-Form Health Survey (SF-36), the Nottingham Health Profile (NHP) and the Sickness Impact Profile (SIP) (deGrauw et al., 1999; Peyrot et al., 1997; Keinanenn-Kiukaanniemi et al., 1996; Rubin et al., 1999).

Jacobsen and colleagues used the SF-36 to assess HRQL in type 1 and type 2 diabetes and found that those with type 1 diabetes reported lower HRQL than those with type 2 diabetes, regardless of therapy regimen (Jacobson et al., 1994). This may be a result of individuals with type 1 diabetes having more advanced disease and/or higher frequency of complications and more extensive treatment regimens (i.e., standard insulin therapy) than those with type 2 diabetes. Other literature suggests few meaningful differences between those with type 1 and type 2 diabetes in functional status, well-being, or depressive symptomatology (Peyrot et al., 1997; Rubin et al., 1999).

Although individuals with type 1 diabetes have generally reported similar subscores on the SF-36 to those with type 2 diabetes, other literature does report that individuals with type 1 diabetes report better physical functioning, more role limitations due to physical health, fewer role limitations due to emotional problems, more energy, less anxiety, and less favorable health perceptions than those with type 2 diabetes These differences may be the result of other factors associated with diabetes type such as age or treatment regimen (Rubin et al., 1999).

Previous experience with the RAND-36 have reported similar trends to that other generic profile measures, where individuals with type 1 diabetes who have macrovascular

and microvascular complications of diabetes show larger HRQL impairments than those without complications; the presence of macrovascular complications had a larger negative influence on HRQL than the presence of microvascular complications (Hart et al, 2003). Also, individuals with co-morbidities reported lower overall physical scores than those without co-morbidities (Hart et al, 2003). An important finding is that the RAND-36 domain scores in type 1 diabetes were found to be similar to those of a comparable age in the general population (with the exception of the general health and bodily pain domains) (Hart et al, 2003).Also, the RAND-36, a norm-based generic profile measure, consistently reported higher HRQL than that of a generic preference-based measure (i.e., the EuroQol) (Hart et al, 2003).

2.4.2. Generic preference-based index measures in diabetes

Previous research using generic preference-based measures (e.g., 15-D, EQ5D, QWB-SA) reveals similar trends to those found in profile measures, where the presence of complications, intensity of treatment (i.e., insulin use), and obesity are associated with HRQL impairments in both type 1 and type 2 diabetes (Tabaei et al., 2003; Coffey et al., 2002; Redekop et al., 2002; Koopmanschap et al., 2002; Hahl et al., 2002; UKPDS 37., 1999). Holmes and colleagues report similar trends for the presence of complications in type 2 diabetes, where individuals with microvascular complications appear to have larger HRQL impairment on the EQ-5D than those with macrovascular complications (Holmes et al., 2000).

Although glycemic control has not been found to be associated with HRQL impairments on health profile measures (i.e., SF-36), recent literature reveals that

symptoms of hyperglycemia may result in impairment in HRQL when evaluated with a preference-based measure (i.e., QWB-SA) (Tabaei et al., 2004).

The limited use of direct preference measures in diabetes reveals similar trends to those found with indirect preference measures (Brown et al., 2000). Brown and colleagues employed a direct TTO approach to elicit diabetes preference scores and found that the requirement for insulin, the presence of depression, the presence of diabetic retinopathy and the presence of co-morbidities had a significant negative effect in HRQL in those individuals with diabetes (Brown et al., 2000).

The literature regarding the use of preference-based index measures in type 1 diabetes is rather limited in comparison to the extensive literature available on health profile measures. Preference-based measures, such as the Self Administered Quality of Well-being Index (QWB-SA), the EQ-5D and EQ-VAS, and the 15D HRQL instrument, have been employed to measure HRQL in type 1 diabetes (Hahl et al., 2002; Coffey et al., 2002; Hart et al., 2003). Like health status profile measures, these measures confirm that those with long-term diabetes complications have lower HRQL (i.e., preference scores) than those without diabetes complications. Reported preference scores for diabetes-associated complications, at various levels of severity, as measured by the QWB-SA, were: retinopathy, 0.35-0.53; nephropathy, 0.45-0.53; neuropathy, 0.41-0.51; cardiovascular disease, 0.39-0.51 (Coffey et al., 2002). In addition, the EQ-5D shows that those with hyperglycemic complaints have a higher diabetes-associated HRQL burden (Hart et al., 2003).

2.4.3. HUI2 and HUI3 in diabetes

The Health Utilities Index is a multiattribute generic-preference based measure, where health states are classified by a set of dimension or attributes of HRQL, with a number of different levels for each attribute. In the HUI2 system, HRQL is classified by six attributes: sensation (i.e., hearing, vision, and speech), mobility, emotion, cognition, self-care, and pain (Feeny et al., 1995). In the HUI3 system, HRQL is classified by eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain.

The HUI2 and HUI3 may be useful in studying HRQL in diabetes because of several attributes that would likely be affected by the severity of diabetes and diabetic complications (Maddigan et al., 2003; Maddigan et al., 2004). Specifically, diabetic complications such as amputation and peripheral neuropathy may affect the mobility and self-care attributes of the HUI2 and the ambulation and dexterity attributes of the HUI3. In addition, neuropathy and myopathy may affect the pain and discomfort attribute of the HUI2 and HUI3 and the dexterity attribute of the HUI3. Retinopathy may affect the vision attribute of the HUI3 and the sensation attribute of the HUI2 (Maddigan et al., 2004). Finally, nephropathy may affect the mobility, pain, self-care attributes of the HUI2 and the ambulation and pain attributes of the HUI3.

Previous experience with the HUI2 and HUI3 in diabetes has shown that the HUI is effective in detecting diabetes-related HRQL. Maddigan and colleagues (2004) recently evaluated the construct validity of the HUI2 and HUI3 in a sample of individuals with type 2 diabetes from northern rural Alberta. Overall, HUI3 scores in type 2 diabetes were lower in individuals above the median duration of diabetes (5.0 years) as compared to those with a shorter duration. HUI3 scores were also lower for individuals whose diabetes

was managed using insulin compared to diet alone. Disease severity was associated with impairment on the ambulation, dexterity, and pain attributes of the HUI3.

Although there is overlap between the HUI2 and HUI3, there are important differences between the two systems. As a result, in type 2 diabetes, the HUI3 describes larger overall HRQL deficits than does the HUI2 (Maddigan et al., 2003). This may be attributable to different types of emotional burden, pain, and sensation assessment more relevant to diabetes with the HUI3 (Maddigan et al., 2003).

The pain attribute of the HUI2 focuses on achievement of pain relief through medications. The HUI3 pain attribute focuses on the disruption of daily activities due to pain. For this reason, the HUI2 may underestimate true HRQL deficits associated with diabetes in individuals with moderate to severe impairment.

The emotion attribute of the HUI2 focuses on worry and anxiety whereas the HUI3 focuses on happiness versus depression. This difference in content may be of particular importance for individuals with type 1 diabetes, as they may have more anxiety associated with more frequent hypoglycemic events than individuals with type 2 diabetes.

The measurement of sensation (vision, hearing, and speech) on the HUI2 is through one overall single attribute; whereas, the HUI3 has individual attributes for the measurement vision, hearing and speech. As retinopathy is likely to affect the vision, this impairment is more likely to be described accurately on the HUI3 than the HUI2.

In addition to differences in the specific attributes contained, utility scoring functions of the HUI2 and HUI3 were derived differently and therefore, have different ranges of scores. The difference in the lowest possible scores can be a result of the different strategies used to assess preferences for states worse than dead (Maddigan et al.,

2003). Also, the HUI3 includes more health states (particularly covering severely impaired states) and contains more attributes and levels, which stretches the valuation space compared to the HUI2. This results in the overall HUI3 scores being generally lower than those of the overall HUI2 scores. In addition, the HUI3 used a standard gamble and a visual analogue scale to assess preferences for states worse than dead; whereas, the HUI2 only used a visual analogue scale (Maddigan et al., 2003). For this reason, the HUI3 may better reflect community preferences for states worse than dead because the SG approach is consistent with economic decision theory under uncertainty. Also, the HUI3 may be more precise in discriminating amoung higher levels of impairment due to the larger number of levels for several attributes (Feeny et al., 2002; Maddigan et al., 2004).

Maddigan and colleagues (2003) showed that the HUI2 failed to find differences in sensation between clinically different subgroups whereas, the HUI3 vision attribute did note differences between subgroups. Overall, the differences between the HUI2 and HUI3 lead to greater burden on the HUI3 than the HUI2. This study contributed evidence of construct validity of the HUI3, HUI2, and RAND-12 in type 2 diabetes. Maddigan and colleagues concluded however, that the HUI2 was not shown to offer any specific advantage over the HUI3, with the exception of the HUI2 emotion attribute (Maddigan et al., 2003).

In addition to containing attributes relevant to diabetes, the HUI3 has relevance as a reference standard for the general Canadian population, as the HUI3 has been included in all recent national health surveys. Recent experience with the HUI3 in the general population (from 1996-1997 National Population Health Survey (NPHS Cycle 2)

provided an overall HUI3 score of 0.88 (95%CI: 0.87-0.89) for respondents with diabetes (Maddigan et al., 2004). This was statistically lower than subjects without diabetes 0.92 (95%CI: 0.92-0.92) ($p<0.001$)

The presence of co-morbidities had a general trend of additional decrements of HRQL with the increasing number of co morbidities, regardless of the medical condition (Maddigan et al., 2004) Paired combinations of co-morbidities were associated with decrements of 0.13-0.15 in overall HUI3 scores (decreased HRQL); triplets were associated with decrements of 0.26-0.30, compared to those with no co-morbidities. Additionally, the combination of diabetes and an additional medical condition (i.e., heart disease, arthritis, or stroke) resulted in a lower overall HUI3 score than those with diabetes alone (Maddigan et al., 2004) From this research it is apparent that across the general population (aged 18 and over), the illness burden experienced by individuals with diabetes was not only associated with diabetes itself, but also with co-morbid medical conditions.

In reviewing the literature, no studies were identified which employed the Health Utilities Index Mark 2 (HUI2) and the Health Utilities Index Mark 3 (HUI3) (Feeny et al., 2002) in type 1 diabetes. It is important to produce evidence of validity and generate norms on these scales in individuals who have type 1 diabetes as we have very minimal experience with the HUI2 and HUI3 in this population.

2.5. Islet Transplantation (IT) in Type 1 Diabetes Mellitus and HRQL

The majority of patients with type 1 diabetes will be controlled by multiple daily injections of insulin and regular monitoring of the blood glucose. In some cases, glycemic control may be difficult to attain. In more extreme cases, patients with labile or brittle diabetes may experiences severe hypo- or hyperglycemic episodes on a regular basis. These episodes can interfere with their daily lives, thus impairing their overall HRQL. In such cases, islet transplantation (IT) is a treatment option. To be eligible for islet transplants adults with type 1 diabetes must display hypoglycemia unawareness, brittle diabetes (which is marked by severely inadequate blood sugar control), or presence of progressive complications (e.g. neuropathy, nephropathy, or cardiovascular problems). Islet transplantation (IT) aims to free or reduce patients' insulin requirements, along with gaining greater glycemic control.

As with any transplantation procedure, it is important to establish a balance between immunosuppressant efficacy and toxicity (Shapiro et al., 2000). The Edmonton Protocol, for IT in patients with type 1 diabetes, involves a glucocorticoid-free immunosuppressive therapy regimen. Glucocorticoid agents are associated with increased adverse post-transplant effects, in particular, derangements of glycemic control, and therefore, are not desirable in this patient population.

Before this treatment can be made available to a larger number of people with type 1 diabetes, a number of important aspects about this treatment must be evaluated. Physiologic measures have demonstrated that islet transplantation can render patients with type 1 diabetes insulin-independent, within the confines of chronic indefinite immunosuppression (Shapiro et al., 2000; Ryan et al., 2001) Sustained normalization of glycosolated hemoglobin and excellent glycemic control is likely to stabilize or possibly

reverse early secondary complications of diabetes in the longer term (Ryan et al., 2001) These benefits must be offset by the potential increased risks of immunosuppressant drug-specific effects such as infection and malignancy. For this reason, the decision to exchange insulin for immunosuppression in type 1 diabetes should include measures of quality of care, clinical and cost effectiveness, and how patients themselves feel.

Johnson and colleagues are currently evaluating HRQL outcomes in patients with type 1 diabetes mellitus undergoing islet transplantation (IT) through the University of Alberta. Initial study data (Johnson et al., 2002) suggest that patients who have undergone IT (compared with patients on a waiting list or pre-IT) have clinically important differences in HRQL, as determined by the HUI3, along with statistically significant differences on other HRQL measures, such as the Hypoglycemia Fear Survey (HFS). The HFS contains 23 questions that assess patients' concerns and worries about hypoglycemia and the behaviors in which patients may engage to avoid low blood glucose (Cox et al., 1987).

Additional analysis of this early study data shows that the fear of hypoglycemia is significantly lower in IT patients compared to pre-IT patients on the HFS total score ($p<0.001$) (Johnson et al., 2004). IT patients also show clinically important higher HUI2 emotion scores than those pre-IT (1.00 vs. 0.86, respectively) (Johnson et al., 2004). Reduction of fear and anxiety associated with episodes of severe hypoglycemia are important for individuals' overall HRQL as these concerns become an overwhelming burden for patients with type 1 diabetes (Cox et al., 1987; Irvine et al., 1994).

Johnson and colleagues examined HRQL in a small sub-section of the type 1 diabetic population, which is not generalizable to all patients with type 1 diabetes. The

proposed study will expand our experience with these HRQL measures to include a general type 1 diabetes population, not just those with hypoglycemia unawareness and brittle diabetes.

2.5.1. Memphis Immunosuppressant-related Quality of Life (IRQOL) Survey

One of the specific HRQL measures employed in the evaluation of IT is the Memphis Immunosuppressant-related quality of life (IRQOL) survey (Winsett et al, 1999). The IRQOL is a post-transplant specific HRQL measure designed to assess the HRQL burden associated with immunosuppressant therapy. Current transplant literature suggests that standard immunosuppressant therapy regimes result in detrimental side effects, which are likely to result in decreased post-transplant HRQL (Gross et al., 1998; Stratta et al., 1997; Sureshkumar et al., 2002).

In order to effectively evaluate the Edmonton Protocol's glucocorticoid-free immunosuppressant regime, it is important that the IRQOL is able to distinguish the specific HRQL burden (if present) of immunosuppression. Interestingly, data collected to date on the domains of the IRQOL revealed that IT patients reported fewer problems than those pre-transplant (i.e. have not yet received an IT). In other words, subjects who were not on immunosuppressive therapy report having more problems than patients receiving immunosuppression (i.e. post-transplant). Additionally, IRQOL scores pre- and post-transplant appeared to be reflective of scores on the concurrently administered generic HRQL measures (i.e. HUI3 and RAND-36) (Johnson et al., 2002).

For these reasons, it is thought that the symptoms and problems contained in the IRQOL are, in fact, more general symptoms/problems. The item content and five subscales of the IRQOL (emotional burden, life role/responsibility, mobility, GI distress,

and miscellaneous) may well reflect a more general assessment of health status. Although these are important and relevant to individuals with long-standing and labile type 1 diabetes, it may not allow for accurate reflection of immunosuppression-specific related quality of life for patients undergoing IT.

Further, the IRQOL was originally developed and validated in subjects undergoing whole organ transplantation, and receiving steroid-containing immunosuppressive regimens (Winsett et al., 1999). The avoidance of corticosteroids in the Edmonton Protocol may result in fewer problems. In addition, the problems now experienced by patients may not be ones picked up by the IRQOL, thus decreasing the sensitivity of this measure for immunosuppression-specific related quality of life. This apparent lack of specificity drives our purpose for further investigation of this instrument's performance in a larger and more general type 1 diabetes population.

2.6. Summary

Type 1 diabetes places a substantial burden on individuals with the disease and their families. This burden arises from the not only diabetes itself, but also its treatment, the complications, and possible co-morbidities associated with type 1 diabetes. Diabetic complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, stroke, and peripheral vascular disease result in significant morbidity and mortality (Ahroni et al., 1994).

Self-reported HRQL is an important outcome to assess in diabetes, in part because clinical measures, such as glycosolated hemoglobin (A1c), may fail to capture the overall impact of the disease on the person's overall health and functional status. Also, the assessment of HRQL is an essential element of health care evaluation, not only in terms

of assessing the effect of the treatment on the well-being of patients, but also to facilitate the development of clinical and public policy guidelines and the conduct of economic analyses.

Disease-specific and generic measures of HRQL have both been used to study HRQL in individuals with diabetes. Generic measures of HRQL have an advantage over disease-specific measures in that they permit comparisons of the impact of various diseases on multiple dimensions of HRQL and allow comparisons across conditions or populations. Generic measures can be classified into health status profiles and preference-based measures (Guyatt et al., 1993).

Health status profile measures reflect an individual's current health status on multiple dimensions or domains and assign a score to each dimension, but do not necessarily create on overall aggregate score to reflect overall HRQL. Some profile measures utilize a norm-based scoring algorithm where each scale score is scored to have a standardized mean and standard deviation, based on the general population scores/norms.

Preference measures include the state of "dead", anchored at a value of "0", such that they capture both morbidity and mortality. Preference-based measures also allow an overall score to be obtained, which allows for comparison between effects of a disease and intervention. Preferences for health states can be elicited under direct (i.e., SG, TTO, VAS) or indirect (i.e., multiattribute) approaches. Indirect preference-based index measures assess multiple domains or dimensions of HRQL/health status and apply a "preference" value to the health state.

Much research has assessed the ability of disease-specific and generic health profile measures of HRQL to discriminate between subgroups of individuals with diabetes expected to have different levels of HRQL. Overall, a large amount of literature exists on use of generic health profile measures in diabetes; however, use of preference-based index measures is less extensive. Generic profile measures (such as the SF-36, RAND-36, NHP, and SIP) and preference-based index measures (such as EQ-5D, 15-D, QWB-SA, HUI) in diabetes reveal similar trends where intensity of treatment, the presence and severity of complications and the presence of co-morbidities have been associated with lower levels of HRQL. Overall HRQL burden and associated trends are similar for those with type 1 and type 2 diabetes, with some differences on specific domains or attributes of measures.

Previous experience with the HUI, a preference-based index measure, in type 2 diabetes has shown that overall, differences between the HUI2 and HUI3 lead to greater burden on the HUI3 than the HUI2. This may be attributable to different types of emotional burden, pain, and sensation assessment more relevant to diabetes with the HUI3. Also, it is apparent that across the general population (aged 18 and over), the illness burden experienced by individuals with diabetes was not only associated with diabetes itself, but also with co-morbid medical conditions.

Current evaluation of HRQL outcomes in patients with type 1 diabetes mellitus undergoing islet transplantation (IT) through the University of Alberta suggest that patients who have undergone IT (compared with patients on a waiting list or pre-IT) have clinically important differences in HRQL, as determined by the HUI3, along with

statistically significant differences on other HRQL measures, such as the Hypoglycemia Fear Survey (HFS) (Johnson et al., 2002).

The IRQOL is a post-transplant specific HRQL measure designed to assess the HRQL burden associated with immunosuppressant therapy. Interestingly, data collected to date on the domains of the IRQOL reveals that IT patients have reported fewer problems than those pre-transplant (i.e. have not yet received an IT). The apparent lack of specificity of the IRQOL for immunosuppressant-related quality of life drives our purpose for further investigation of this instrument's performance in a larger and more general type 1 diabetes population. Also, the lack of construct validity evidence and population norms for the HUI 2 and 3 in type 1 diabetes drive our objectives for investigation on the use of this generic preference-based index measure in this population.

Chapter 3: Methods

3.1. Study Design

This study used a cross-sectional survey design. All data were collected by self-report, through self-completed questionnaires, mailed to adult type 1 diabetes patients.

The questionnaire package (Appendix A) included standardized measures of generic and specific health status and health-related quality of life. In addition, we collected data on people's self-reported symptoms that could indicate diabetes-related complications. Furthermore, we also assessed indicators such as disease advancement and duration.

A cover letter (Appendix B) attached to the questionnaire discussed all ethical considerations. Initial mailouts were sent in September 2003 (Edmonton) and January 2004 (Calgary). A reminder letter (Appendix C) was mailed 2 weeks after the initial mailing if the questionnaire had not been returned. A second questionnaire package was then sent to all initial non-responders in Edmonton and Calgary in February 2004. A two-week reminder card was not sent after this mailout.

All questionnaires were assigned a unique study ID number, and responders were tracked accordingly. All completed returned survey data were entered into a Microsoft Access Database.

3.2. Sample

We included adults (i.e., ≥18 yrs) with clinically diagnosed type 1 diabetes. Patients had to be 18 years of age at the time of survey completion, English-speaking, and have a fixed address. Patients who were not able to complete the questionnaires on their

own were allowed to have a proxy help or complete the survey for them (this situation was declared in the last page of the survey package).

All subjects are type 1 diabetes patients of diabetes clinics of Dr. Edmond Ryan Endocrinologist) and Dr. Ellen Toth (Diabetes Internal Specialist) at the University of Alberta, and Dr. Alun Edwards (Endocrinologist) at the University of Calgary. Patient names and addresses were provided by physicians and/or clinic staff. Edmonton clinics provided patient names and addresses for those individuals with type 1 diabetes who have been seen by Dr. Ryan or Dr. Toth at the respective clinic, at some point in time. These patient names and addresses were not pre-screened for any reason by clinic staff therefore, this list could include individuals who had moved or deceased (as this information would not have been available) and/or had not been seen recently at the clinic, thus limiting the selection bias of this sample.

The Calgary diabetes clinic provided patient names for those individuals with type 1 diabetes who have been seen by Dr. Edwards from 01/01/2003 – 12/31/2003. Current patient addresses were then abstracted from patient charts to obtain a mailing list for the Calgary clinic. This list excluded individuals who were deceased, as this information was available from the patient chart. No other selection factors were used to generate a Calgary clinic mailing list.

3.3 Ethical Consideration

If participants returned the questionnaire, we assumed they had provided implied consent to participate in the study. Clinical data was not abstracted from charts, so participants were able to return their questionnaires confidentially. Ethical approval for

this study was obtained through the University of Alberta Health Research Ethics Board Panel B and the University of Calgary Research Ethics Board.

3.4. Measures

3.4.1. Health Utilities Index Mark 2 (HUI2) and the Health Utilities Index Mark 3 (HUI3)

The HUI2 and HUI3 are preference-based multi-attribute utility measures of HRQL. These measures assess multiple domains of health status and assign a valuation to each health state (Feeny et al., 1995; Feeny et al., 2002). Health states are classified by a set of dimension or attributes of HRQL, with a number of different levels for each attribute.

In the HUI2 system (Appendix D), HRQL is classified by six attributes: sensation (i.e., hearing, vision, and speech), mobility, emotion, cognition, self-care, and pain (Feeny et al., 1995). Fertility is a seventh attribute of the HUI2 (Feeny et al., 1995), but was not included in this study and therefore, assumed to be normal. In the HUI2 system, each of the six attributes has four or five different levels; these levels and attributes describe 24,000 unique HUI2 health states. Overall utility scores on the HUI2 range from -0.03 to 1.0, where -0.03 represents the worst possible HUI2 health state, 0.0 represents dead, and 1.0 represents full health (Feeny et al., 1995).

In the HUI3 system (Appendix E), HRQL is classified by eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. In the HUI3 system, each of the eight attributes has five or six different levels; these levels describe 972,000 unique HUI3 health states (Feeny et al., 2002). Overall utility scores on the HUI3 range from -0.36 to 1.0, where -0.36 represents the worst possible HUI3 health state, 0.0 represents dead, and 1.0 represents full health (Feeny et al., 2002).

Differences greater than 0.03 on the HUI2 and HUI3 overall scores are considered to be clinically important (Grootendorst et al., 2000; Drummond, 2001). HUI3 overall scores have been found to have a test-retest reliability of 0.77 over one month, in a population health survey, using the intra-class correlation coefficient (Feeny et al., 2002). Suarez-Almazor and colleagues report three-month and six-month test-retest reliability ICCs of 0.78 and 0.80 for the HUI2 in a cohort of patients with low back pain (Suarez-Almazor et al., 2000)

In addition to overall utility scores, single attribute utility scores (SAUS) can be obtained for each attribute of the HUI2 and HUI3 (Feeny et al, 1995; Feeny et al., 2002). For the single attribute utilities, scores range from 0.0 to 1.0, where 0.0 represents the lowest level of functioning on an attribute and 1.0 represents full functional capacity. Differences greater than 0.05 on the HUI2 and HUI3 SAUS can be considered to be clinically important (HUI, 2004; Maddigan et al., 2004). The burden of morbidity on each individual attribute can also be denoted by the distribution of individuals on each level of the attribute.

3.4.2. Memphis Immunosuppressant-related Quality of Life (IRQOL) Survey (Appendix A)

The Memphis IRQOL Survey is a post-transplant HRQL measure designed to assess the HRQL burden associated with immunosuppressant therapy (Winsett, 1998). This measure contains 5 scales (emotional burden, life role/responsibility, mobility, gastrointestinal (GI) distress, miscellaneous) based on important factors in HRQL post-transplant, specifically related to immunosuppression effects of therapy.

A total IRQOL score is generated by the sum of the 5 scale scores. Each scale contains 5-10 items; all items and scales are equally weighted towards the total IRQOL

score. IRQOL scores can range from 0.0 – 160.0. HRQL is inversely related to the IRQOL score (i.e., an individual with severe physical and mental burdens would produce a high IRQOL score); therefore, a high IRQOL score indicates more HRQL burden.

IRQOL scores can be interpreted as follows: low IRQOL burden (scores 0.0-20.0); moderate IRQOL burden (scores 21.0-40.0); moderately high IRQOL burden (scores 41.0-80.0); high IRQOL burden (scores 81.0-120.0) and extremely high IRQOL burden (scores 121.0-160.0) (Winsett, 2001).

The IRQOL is currently being employed by the Islet Transplant (IT) program to assess HRQL burden associated with immunosuppressant therapy. Interestingly, data collected to date on the domains of the IRQOL reveals that IT patients have reported fewer problems than those pre-transplant (i.e. have not yet received an IT). In other words, subjects who are not on immunosuppressive therapy report having more problems than patients receiving immunosuppression (i.e. post-transplant). Additionally, IRQOL scores pre- and post-transplant appear to be reflective of scores on the concurrently administered generic HRQL measures (i.e. HUI3 and RAND-36) (Johnson et al., 2002). For these reasons, it is thought that the symptoms and problems contained in the IRQOL are, in fact, more general symptoms/problems. The item content and five subscales of the IRQOL (emotional burden, life role/responsibility, mobility, GI distress, and miscellaneous) may well reflect a more general assessment of health status. Although these are important and relevant to individuals with long-standing and labile type 1 diabetes, it does not allow for accurate reflection of immunosuppression-specific related quality of life.

3.4.3. The RAND-36 Health Status Inventory

The RAND-36 is a commonly used health profile instrument (Hays, 1998). It is designed to evaluate 8 areas of behavior or experience including physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, and role limitations due to emotional problems, mental health and health transition (Hays, 1998).

Physical functioning measures the individual's limitations in physical activities because of health. The extent to which physical health interferes with doing work or other regular daily activities is measured by the 'role limitations due to physical health problems' construct. The pain construct measures the frequency of pain and the extent of role interference due to pain. General health perceptions measure the individual's perceptions of health in general (i.e., feeling well vs. ill). Emotional well-being measures an individual's general mood or affect. The extent to which emotional problems interfere with doing work or other regular daily activities is measured by the 'role limitations due to emotional problems' construct. Lastly, the social functioning construct measures the extent to which health interferes with social activities with family, friends, neighbors, or groups. In addition, overall summary scores representing physical (Physical Health Composite - PHC) and mental (Mental Health Composite– MHC) health are generated (Hay, 1998).

The RAND-36 (or the related SF-36) has been frequently applied in the assessment of health status in diabetes (DCCT Research Group, 1996; Jacobson et al., 1994; Johnson et al., 1996; Maddigan et al., 2004). The RAND-36 summary scores are T-score norm-based scoring approaches; therefore, interpretation of these T-scores is

based on a general US population mean of 50.0, with a standard deviation of 10.0 (Hays, 1998).

For reasons outlined previously, it is felt that the RAND-36 provides a more rational, clinically sound and discriminative scoring system for HRQL for diabetes (Johnson et al., 2004; Hays et al., 1998). Therefore, we have employed the RAND-36 rather than the SF-36.

3.4.4. Other Specific Measures

In addition to the HUI2/3, RAND-36 and IRQOL, the questionnaire package included two other specific measures for patients with diabetes. These instruments are identified here for information. Data from these questionnaires are not considered for the purposes of the analysis reported in this thesis.

Audit of Diabetes Dependent Quality of Life (ADDQOL)

The ADDQOL is a diabetes-specific measure of HRQL designed to measure individuals' perception of the impact of diabetes on their quality of life (Bradley et al., 1999). Evidence indicates that the ADDQOL is valid and reliable in measuring diabetes-related HRQL in adults with type 1 and type 2 diabetes (Bradley et al., 1999). As it is a diabetes-specific measure of HRQL, it may be more sensitive to treatment related differences in HRQL.

Hypoglycemia Fear Survey (HFS)

The HFS is diabetes-specific HRQL measure that contains 23 questions that assess patients' concerns and worries about hypoglycemia and the behaviors in which patients may engage to avoid low blood glucose (Cox et al., 1987). The HFS generates two subscores, HFS Behavior Score and HFS Worry Score. These subscores are

generated by items which are relevant to individuals' behaviors or worries, respectively, about hypoglycemia events. In addition, an overall HFS Total score (i.e., the sum of the two subscores) is generated (Cox et al., 1987).

3.4.5. Demographics & Clinical Characteristics Questionnaire

Patients also completed a sociodemographic and clinical self- report questionnaire (Appendix A). The sociodemographic component of the questionnaire contained questions about their age, sex, marital and occupational status, highest level of education, and main activity in the last twelve months. The clinical self-report component of the questionnaire contained questions regarding diagnosis, duration, glycemic control and advancement of diabetes. Also, it contained questions regarding signs and symptoms of diabetic complications. Lastly, the questionnaire contained a self-report list of co-morbidities, taken from the questionnaire for the National Population Health Survey (Statistics Canada).

3.5. Data Analysis

3.5.1. Descriptive Statistics

All HRQL measures were scored according to the developers' guidelines. Descriptive statistics were calculated to present the minimum, maximum, median and mean (SD) for the HRQL scores for the patients. We have created local norms for the battery of measures in a population with type 1 diabetes for further comparisons. The respondent sample was described by self-reported demographic and clinical characteristics.

3.5.2. Known Group Comparisons

To assess the construct validity of the measures in type 1 diabetes, a known-groups approach was used. We determined the ability of these instruments to distinguish between subgroups of individuals anticipated to differ in HRQL, as employed similarly in previous validation studies in type 2 diabetes (Maddigan et al., 2004). We conducted analysis of variances (ANOVAs) and analysis of co variances (ANCOVAs) for the known groups. ANCOVAs controlled for the following co-variates: age, sex, highest level of completed education, marital status, income, duration of diabetes (if applicable) and the presence of co-morbidities (if applicable). For all comparisons, a p-value of less than 0.05 was considered to be statistically significant; no adjustments were made for multiple testing.

In addition to statistical interpretation of group comparisons, differences of 0.03 or greater on the HUI2 and HUI3 overall scores are considered to be clinically important (Grootendorst et al., 2000; Drummond, 2001); differences of 0.05 or greater on the HUI2 and HUI3 single utility attribute scores are considered to be clinically important (HUI, 2004).

3.5.2.1. Duration and Advancement of Diabetes

Known-groups were formed based on self-report indicators of disease advancement and duration, as we anticipate the HRQL of these groups to differ. Based on the mean self-reported duration of diabetes, HRQL scores of individuals below or equal to the mean duration of diabetes were compared to those above the mean duration of diabetes. Subgroups were also determined using indicators for disease advancement (defined respectively as the diabetes-related number of work days off work and emergency room (ER) visits in the last three months) and glycemic control (defined as

those experiencing low blood sugars and needing help from someone else in the last three months).

3.5.2.2. Presence of Diabetic Complications

Known groups for the presence of diabetic complications were formed based on self-report indicators for the presence of the complication, as these groups are anticipated to differ in HRQL. The specific items for self-reported symptoms, problems or co-morbidities are included in the questionnaire (Appendix A).

Presence of Cardiovascular Disease

The presence of cardiovascular disease was determined by an individual indicating they had been told by a health professional that they had hypertension or heart disease or that they had a heart attack and/or a stroke.

Presence of Retinopathy or Diabetic Eye Disease

The presence of retinopathy or diabetic eye disease was determined by an individual indicating they had vision damage, retinal damage and/or cataracts due to diabetes.

Presence of Neuropathy or Peripheral Vascular Disease (PVD)

The presence of neuropathy or peripheral vascular disease was determined by an individual indicating they had pain/numbness, blood circulation problems, and/or surgical operation of their legs or feet due to diabetes.

Presence of Nephropathy

The presence of nephropathy was determined by an individual indicating they had kidney damage due to diabetes.

3.5.2.3. Presence of Co-morbidities

The presence of co-morbidities was determined using a list of other co-morbidities (Statistics Canada) where an individual indicates they have been told by a health professional that they have a listed condition (Appendix A). As the presence of cardiovascular disease had already been covered, those items were omitted from the Statistics Canada list.

3.5.3. Construct Validity

3.5.3.1. HUI2 and HUI3 Construct Validity

To assess the validity of the HUI2 and HUI3 in type 1 diabetes, the ability of each instrument to distinguish between subgroups of individuals (as outlined above) was determined using overall scores. The following hypotheses were generated:

H1) - HUI2 and HUI3 overall scores will be lower for individuals above the mean duration of diabetes compared to individuals below the mean duration of diabetes.

H2) - HUI2 and HUI3 overall scores will be lower for individuals who reported having co-morbidities compared to individuals who did not report any co-morbidities.

H3) – HUI2 and HUI3 overall scores will be lower for individuals who reported having cardiovascular disease compared to individuals who did not report having cardiovascular disease.

H4) – HUI2 and HUI3 overall scores will be lower for individuals who reported having retinopathy or diabetic eye disease compared to individuals who did not report having retinopathy or diabetic eye disease.

H5) – HUI2 and HUI3 overall scores will be lower for individuals who reported having neuropathy or peripheral vascular disease compared to individuals who did not report having neuropathy or peripheral vascular disease.

H6) – HUI2 and HUI3 overall scores will be lower for individuals who reported having nephropathy compared to individuals who did not report having nephropathy.

HUI2/3 Single Attribute Utility Scores

The above known groups comparisons and hypothesis tests were also performed for all SAUS of the HUI2 and HUI3.

3.5.3.2. IRQOL Construct Validity

To assess the validity of the IRQOL in type 1 diabetes, IRQOL scores were compared in the same known groups as described above for the HUI2 and HUI3. For these known group comparisons and hypothesis tests, we assessed differences between groups on overall IRQOL scores.

IRQOL scores were also compared to those of generic benchmark HRQL scores collected (i.e. HUI3 and RAND-36). Overall measure scores of all instruments were compared using Pearson's correlation coefficient. The following hypothesis was generated:

H7) – Overall IRQOL scores will be similar, with moderate to strong correlations, to those of generic benchmark HRQL scores (i.e., HUI2, HUI3, and RAND-36), as seen with previous pilot study data.

3.5.3.3. Interscale Correlations

Interscale correlations were calculated to assess further cross-sectional construct validity of the HUI2, HUI3, and IRQOL. This included comparisons of all overall and single attribute/component scores of the HUI2, HUI3, IRQOL and RAND-36. Pearson's correlation coefficient was used to test the strength of association between domain and overall scores of the HUI2, HUI3, RAND-36, and IRQOL. Parametric and non-

parametric correlation tests were used, as the distribution of the data was skewed to the right. Because results were very similar, only the results of the parametric correlation tests are reported.

The predicted correlation matrix for the domain and overall scores of the HUI2, HUI3, RAND-36 and IRQOL is outlined in Table 3.1. The predicted relationships were determined by consensus among the supervisory committee members, and previous experience with these measures (Maddigan et al., 2004). Correlations of greater than 0.50 were considered to be strong, correlations from 0.35 to 0.50 were considered moderate, correlations from 0.20 to 0.34 were considered weak and less than 0.19 were considered negligible or not correlated (Guyatt et al., 1987; Juniper EF et al., 1996). The predicted correlations were then compared to the observed correlations; agreement is reported as percentage of predictions that were correct.

Table 3.1 Predicted Correlation Matrix

	IRQOL						RAND-36									
	IRQOL overall	Emotional burden	Life role/responsibility	Mobility	GI distress	Misc.	PHC	MHC	PF	RP	BP	GH	VT	SF	RE	MH
HUI2-overall	S	M	W	M	W	W	S	S	W	W	M	M	W	M	M	M
Sensation	W	-	W	-	-	-	-	W	-	-	-	W	-	W	-	-
Mobility	M	-	W	S	-	-	M	W	S	M	W	M	W	M	W	W
Emotion	M	S	W	-	W	-	M	S	-	-	-	W	-	W	M	S
Cognition	W	W	W	-	-	-	W	M	-	-	-	W	-	-	-	-
Self-care	W	-	W	W	-	-	W	-	S	M	-	M	M	M	-	-
Pain/discomfort	M	M	W	M	S	W	S	M	W	W	S	M	-	-	W	W
HUI3 – overall	S	W	W	M	W	W	S	S	W	W	M	M	M	M	M	M
Vision	-	-	W	-	-	-	-	-	M	M	-	W	-	W	-	-
Ambulation	M	-	W	S	-	-	M	W	M	M	W	M	-	W	-	-
Dexterity	W	-	W	W	-	-	W	W	S	M	-	W	W	W	-	-
Pain	M	M	W	S	W	-	S	M	M	M	S	M	W	W	W	W
Hearing	-	-	W	-	-	-	-	W	-	-	-	W	-	W	-	-
Speech	-	-	W	-	-	-	-	W	-	-	-	W	-	W	-	-
Emotion	S	S	W	W	-	-	M	S	-	-	-	W	-	W	M	S
Cognition	-	-	W	-	-	-	W	M	-	-	-	W	-	-	-	-

Correlation legend:
S = strongly correlated (> 0.50)
M = moderately correlated (0.35 to 0.50)
W = weakly correlated (0.20 to 0.34)
- = negligible or not correlated (0.00 to 0.19)

IRQOL	RAND-36									
	PF	RP	BP	GH	VT	SF	RE	MH	MHC	PHC
Overall	W	W	W	M	W	W	M	W	M	M
Emotional burden	-	-	W	W	W	W	S	S	S	W
Life role/responsibility	W	W	W	W	W	M	W	W	M	M
Mobility	S	S	M	M	M	W	W	W	W	S
GI distress	M	W	S	M	W	W	W	W	W	S
Miscellaneous	-	-	-	-	-	-	-	-	-	-

3.6. Missing Data

As all data were self-reported, through mailed questionnaires, we anticipated the problem of missing data. The main concern with missing data is bias, where subjects who respond or complete questionnaires are systematically different from non-responders or those with incomplete questionnaires. This can result in an unrepresentative sample and therefore, yield results which are difficult to interpret (Curran, 1998). As data regarding demographic and clinical characteristics of non-responders were not available (i.e., this data was collected in a self-report questionnaire that was returned with the HRQL measures), a response bias analysis was not possible.

It was assumed that all missing data was missing at random (MAR) or missing completely at random (MCAR), as we did not have data on non-responders. *A priori* methods of handling missing data for the primary HRQL measures evaluated are outlined below.

3.6.1. Health Utilities Index

Missing items in the HUI do not allow an overall HUI score to be generated (Feeny et al., 1995). Therefore, imputation of missing data for the HUI can be crucial for study power. As many items on the HUI are comparable to those of the RAND-36, missing items on the HUI could be imputed by considering the individual's response on a similar RAND-36 item. This method will maintain sample variation and does not require complicated statistical methods.

3.6.2. RAND-36

The RAND-36 permits only one item per scale to have a missing response, and only three items may have missing responses for the entire inventory (Hays, 1998). As

with the HUI, imputation of missing data for the RAND-36 can be crucial for study power. As outlined above for the HUI, missing items on the RAND-36 could be imputed by considering the individual's response on a similar HUI item.

3.6.3. IRQOL

The IRQOL requires an individual to rate how often they have problems with a particular problem and next, how troubling this problem is. Subscale scores of the IRQOL are generated from a subject's response to only the first component of the question; the overall IRQOL score includes how troubling this problem is to the individual. Previous experience with this survey has shown that subjects who report 'no problems' on the first component of the question, are likely not to answer (or leave blank) the second component of the question (Johnson et al., 2002). It can be assumed that subjects who report 'no problems' for a particular item, would then rate the item not troublesome. In this circumstance, imputation of the second component of the question could be made. Additional imputations on specific content items could not be made due to lack of similarities between this survey and the others employed (i.e., HUI, RAND-36) In addition, previous literature on the IRQOL provides no evidence on the methods for imputation.

3.7. Sample Size Considerations

As previously stated, differences of 0.03 on overall HUI3 scores are considered to be clinically important (Feeny et al., 1996; Maddigan et al., 2004). Based on previous experience (Maddigan et al., 2003) in people with type 2 diabetes, we have observed HUI2 and HUI3 score differences of up to 0.10 (on a scale of 0.0 to 1.0) between groups, and standard deviation of 0.25 to 0.30.

Additionally, in our pilot study (Johnson et al., 2000), we observed IRQOL differences (SD) of 40.97 (40.98), 32.38 (37.18), and 30.10 (37.81) on its components of emotional burden, life role/responsibility and mobility, respectively. To our knowledge, a clinically important difference (CID) for IRQOL scales has not been determined. These previous experiences and pilot data serve as the basis of our sample size calculation for this study.

In accordance with our sample size calculations, an ideal sample would have been 3 000, in order to have 80% power to detect a 0.03 difference in means for the HUI2 and HUI3 (Table 3.2). As it was not feasible to attain a sample of such magnitude, a sample size of a minimum of 200 provided us with 80% power to detect a difference in means of 0.10 on the HUI2 and HUI3 (Table 3.2) and various IRQOL mean differences (Table 3.3). These calculations assumed standard deviations of 0.20-0.30, using a two-group t-test with a 0.05 two-sided significance level. If these assumptions are correct, then a minimum of 100 participants per group (e.g., subjects above and below the median duration of diabetes) would have provided us with sufficient power for our planned comparisons and allowed a balance between a CID (for the HUI3) and the practical and feasible aspects of this study.

Table 3.2 Sample size considerations* Health Utilities Index Mark 2 and Mark 3

Measured Difference	Standard Deviation (SD)	n per group
0.03	0.20	697
0.05	0.20	251
0.07	0.20	128
0.10	0.20	63
0.03	0.25	1 089
0.05	0.25	392
0.07	0.25	200
0.10	0.25	98
0.03	0.30	1568
0.05	0.30	565
0.07	0.30	288
0.10	0.30	141

*assuming 2-sided alpha 0.05, independent t-test and power of 80%.

Table 3.3 Sample size considerations* Immunosuppressant-Related Quality of Life

Measured Difference	Standard Deviation (SD)	n per group
40	40	16
40	30	9
30	40	28
30	30	16
25	40	41
25	30	23

*assuming 2-sided alpha 0.05, independent t-test and power of 80%.

Chapter 4: Results

4.1. Response Rate

The initial mail out, with two week reminder letters, produced response rates of 47% and 58% in Edmonton and Calgary, respectively (Table 4.1) A second mail out, with no reminder letters, to non-responders resulted in an overall response rate of 53% for Edmonton and 69% in Calgary. This resulted in 221 completed, returned surveys, for a 61% overall response rate.

Table 4.1 Results of Study Mail out

	Initial Mail out*	Second Mail out*	Total†
Edmonton	138 / 297 (46.5%)	7 / 138 (5.1%)	145 / 276 (55.1%)
Calgary	62 / 115 (58.3%)	9 / 43 (20.9%)	76 / 110 (69.1%)
Total	221 / 412 (53.6%)	16 / 181 (8.9%)	221 / 386 (61.2%)

*denominator is total surveys sent minus return to senders (RTS) received
†denominator is total number of potential respondents minus total RTS received

4.2. Sample Demographics

Of the 221 respondents, five were excluded from the analysis as they were found to be under the age of 18 years, as outlined in the study inclusion criteria. No proxies were utilized to complete the surveys, although this option was available to subjects. Of the 216 respondents who met all study inclusion criteria, the majority were female (127, 58.8%) and were married or in a partnership (131, 60.6%) (Table 4.2). The highest level of completed education for most respondents included high school (19.4%), some college education (19.9%), and a college degree (19.0%). Working was the main activity in the last twelve months for the majority of respondents (58.3%). Total household income last year for the sample ranged from ≤ $10 000 (9.7%) - ≥ $70 000 (30.6%).

Table 4.2 Sample Demographics

Characteristic	Valid n	Total*
Age (yrs) – mean (SD)	215	37.13 (14.28)
Sex	216	
Female		127 (58.8)
Male		89 (41.2)
Marital Status	216	
Single		69 (31.9)
Married/In a partnership		131 (60.6)
Separated/Divorced		13 (6.0)
Widowed		3 (1.4)
Highest Level of Completed Education	216	
Less than high school		16 (7.4)
High school		42 (19.4)
Some college		43 (19.9)
College degree		41 (19.0)
Some university		27 (12.5)
University degree		401 (8.5)
Other		7 (3.2)
Main Activity in Last 12 months	216	
Working		126 (58.3)
Looking for work		11 (5.1)
Keeping house		18 (8.3)
Student		301(3.9)
Disability		16 (7.4)
Retired		15 (6.9)
Total Household Income Last Year	196	
≤ $10 000		19 (9.7)
$10 000 – 29 999		44 (22.4)
$30 000 – 49 999		37 (18.9)
$50 000 – 69 999		36 (18.4)
≥ $70 000		60 (30.6)

n (%) unless otherwise specified

4.2.1. Sample Clinical Characteristics

Respondents had a mean (SD) age of 37.1 (14.3) years, mean (SD) duration of diabetes of 20.9 (12.4) years (median of 19.0 years), with a median age of diagnosis of 12.0 years (Table 4.3) The majority of respondents were at a normal weight (47.9%) at diagnosis, with 92.9% of individuals starting insulin therapy within 3 months of diagnosis

and a median of 4 insulin injections per day. These characteristics affirm that the subjects in this sample would be considered to have type 1 diabetes.

Table 4.3 Sample Clinical Characteristics

Characteristic	Valid n	Total*
Duration of Diabetes (yrs) - mean (SD)	215	20.91 (12.43)
Age at Diagnosis (yrs) - median (SD)	215	12.0
Weight at Diagnosis	211	
Underweight		89 (42.2)
Normal weight		101 (47.9)
Overweight		21 (10.0)
Started insulin within 3 months	210	195 (92.9)
Insulin injections per day -median (min, max)	214	4.0 (1.0-5.0)

n (%) unless otherwise specified

4.2.2. Self-reported glycemic control

The majority of respondents rated their overall diabetes control as good (41.8%), where ratings ranged from poor (7.5%) to excellent (5.6%) (Table 4.4). Most individuals have had an A1c reading within the last six months (80.9%); of those that reported their last A1c reading, the mean A1c was 7.89% (±1.56). Overall, respondents had adequate control of their blood sugars on their own; 93.5% of respondents reported experiencing low blood sugars in that last 3 months, that they were able to treat themselves, with only 13.3% reporting needing help from someone else to treat recent low blood sugars. Over one-third (36.9%) of respondents reported previous experience with diabetic ketoacidosis, either at the time of their diagnosis or since then.

Table 4.4 Sample Self-reported glycemic control

Characteristic	Valid n	Total*
Rating of Overall Diabetes Control	213	
Poor		16 (7.5)
Fair		54 (25.4)
Good		89 (41.8)
Very Good		42 (19.7)
Excellent		12 (5.6)
Time Since Last A1c Reading	215	
During the last 4 weeks		35 (16.3)
1-3 months ago		83 (38.6)
4-6 months ago		56 (26.0)
> 6 months ago		37 (17.2)
Last A1c Reading (% ± SD)	126	7.89 (1.56)
Experienced low blood sugars that were able to treat yourself	214	200 (93.5)
Experienced low blood sugars that needed help from someone else	211	28 (13.3)
Mean number of diabetes-related ER visits in the last month	215	0.05 (0.3)
Mean number of diabetes-related days off work in the last 3 months	214	0.43 (2.40)
Mean number of diabetes-related overnight hospital stays in the last 3 months	214	0.08 (0.90)
Previously experienced diabetic ketoacidosis	214	79 (36.9)

n (%) unless otherwise specified

4.3. Presence of Complications

The prevalence of indicators for the presence of diabetic complications is shown in Table 4.5. Based on the previously established criteria for the presence of diabetic complications, the self-reported prevalence of diabetic complications in this sample was: retinopathy/diabetic eye disease (n=88, 40.7%); neuropathy/peripheral vascular disease (n=73, 33.8%); cardiovascular disease (n=55, 25.5%); nephropathy (n=40, 18.5%).

Table 4.5 Indicators for the Presence of Diabetic Complications

Characteristic	Valid n	Total*
Presence of Retinopathy		
Retinal Damage	216	79 (36.6)
Vision deterioration due to diabetes-related retinal deterioration	215	52 (24.2)
Cataracts due to diabetes	215	28 (13.0)
Presence of Nephropathy		
Kidney Damage	215	40 (18.6)
Receiving treatment for kidney damage	214	33 (15.4)
Medication	216	27 (12.5)
Peritoneal dialysis	216	2 (0.9)
Kidney transplantation	216	5 (2.3)
Presence of Neuropathy		
Pain/numbness in legs	213	57 (26.8)
Blood circulation problems in legs/feet	213	45 (21.1)
Surgical operation of leg due to diabetes	214	4 (1.9)

n (%) unless otherwise specified

4.4 Presence of Co-morbidities

The self-reported prevalence of co-morbidities is shown in Table 4.6. A thyroid condition (21.2%) was the most prevalent, followed by arthritis/rheumatism (16.8%) and asthma (11.4%), respectively. As previously outlined, co-morbidities of high blood pressure (31.1%), heart disease/heart attack (6.6%), and stroke (1.2%) were excluded from establishing subgroups, as they were used to determine the presence of cardiovascular disease.

Table 4.6 Presence of Co-morbidities

Characteristic	Valid n	Total*
Co morbidities (median)	166	1.0
Co-morbidities listed:		
Asthma	166	19 (11.4)
Arthritis/rheumatism	167	28 (16.8)
Back problems, excluding arthritis	167	23 (13.8)
High blood pressure	167	52 (31.1)
Migraine headaches	167	12 (7.2)
Chronic bronchitis/emphysema	167	6 (3.6)
Sinusitis	167	11 (6.6)
Epilepsy	167	4 (2.4)
Heart disease/had a heart attack	167	11 (6.6)
Stroke	167	2 (1.2)
Cancer	167	2 (1.2)
Stomach or intestinal ulcers	167	7 (4.2)
Urinary incontinence	167	6 (3.6)
Bowel disorder	167	8 (4.8)
Glaucoma	167	8 (4.8)
Thyroid condition	167	35 (21.2)
Other	167	18 (10.8)

n (%) unless otherwise specified

4.5. HRQL Measure Scores – Descriptive Statistics

4.5.1. HUI2 and HUI3

Overall mean (± SD) HUI2 and HUI3 scores were 0.84 ± 0.14 and 0.78 ± 0.23, respectively (Tables 4.7A and 4.7B). Overall HUI2 scores ranged from 0.29-1.00; overall HUI3 scores ranged from -0.08-1.00. The distribution of overall HUI2 and HUI3 scores is shown not to be a normal distribution, with skew to the left (Figures 4.1 and 4.2). The majority of single attribute utility scores (SAUS) on the HUI2 and HUI3 were similar. Distribution of levels on the HUI2 and HUI3 attributes and SAUS are shown in Tables 4.7 through 4.9.

The percentage of the study sample with missing data ranged from none on certain HUI2 and HUI3 attributes to a high of 1.9% (n=4) on the overall HUI2 score (Tables 4.7A and 4.7B). Missing data was a result of either a missing item on the

questionnaire or missing categorical data of a co-variate, which in turn results in an unavailable utility score. As missing data was minimal for the HUI2 and HUI3, no imputations were made.

Table 4.7A Descriptive statistics for Health Utilities Index Mark 2

	N	Missing N (%)	Min	Max	Mean	SD	Median	IQR (25th-75th Percentile)
HUI2 Overall	212	4 (1.9%)	0.29	1.00	0.84	0.14	0.88	0.80-0.94
HUI2 Sensation	215	1 (0.5%)	0.00	1.00	0.89	0.01	0.87	0.87-1.00
HUI2 Mobility	215	1 (0.5%)	0.34	1.00	0.99	0.06	1.00	1.00-1.00
HUI2 Emotion	216	-	0.00	1.00	0.88	0.16	0.86	0.86-1.00
HUI2 Cognition	216	-	0.66	1.00	0.95	0.77	1.00	0.86-1.00
HUI2 Self-care	215	1 (0.5%)	0.00	1.00	0.99	0.10	1.00	1.00-1.00
HUI2 Pain	215	1 (0.5%)	0.00	1.00	0.94	0.14	0.95	0.95-1.00

Table 4.7B Descriptive statistics for Health Utilities Index Mark 3

	N	Missing N (%)	Min	Max	Mean	SD	Median	IQR (25th-75th Percentile)
HUI3 Overall	213	3 (1.4%)	-0.08	1.00	0.78	0.23	0.85	0.68-0.95
HUI3 Vision	216	-	0.38	1.00	0.95	0.09	0.95	0.95-1.00
HUI3 Hearing	215	1 (0.5%)	0.00	1.00	0.99	0.09	1.00	1.00-1.00
HUI3 Speech	216	-	0.67	1.00	1.00	0.31	1.00	1.00-1.00
HUI3 Ambulation	216	-	0.16	1.00	0.98	0.08	1.00	1.00-1.00
HUI3 Dexterity	215	1 (0.5%)	0.45	1.00	0.98	0.65	1.00	1.00-1.00
HUI3 Emotion	215	1 (0.5%)	0.00	1.00	0.90	0.18	0.91	0.91-1.00
HUI3 Cognition	216	-	0.32	1.00	0.94	0.13	1.00	0.92-1.00
HUI3 Pain	216	-	0.00	1.00	0.90	0.14	0.92	0.92-1.00

Figure 4.1 Histogram of Overall HUI2 Scores

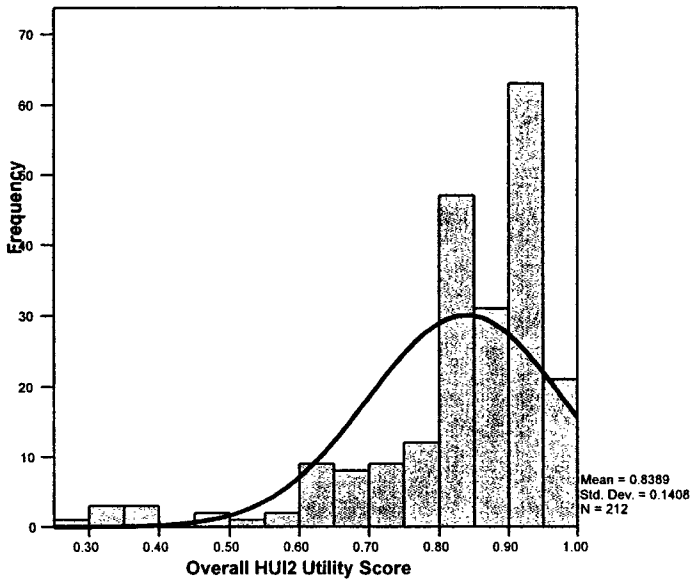


Figure 4.2 Histogram of Overall HUI3 Scores

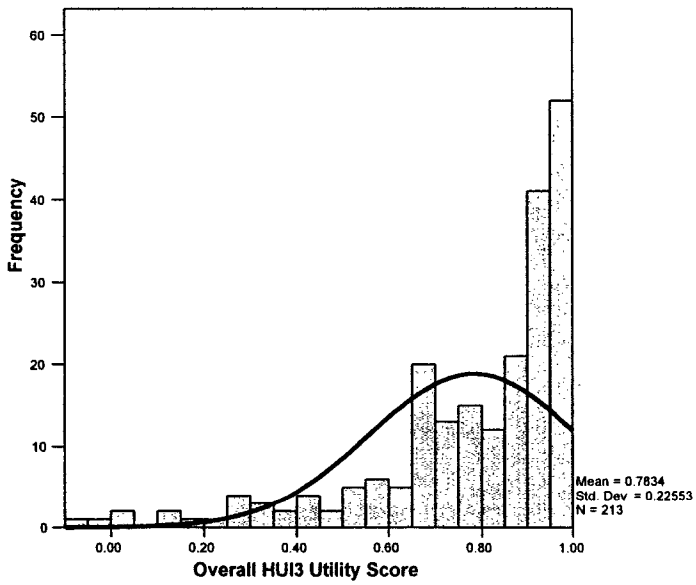


Table 4.8 Distribution of Levels on HUI2 Attributes (% of Subjects) and Single-Attribute Utility Scores

	Sensation		Mobility		Emotion		Cognition		Self-Care		Pain	
	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%
Level 1	1.00	28.2	1.00	91.7	1.00	43.5	1.00	70.4	1.00	97.2	1.00	43.5
Level 2	0.87	63.9	0.92	6.5	0.86	45.8	0.86	27.3	0.85	0.9	0.95	45.8
Level 3	0.65	6.9	0.61	0.9	0.60	7.9	0.66	2.3	0.55	0.5	0.75	6.5
Level 4	0.00	0.5	0.34	0.5	0.37	1.9	0.00	-	0.00	0.9	0.42	2.8
Level 5	n/a	-	0.00	-	0.00	0.9	-	-	-	-	0.00	0.9
Missing	-	0.5	-	0.5	-	-	-	-	-	0.5	-	0.5

HUI2 – Health Utilities Index Mark 2; n/a means not applicable

Table 4.9 Distribution of Levels on HUI3 Attributes (% of Subjects) and Single-Attribute Utility Scores

	Vision		Hearing		Speech		Ambulation		Dexterity		Emotion		Cognition		Pain	
	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%	Utility	%
Level 1	1.00	28.7	1.00	97.7	1.00	98.1	1.00	91.7	1.00	85.6	1.00	48.1	1.00	70.4	1.00	42.1
Level 2	0.95	67.1	0.86	0.5	0.82	1.4	0.83	6.9	0.88	13.0	0.91	31.9	0.86	13.0	0.92	35.6
Level 3	0.73	1.4	0.71	0.9	0.67	0.5	0.67	0.9	0.73	0.9	0.73	15.3	0.92	6.0	0.77	17.1
Level 4	0.59	1.4	0.48	0.5	0.41	-	0.36	0.5	0.45	-	0.33	2.3	0.70	8.3	0.48	4.6
Level 5	0.38	1.4	0.32	-	0.00	-	0.16	-	0.20	-	0.00	1.9	0.32	2.3	0.00	0.5
Level 6	0.00	-	0.00	-	n/a	-	0.00	-	0.00	-	n/a		0.00	-	n/a	-
Missing	-	-	-	0.5	-	-	-	-	-	0.5	-	0.5	-	-	-	-

HUI3 – Health Utilities Index Mark 3; n/a means not applicable

4.5.2. RAND-36

The RAND-36 physical health composite score (PHC) 58.2 ± 11.8 was slightly higher than the mental health composite score (MHC) 56.9 ± 9.3; medians for the PHC and MHC are 59.9 and 61.0, respectively (Table 4.10). These composite scores were approximately one standard deviation above the US general population norm of 50.0. Like the HUI2 and HUI3, the distributions of the RAND-36 PHC and MHC scores were also slightly skewed to the left (Figures 4.3 and 4.4).

For the RAND-36, the percentage of the study sample with missing data ranged from none on certain domain scores, to a high of 2.8% (n=6) on the physical health composite (PHC) score (Table 4.10). As missing data was minimal for the RAND-36, no imputations were made.

Table 4.10 Descriptive statistics for the RAND-36 Health Status Inventory

	N	Missing N (%)	Min	Max	Mean	SD	Median	IQR (25^{th}-75^{th} Percentile)
RAND-36 MHC	213	3 (1.4%)	26.38	77.05	56.94	9.27	61.00	49.16-67.68
RAND-36 PHC	210	6 (2.8%)	26.16	69.46	58.21	11.76	59.89	52.07-53.87
Physical health	216	-	10.00	100.00	87.48	19.52	95.00	85.00-100.00
Role limitations Physical	211	5 (2.3%)	0.00	100.00	76.97	33.04	100.00	50.00-100.00
Pain	216	-	0.00	100.00	79.43	22.14	90.00	67.50-90.00
General health	216	-	0.00	100.00	57.09	23.38	60.00	40.00-75.00
Emotional well-being	216	-	5.00	100.00	74.18	18.61	76.00	64.00-88.00
Role limitations emotional	214	2 (0.9%)	12.00	100.00	70.64	38.71	100.00	33.33-100.00
Social functioning	215	1 (0.5%)	0.00	100.00	81.45	22.86	87.50	62.50-100.00
Energy/fatigue	216	-	0.00	100.00	58.75	22.16	65.00	45.00-100.00

Figure 4.3 Histogram of RAND-36 PHC Scores

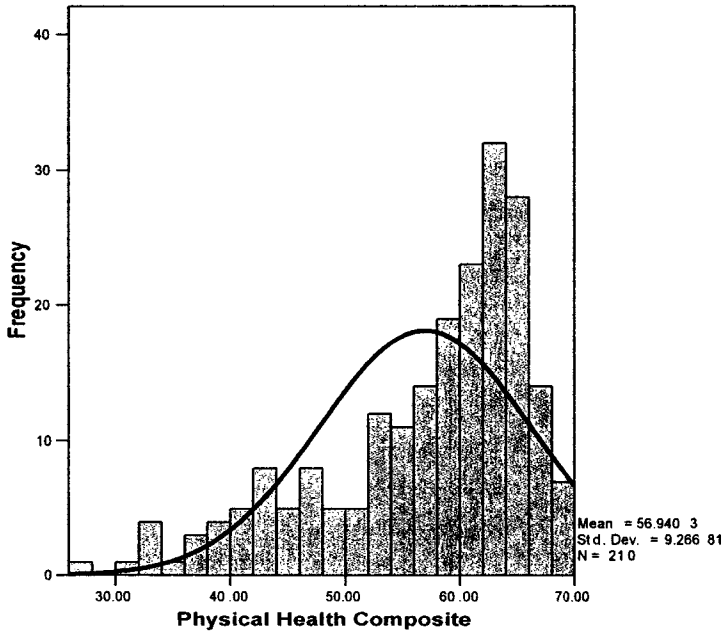
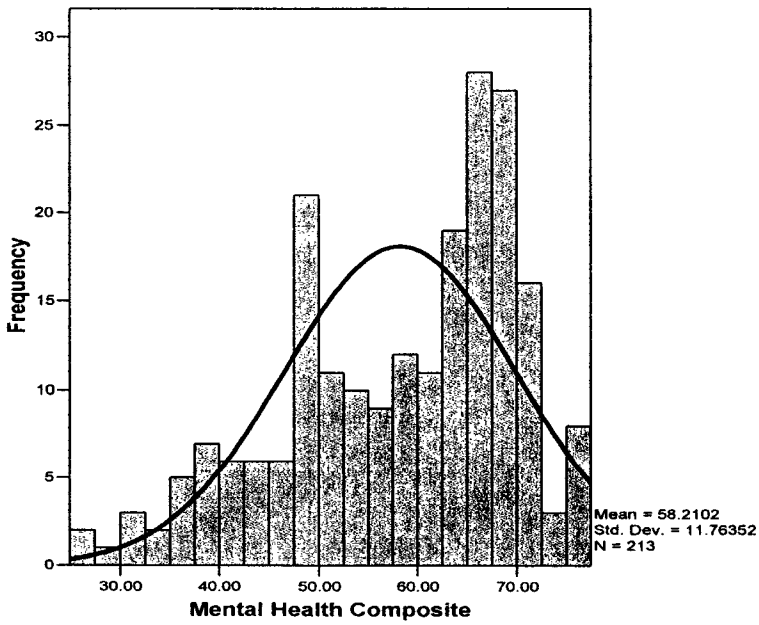


Figure 4.4 Histogram of RAND-36 MHC Scores



4.5.3. IRQOL

As anticipated, missing data was a larger issue for the IRQOL; 28.7% (n=62) of subjects were missing the total IRQOL score (Table 4.11). After imputation, the amount of IRQOL missing data was decreased to 22.7% (n=49) for the total IRQOL score. IRQOL descriptives are based on imputed IRQOL scores.

Overall IRQOL scores generally reflected a moderately high burden, with a mean total IRQOL score of 42.71 ± 28.19 for the sample (Table 4.11). While the overall mean for the total IRQOL score is rather low, scores ranged from 10.00 to 145.33. IRQOL component scores reflect similar IRQOL burden to the total IRQOL score, with the IRQOL emotional burden component score showing the highest IRQOL burden (56.80 ± 39.69) and the IRQOL life/role responsibility component score showing the lowest IRQOL burden (34.75 ± 31.16).

Table 4.11 Descriptive Statistics for the Memphis Immunosuppressant-related Quality of Life Survey (IRQOL)

	N	Missing N* (%)	Min	Max	Mean	SD	Median	IQR (25th-75th Percentile)
Total IRQOL Score	167	49 (22.7%)	10.0	145.33	42.71	28.19	36.89	22.83-58.28
IRQOL Emotional burden	205	1 (0.5%)	10.0	200.0	56.80	39.69	47.72	26.39-75.45
IRQOL Life/role responsibility	189	27 (12.5%)	10.0	170.91	34.75	31.16	21.81	11.36-46.36
IRQOL Mobility	210	6 (2.8%)	10.0	230.0	38.88	38.34	22.86	11.43-57.14
IRQOL GI distress	206	-	10.0	208.33	34.86	31.53	23.33	11.67-44.17
IRQOL Misc.	196	20 (9.3%)	10.0	172.00	48.18	31.75	44.00	19.75-67.25

*missing N after imputation

4.6 Construct Validity - Known Group Analyses

ANOVAs and ANCOVAs were performed for known groups, with subgroups of individuals anticipated to differ in HRQL, as outlined in study methods. Planned known group comparisons were based on duration of diabetes, the presence of diabetic complications (i.e., cardiovascular disease, nephropathy, neuropathy, and retinopathy), and the presence of co-morbidities. Planned known groups analyses were not performed based on indicators for disease advancement (defined respectively as the diabetes-related number of work days off work and ER visits in the last three months) and glycemic control (defined as those experiencing low blood sugars and needing help from someone else in the last three months), as projected in study methods, due to low numbers in one of the subgroups for these items (Table 4.4).

Known groups comparison and results for the HUI2, HUI3 and IRQOL will be presented as they pertain to the main study hypotheses and objectives. The same known group analyses were performed for the RAND-36, but those results are not discussed below, as they do not directly relate to the study objectives. The RAND-36 results can be found in Appendix F.

4.6.1. Duration of Diabetes

Subgroups were formed based on the self-reported mean of 20.0 years, for the duration of diabetes (Table 4.3), where individuals at or below the mean duration of diabetes were compared to individuals above the mean duration of diabetes.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those subjects with a duration of diabetes greater than 20 years ($p \leq 0.001$ and $p < 0.05$,

respectively) than those subjects with a duration of diabetes less than the mean of 20 years (Table 4.11). The differences in overall HUI2 and HUI3 scores between groups were also clearly clinically important (differences > 0.03).

After adjusting for age, sex, education, marital status, income and the presence of co-morbidities, the between group differences on the overall HUI2 and HUI3 scores remained clinically important differences (0.04) between subgroups, with those individuals above the mean duration of diabetes having larger HRQL burden than those at or below the mean duration of diabetes (Table 4.12). The differences were not statistically significant, however.

After adjusting for potential confounders, the HUI3 single attribute score (SAUS) for pain was significantly lower for individuals with longer duration of diabetes ($p<0.05$), but none of the adjusted SAUS comparisons were clinically important. Nonetheless, it is interesting to note that the differences between groups for the HUI2 and HUI3 emotion were substantial, at 0.04.

IRQOL

The total IRQOL score shows significantly more burden in those individuals above the mean duration of diabetes, compared to those at or below the mean duration of diabetes ($p<0.05$) (Table 4.12). After adjusting for age, sex, education, marital status, income, and the presence of co-morbidities, this trend remained; however, the difference was no longer statistically significant (Table 4.13).

Table 4.12 Comparison of individuals above and below mean duration of diabetes

Variable and Category	Duration of Diabetes ≤ 20Years (n=90-118)[1]	Duration of Diabetes > 20 Years (n=76-96)[1]	Difference Between Groups[2]
Total IRQOL Score*	38.48 (23.68)	48.01 (32.20)	9.53
HUI2 overall utility***	0.86 (0.11)	0.80 (0.17)	**0.06**
HUI2 SAUS			
Sensation***	0.91 (0.09)	0.86 (0.12)	**0.05**
Mobility	0.99 (0.05)	0.98 (0.07)	0.01
Emotion	0.89 (0.14)	0.87 (0.18)	0.02
Cognition	0.95 (0.07)	0.95 (0.08)	0.00
Self-Care	0.99 (0.10)	0.99 (0.10)	0.00
Pain	0.96 (0.08)	0.91 (0.19)	**0.05**
HUI3 overall utility*	0.82 (0.20)	0.74 (0.25)	**0.08**
HUI3 SAUS			
Vision*	0.96 (0.73)	0.93 (0.10)	0.03
Hearing	1.00 (0.48)	0.98 (0.12)	0.01
Speech	1.00 (0.35)	1.00 (0.03)	0.00
Ambulation	0.99 (0.05)	0.97 (0.10)	0.02
Dexterity***	1.00 (0.02)	0.96 (0.09)	0.04
Emotion	0.91 (0.17)	0.88 (0.19)	0.02
Cognition	0.95 (0.12)	0.93 (0.14)	0.01
Pain*	0.92 (0.13)	0.88 (0.16)	0.04

* $p < 0.05$
** $p < 0.01$
*** $p \leq 0.001$
[1]n varied depending on number of subjects with missing data for each global and single attribute utility score
[2] Differences in **bold** can be considered clinically important

Table 4.13 Comparison of individuals below and above the mean duration of diabetes (20 years)[†]

Variable and Category	Duration of Diabetes (≤ 20 yrs) (n=77-106)[1]	Duration of Diabetes (>20 yrs) (n=65-85)[1]	Difference Between Groups[2]
Total IRQOL Score	33.25 (18.23,48.27)	38.74(22.50,54.99)	5.49
HUI2 overall utility	0.83 (0.78, 0.89)	0.79 (0.73, 0.85)	**0.04**
HUI2 SAUS			
Sensation	0.92 (0.88, 0.97)	0.91 (0.86, 0.95)	0.01
Mobility	0.98 (0.95, 1.00)	0.97 (0.95, 1.00)	0.01
Emotion	0.87 (0.81, 0.94)	0.83 (0.76, 0.90)	0.04
Cognition	0.96 (0.93, 0.99)	0.97 (0.94, 1.00)	-0.01
Self-Care	1.00 (0.97, 1.04)	1.01 (0.98, 1.05)	-0.01
Pain	0.90 (0.84, 0.96)	0.88 (0.81, 0.94)	0.02
HUI3 overall utility	0.75 (0.66-0.84)	0.71 (0.61,0.80)	**0.04**
HUI3 SAUS			
Vision	0.96 (0.93, 1.00)	0.96 (0.92, 0.99)	0
Hearing	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)	0.01
Speech	0.99 (0.98, 1.01)	1.00 (0.99, 1.02)	-0.01
Ambulation	0.97 (0.94, 1.00)	0.96 (0.92, 0.99)	0.01
Dexterity	0.95 (0.93, 0.98)	0.93 (0.90, 0.96)	0.02
Emotion	0.86 (0.79, 0.93)	0.82 (0.75, 0.90)	0.04
Cognition	0.94 (0.89, 1.00)	0.97 (0.91, 1.02)	-0.03
Pain*	0.88 (0.82, 0.93)	0.85 (0.79, 0.91)	0.03

[†]**Adjusted for age, sex, education, martial status, income and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

4.6.2. Presence of Co-morbidities

Subgroups were formed based on the self-reported presence of co-morbidities, as listed in the National Population Health Survey (NPHS) (Statistics Canada), where an individual who reported that they have a been told by a health professional that they have a listed condition (with the exception of those conditions used to form the subgroups for the presence of cardiovascular disease, outlined previously) were placed in the subgroup for the presence of co-morbidities. Individuals who did not report any of the listed conditions were placed in the subgroup with no reported co-morbidities present.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those individuals with co-morbidities, compared to those without co-morbidities (Table 4.14) ($p<0.01$). The differences in overall HUI2 and HUI3 scores between groups were both clinically important (differences > 0.03).

After adjusting for age, sex, marital status, income, and duration of diabetes, the overall HUI2 and HUI3 scores showed clinically important differences (0.03 and 0.04, respectively) between subgroups, with those individuals reporting co-morbidities having larger HRQL burden than those reporting no co-morbidities (Table 4.15).

The HUI3 SAUS for Pain was significantly lower for those with co-morbidities, with a 0.06 clinically important difference between groups. All other HUI2 and HUI3 SAUS were not clinically or statistically significantly different between groups.

IRQOL

The total IRQOL score shows significantly more IRQOL burden in those individuals with reported co-morbidities, than those without co-morbidities ($p<0.05$)

(Table 4.14). After adjusting for age, sex, education, marital status, income, and the presence of co-morbidities, this trend remained; however, the difference was no longer statistically significant (Table 4.15).

Table 4.14 Comparison of individuals with versus co-morbidities without co morbidities

Variable and Category	No co morbidities (n=116-119)[1]	Co morbidities (n=92-97)[1]	Difference Between Groups[2]
Total IRQOL Score*	35.21 (26.04)	47.47 (27.74)	12.26
HUI2 overall utility**	0.88 (0.14)	0.83 (0.14)	**0.06**
HUI2 SAUS			
Sensation	0.90 (0.08)	0.87 (0.13)	0.02
Mobility	0.99 (0.05)	0.99 (0.07)	
Emotion	0.89 (0.17)	0.88 (0.15)	0.00
Cognition	0.95 (0.09)	0.96 (0.07)	-0.01
Self-Care	0.99 (0.10)	0.99 (0.10)	0.00
Pain	0.94(0.15)	0.92 (0.13)	0.02
HUI3 overall utility**	0.85 (0.22)	0.75 (0.23)	**0.10**
HUI3 SAUS			
Vision	0.95 (0.09)	0.95 (0.09)	0.01
Hearing	1.00 (0.05)	0.98 (0.12)	0.01
Speech	1.00 (0.02)	0.99 (0.04)	0.01
Ambulation	0.98 (0.06)	0.98 (0.09)	0.00
Dexterity	0.98 (0.06)	0.97 (0.07)	0.01
Emotion	0.90 (0.18)	0.89 (0.18)	0.02
Cognition	0.94 (0.15)	0.94 (0.10)	0.00
Pain**	0.93 (0.11)	0.87 (0.17)	**0.06**

* $p < 0.05$
** $p < 0.01$
*** $p \leq 0.001$
[1] n varied depending on number of subjects with missing data for each global and single attribute utility score
[2] Differences in **bold** can be considered clinically important

Table 4.15 Comparison of individuals with co-morbidities versus without co-morbidities†

Variable and Category	No co morbidities (n=88-119)[1]	Co morbidities (n=68-97)[1]	Difference Between Groups[2]
Total IRQOL Score	31.19 (14.87, 47.52)	36.55 (20.59, 52.51)	5.36
HUI2 overall utility	0.83 (0.77, 0.88)	0.80 (0.75, 0.86)	**0.03**
HUI2 SAUS			
Sensation	0.93 (0.88, 0.97)	0.90 (0.86, 0.94)	0.03
Mobility	0.97 (0.95, 1.00)	0.98 (0.95, 1.00)	-0.01
Emotion	0.86 (0.79, 0.92)	0.85 (0.78, 0.91)	0.01
Cognition	0.96 (0.93, 0.99)	0.97 (0.93, 1.00)	-0.01
Self-Care	1.02 (0.98, 1.05)	1.00 (0.97, 1.04)	0.02
Pain	0.90 (0.84, 0.96)	0.88 (0.83, 0.94)	0.02
HUI3 overall utility	0.75 (0.67, 0.64)	0.71 (0.62, 0.80)	**0.04**
HUI3 SAUS			
Vision	0.96 (0.92, 1.00)	0.96 (0.92, 1.00)	0
Hearing	1.01 (0.97, 1.04)	0.99 (0.96, 1.03)	0.02
Speech	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	0.01
Ambulation	0.96 (0.93, 1.00)	0.96 (0.93, 0.99)	0
Dexterity	0.94 (0.92, 0.97)	0.94 (0.91, 0.97)	0
Emotion	0.86 (0.78, 0.93)	0.83 (0.76, 0.91)	0.03
Cognition	0.95 (0.90, 1.01)	0.96 (0.90, 1.01)	0
Pain*	0.89 (0.83, 0.94)	0.84 (0.78, 0.90)	**0.06**

†**Adjusted for age, sex, education, martial status, duration of diabetes, and income**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

4.6.3. Presence of Complications

Presence of Cardiovascular Disease

Subgroups were formed based on the self-reported presence of cardiovascular disease, where an individual who indicated that they had hypertension, heart disease/heart attack and/or stroke were placed in the subgroup for the presence of cardiovascular disease. Individuals not reporting hypertension, heart disease/heart attack, and/or stroke were placed in the subgroup 'no cardiovascular disease'.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those individuals with cardiovascular disease, compared to those without cardiovascular disease (Table 4.16) ($p \leq 0.001$ and $p < 0.01$, respectively). The differences in overall HUI2 and HUI3 scores between groups were clinically important (differences of 0.07-0.10).

After adjusting for age, sex, marital status, income, duration of diabetes, and the presence of co-morbidities, the overall HUI2 and HUI3 scores showed that individuals having cardiovascular disease have larger HRQL burden than those who do not have cardiovascular disease (Table 4.17). HUI3 showed a clinically important difference of 0.04 between subgroups.

The HUI3 SAUS for Emotion was significantly lower for those with cardiovascular disease, with a 0.05 clinically important difference between groups. All other HUI2 and HUI3 SAUS were not clinically or statistically significantly different between groups.

IRQOL

The total IRQOL score shows significantly more IRQOL burden in those individuals with cardiovascular disease, than those without cardiovascular disease ($p<0.01$) (Table 4.16). After adjusting for age, sex, education, marital status, income, duration of diabetes, and the presence of co-morbidities, those with cardiovascular disease still showed significantly larger IRQOL burden than those without cardiovascular disease (Table 4.17) ($p<0.05$).

Table 4.16 Comparison of individuals for the presence of cardiovascular disease

Variable and Category	CVD not present (n=82-111)[1]	CVD Present (n=42-54)[1]	Difference Between Groups[2]
Total IRQOL Score**	36.24 (23.56)	51.92 (21.11)	15.68
HUI2 overall utility***	0.87 (0.11)	0.80 (0.15)	**0.07**
HUI2 SAUS			
Sensation	0.90 (0.12)	0.87 (0.09)	0.03
Mobility**	1.00 (0.01)	0.97 (0.12)	0.03
Emotion	0.91 (0.12)	0.87 (0.17)	0.04
Cognition	0.96 (0.07)	0.96 (0.07)	0.01
Self-Care**	1.00 (0.00)	0.95 (0.20)	**0.05**
Pain	0.96 (0.09)	0.92 (0.14)	0.03
HUI3 overall utility**	0.83 (0.20)	0.73 (0.25)	**0.10**
HUI3 SAUS			
Vision*	0.96 (0.05)	0.93 (0.12)	0.03
Hearing	0.98 (0.11)	0.99 (0.07)	0.00
Speech	1.00 (0.04)	1.00 (0.02)	0.00
Ambulation**	1.00 (0.03)	0.96 (0.13)	0.04
Dexterity	0.98 (0.06)	0.98 (0.04)	0.00
Emotion*	0.92 (0.13)	0.85 (0.24)	**0.07**
Cognition	0.95 (0.11)	0.95 (0.09)	0.00
Pain	0.92 (0.12)	0.88 (0.18)	0.04

* $p < 0.05$
** $p < 0.01$
*** $p \leq 0.001$
[1] n varied depending on number of subjects with missing data for each global and single attribute utility score
[2] Differences in **bold** can be considered clinically important

Table 4.17 Comparison of individuals for the presence of cardiovascular disease†

Variable and Category	CVD not present (n=95-100)[1]	CVD Present (n=48)	Difference Between Groups[2]
Total IRQOL Score*	47.80 (28.2, 67.4)	59.50 (39.1, 79.9)	11.70
HUI2 overall utility	0.78 (0.73, 0.87)	0.76 (0.69, 0.83)	0.02
HUI2 SAUS			
Sensation	0.89 (0.82, 0.96)	0.90 (0.83, 0.97)	-0.01
Mobility	0.95 (0.91, 0.99)	0.93 (0.89, 0.97)	0.02
Emotion	0.83 (0.75, 0.91)	0.79 (0.71, 0.87)	0.04
Cognition	0.94 (0.90, 0.98)	0.94 (0.89, 0.98)	0
Self-Care	1.01 (0.96, 1.07)	1.00 (0.94, 1.06)	0.01
Pain	0.89 (0.83, 0.95)	0.89 (0.83, 0.95)	0
HUI3 overall utility	0.66 (0.54, 0.78)	0.62 (0.50, 0.74)	**0.04**
HUI3 SAUS			
Vision	0.97 (0.92, 1.02)	0.96 (0.91, 1.01)	0.01
Hearing	0.99 (0.92, 1.05)	0.99 (0.93, 1.06)	0
Speech	0.98 (0.96, 1.00)	0.99 (0.97, 1.01)	-0.01
Ambulation	0.93 (0.89, 0.98)	0.91 (0.86, 0.95)	0.02
Dexterity	0.97 (0.93, 1.00)	0.98 (0.94, 1.01)	-0.01
Emotion	0.83 (0.73, 0.93)	0.78 (0.68, 0.89)	**0.05**
Cognition	0.92 (0.85, 0.98)	0.93 (0.86, 1.00)	-0.01
Pain	0.78 (0.71, 0.85)	0.77 (0.70, 0.84)	0.01

†**Adjusted for age, sex, education, martial status, income, duration of diabetes and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

Presence of Nephropathy

Subgroups were formed based on the self-reported presence of nephropathy, where individuals who indicated that they had kidney damage caused by diabetes were placed in the subgroup for the presence of nephropathy. Of those with reported nephropathy, 33 (15.4%) were receiving treatment for kidney damage. Of those receiving treatment , 27 (82%) were receiving medication, 5 (15.2%) were receiving or had received peritoneal dialysis and 2 (6.1%) have had a kidney transplant. Individuals who indicated they did not have kidney damage caused by diabetes were placed in the subgroup for no presence of nephropathy.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those individuals with nephropathy, compared to those without nephropathy (Table 4.18) ($p \leq 0.001$). The differences in overall HUI2 and HUI3 scores between groups were quite substantial (differences of 0.14 and 0.21, respectively).

After adjusting for age, sex, marital status, income, duration of diabetes, and the presence of co-morbidities, the overall HUI2 and HUI3 scores showed that individuals with self-reported nephropathy have significantly larger HRQL burden than those who do not have self-reported nephropathy (Table 4.19) ($p \leq 0.001$), where the HUI2 and HUI3 differences of 0.10 and 0.15, respectively, between subgroups remained clinically important.

The HUI2 SAUS for mobility, emotion, cognition, and pain showed significantly lower utility scores for those individuals with reported nephropathy ($p<0.05$); the differences on the HUI2 SAUS for emotion and pain were also clinically important

differences (differences >0.05) of 0.07 and 0.08, respectively. The HUI3 SAUS for emotion, cognition, and pain showed significantly lower utility scores for those individuals with reported nephropathy ($p<0.05$); all of these differences were also clinically important (differences >0.05) with differences of 0.09, 0.06 and 0.08, respectively. All other HUI2 and HUI3 SAUS were not clinically or statistically significantly different between groups.

IRQOL

The total IRQOL score shows significantly more IRQOL burden in those individuals with self-reported nephropathy, than those without self-reported nephropathy ($p\leq0.001$) (Table 4.18). After adjusting for age, sex, education, marital status, income, duration of diabetes, and the presence of co-morbidities, those with nephropathy still showed significantly larger IRQOL burden than those without nephropathy (Table 4.19) ($p<0.05$).

Table 4.18 Comparison of individuals for the presence of nephropathy

Variable and Category	Nephropathy not present (n=137-174)[1]	Nephropathy Present (n=29-40)[1]	Difference Between Groups[2]
Total IRQOL Score***	38.54 (25.06)	61.39 (34.37)	22.85
HUI2 overall utility***	0.87 (0.11)	0.72 (0.20)	**0.14**
HUI2 SAUS			
Sensation***	0.90 (0.09)	0.84 (0.16)	**0.06**
Mobility**	0.99 (0.05)	0.97 (0.09)	0.03
Emotion***	0.90 (0.12)	0.80 (0.25)	**0.10**
Cognition**	0.96 (0.07)	0.92 (0.10)	0.04
Self-Care	0.99 (0.08)	0.96 (0.17)	0.03
Pain***	0.95 (0.10)	0.86 (0.24)	**0.10**
HUI3 overall utility***	0.82 (0.19)	0.61 (0.30)	**0.21**
HUI3 SAUS			
Vision	0.95 (0.08)	0.93 (0.10)	0.02
Hearing*	1.00 (0.04)	0.96 (0.18)	0.03
Speech	1.00 (0.03)	1.00 (0.03)	0.00
Ambulation*	0.99 (0.07)	0.95 (0.09)	0.03
Dexterity*	0.98 (0.05)	0.96 (0.10)	0.03
Emotion***	0.92 (0.14)	0.79 (0.28)	**0.13**
Cognition**	0.95 (0.11)	0.89 (0.19)	**0.06**
Pain***	0.92 (0.12)	0.82 (0.18)	**0.10**

* $p < 0.05$
** $p < 0.01$
*** $p \leq 0.001$
[1]n varied depending on number of subjects with missing data for each global and single attribute utility score
[2] Differences in **bold** can be considered clinically important

Table 4.19 Comparison of individuals for the presence of nephropathy†

Variable and Category	Nephropathy not present (n=127-151)[1]	Nephropathy Present (n=28-39)[1]	Difference Between Groups[2]
Total IRQOL Score*	55.32 (37.59, 73.04)	67.27 (48.12, 86.42)	11.95
HUI2 overall utility***	0.77 (0.71, 0.83)	0.67 (0.60, 0.74)	**0.10**
HUI2 SAUS			
Sensation	0.90 (0.84, 0.95)	0.87 (0.81, 0.93)	0.03
Mobility*	0.95 (0.92, 0.98)	0.92 (0.89, 0.96)	0.02
Emotion*	0.84 (0.76, 0.92)	0.77 (0.68, 0.86)	**0.07**
Cognition**	0.95 (0.91, 0.99)	0.91 (0.87, 0.95)	0.04
Self-Care	1.00 (0.96, 1.04)	0.97 (0.92, 1.01)	0.03
Pain**	0.86 (0.79, 0.93)	0.78 (0.70, 0.86)	**0.08**
HUI3 overall utility***	0.65 (0.55, 0.75)	0.50 (0.39, 0.61)	**0.15**
HUI3 SAUS			
Vision	0.95 (0.91, 1.00)	0.95 (0.90, 1.01)	0
Hearing	1.00 (0.95, 1.04)	0.97 (0.92, 1.02)	0.03
Speech	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)	0
Ambulation	0.92 (0.88, 0.96)	0.90 (0.86, 0.94)	0.02
Dexterity	0.94 (0.91, 0.97)	0.93 (0.89, 0.96)	0.01
Emotion**	0.82 (0.74, 0.91)	0.73 (0.63, 0.83)	**0.09**
Cognition*	0.94 (0.87, 1.01)	0.88 (0.81, 0.96)	**0.06**
Pain***	0.78 (0.73, 0.84)	0.70 (0.64, 0.77)	**0.08**

†**Adjusted for age, sex, education, martial status, income, duration of diabetes and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

Presence of Retinopathy or Diabetic Eye Disease

Subgroups were formed based on the self-reported presence of indicators for retinopathy caused by diabetes. Individuals who reported that they had retinal damage, vision deterioration due to diabetes-related retinal deterioration, and/or cataracts due to diabetes were placed in the subgroup for the presence of retinopathy. Individuals who did not indicate that they had retinal damage, vision deterioration due to diabetes-related retinal deterioration, and/or cataracts due to diabetes were placed in the subgroup 'no presence of retinopathy'.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those individuals with retinopathy, compared to those without retinopathy (Table 4.20) ($p<0.01$ and $p\leq0.001$, respectively). The differences in overall HUI2 and HUI3 scores between groups were quite large (differences of 0.12 and 0.19, respectively).

After adjusting for age, sex, marital status, income, duration of diabetes, and the presence of co-morbidities, the overall HUI2 and HUI3 scores showed that individuals with indicators for retinopathy have significantly larger HRQL burden than those who do not have indicators for retinopathy (Table 4.21) ($p\leq0.001$ and $p<0.01$, respectively), where the HUI2 and HUI3 showed clinically important differences of 0.06 and 0.09, respectively, between subgroups.

The HUI2 SAUS for emotion showed significantly lower utility scores for those individuals with retinopathy ($p<0.05$); this difference also proved to be a clinically important difference of 0.06. The HUI3 SAUS for vision, ambulation and pain showed significantly lower utility scores for those individuals with retinopathy ($p<0.05$); the

differences of the HUI3 SAUS of emotion was also clinically important with a differences of 0.05. All other HUI2 and HUI3 SAUS were not clinically or statistically significantly different between groups.

IRQOL

The total IRQOL score shows significantly more IRQOL burden in those individuals with retinopathy, than those without retinopathy ($p \leq 0.001$) (Table 4.20). After adjusting for age, sex, education, marital status, income, duration of diabetes, and the presence of co-morbidities, those with retinopathy still showed significantly larger IRQOL burden than those without retinopathy (Table 4.21) ($p<0.01$).

Table 4.20 Comparison of individuals for the presence of retinopathy or diabetic eye disease

Variable and Category	Retinopathy not present (n=102-86)[1]	Retinopathy Present (n=63-126)[1]	Difference Between Groups[2]
Total IRQOL Score***	32.70 (18.85)	58.78 (33.35)	26.08
HUI2 overall utility**	0.89 (0.09)	0.77 (0.17)	**0.12**
HUI2 SAUS			
Sensation***	0.91 (0.09)	0.85 (0.13)	**0.06**
Mobility***	1.00 (0.00)	0.97 (0.09)	0.03
Emotion**	0.91 (0.12)	0.84 (0.19)	**0.07**
Cognition***	0.97 (0.07)	0.93 (0.09)	0.04
Self-Care	0.99 (0.09)	0.98 (0.12)	0.01
Pain***	0.97 (0.05)	0.89 (0.20)	**0.08**
HUI3 overall utility***	0.86 (0.16)	0.67 (0.26)	**0.19**
HUI3 SAUS			
Vision***	0.97 (0.04)	0.92 (0.12)	**0.05**
Hearing	1.00 (0.05)	0.98 (0.12)	0.02
Speech	0.99 (0.04)	1.00 (0.00)	-0.01
Ambulation***	1.00 (0.00)	0.95 (0.00)	**0.05**
Dexterity***	0.99 (0.03)	0.96 (0.09)	0.03
Emotion***	0.93 (0.13)	0.85 (0.23)	**0.08**
Cognition**	0.96 (0.11)	0.91 (0.15)	0.04
Pain***	0.94 (0.09)	0.85 (0.18)	**0.09**

* $p < 0.05$
** $p < 0.01$
*** $p \leq 0.001$
[1]n varied depending on number of subjects with missing data for each global and single attribute utility score
[2] Differences in **bold** can be considered clinically important

Table 4.21 Comparison of individuals for the presence of retinopathy or diabetic eye disease†

Variable and Category	Retinopathy not present (n=57-79)[1]	Retinopathy Present (n=97-110)[1]	Difference Between Groups[2]
Total IRQOL Score**	47.96 (30.11, 65.81)	64.36 (47.33, 81.39)	16.40
HUI2 overall utility***	0.79 (0.72, 0.86)	0.72 (0.65, 0.78)	**0.06**
HUI2 SAUS			
Sensation	0.90 (0.85, 0.96)	0.88 (0.83, 0.94)	0.02
Mobility	0.95 (0.92, 0.98)	0.93 (0.90, 0.96)	0.02
Emotion*	0.86 (0.77, 0.94)	0.80 (0.72, 0.88)	**0.06**
Cognition	0.95 (0.91, 1.00)	0.93 (0.90, 0.97)	0.02
Self-Care	0.99 (0.95, 1.04)	0.99 (0.94, 1.03)	0
Pain	0.86 (0.78, 0.93)	0.82 (0.75, 0.89)	0.04
HUI3 overall utility**	0.68 (0.57, 0.79)	0.57 (0.46, 0.67)	**0.09**
HUI3 SAUS			
Vision*	0.97 (0.93, 1.02)	0.94 (0.89. 0.98)	0.03
Hearing	0.99 (0.94, 1.04)	0.99 (0.94, 1.04)	0
Speech	0.99 (0.97, 1.01)	1.00 (0.98, 1.01)	0.01
Ambulation*	0.93 (0.89, 0.97)	0.90 (0.87, 0.94)	0.03
Dexterity	0.94 (0.91, 0.98)	0.93 (0.90, 0.96)	0.01
Emotion	0.83 (0.73, 0.92)	0.78 (0.69, 0.87)	**0.05**
Cognition	0.94 (0.87, 1.01)	0.92 (0.85, 0.98)	0.02
Pain*	0.79 (0.72, 0.85)	0.75 (0.69, 0.81)	0.04

†**Adjusted for age, sex, education, martial status, income, duration of diabetes and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

Presence of Neuropathy or Peripheral Vascular Disease (PVD)

Subgroups were formed based on the self-reported presence of indicators for neuropathy, where individuals who reported having pain/numbness in legs, blood circulation problems in legs/feet, and/or surgical operation of leg(s) due to diabetes were placed in the subgroup for the presence of neuropathy. Individuals who did not report pain/numbness in legs, blood circulation problems in legs/feet, and/or surgical operation of leg due to diabetes were placed in the subgroup for no presence of neuropathy.

HUI2 and HUI3

As hypothesized, overall HUI2 and HUI3 scores were significantly lower for those individuals with neuropathy, compared to those without neuropathy (Table 4.22) ($p \leq 0.001$). The differences in overall HUI2 and HUI3 scores between groups were clinically important (differences of 0.12 and 0.21, respectively).

After adjusting for age, sex, marital status, income, duration of diabetes, and the presence of co-morbidities, the overall HUI2 and HUI3 scores showed that individuals with indicators for neuropathy have significantly larger HRQL burden than those who do not have indicators for neuropathy (Table 4.23) ($p \leq 0.001$). HUI2 and HUI3 showed highly clinically important differences of 0.08 and 0.14, respectively, between subgroups.

The HUI2 SAUS for emotion, cognition, and pain showed significantly lower utility scores for those individuals with neuropathy ($p<0.05$); the differences on the HUI2 SAUS for emotion and pain were also clinically important differences (differences >0.05) of 0.07 and 0.06, respectively. The HUI3 SAUS for cognition and pain showed significantly lower utility scores for those individuals with neuropathy ($p<0.01$); the differences of the HUI3 SAUS for emotion, cognition, and pain was also clinically

important, with differences of 0.05-0.07. All other HUI2 and HUI3 SAUS were not clinically or statistically significantly different between groups.

IRQOL

The total IRQOL score shows significantly more IRQOL burden in those individuals with neuropathy, than those without neuropathy ($p \leq 0.001$) (Table 4.22). After adjusting for age, sex, education, marital status, income, duration of diabetes, and the presence of co-morbidities, those with neuropathy still showed significantly larger IRQOL burden than those without neuropathy (Table 4.23) ($p<0.01$).

Table 4.22 Comparison of individuals for the presence of neuropathy/peripheral vascular disease

Variable and Category	Neuropathy/PVD not present (n=110-138)[1]	Neuropathy/PVD Present (n=54-72)[1]	Difference Between Groups[2]
Total IRQOL Score***	33.02 (18.86)	62.12 (33.99)	29.10
HUI2 overall utility***	0.88 (0.10)	0.76 (0.17)	**0.12**
HUI2 SAUS			
Sensation***	0.90 (0.08)	0.85 (0.14)	**0.05**
Mobility***	1.00 (0.01)	0.97 (0.14)	0.03
Emotion**	0.91 (0.13)	0.84 (0.19)	**0.07**
Cognition***	0.97 (0.06)	0.92 (0.09)	**0.05**
Self-Care	0.99 (0.08)	0.98 (0.13)	0.02
Pain***	0.96 (0.11)	0.88 (0.18)	**0.08**
HUI3 overall utility***	0.86 (0.16)	0.64 (0.27)	**0.21**
HUI3 SAUS			
Vision*	0.96 (0.07)	0.93 (0.12)	0.03
Hearing	1.00 (0.05)	0.98 (0.13)	0.02
Speech	1.00 (0.01)	0.99 (0.05)	0.01
Ambulation***	1.00 (0.02)	0.95 (0.12)	0.04
Dexterity***	0.99 (0.03)	0.96 (0.10)	0.03
Emotion**	0.92 (0.16)	0.85 (0.21)	**0.07**
Cognition***	0.97 (0.09)	0.88 (0.18)	**0.08**
Pain***	0.94 (0.09)	0.82 (0.18)	**0.12**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1] n varied depending on number of subjects with missing data for each global and single attribute utility score

[2] Differences in **bold** can be considered clinically important

Table 4.23 Comparison of individuals for the presence of neuropathy/peripheral vascular disease (PVD)[†]

Variable and Category	Neuropathy/PVD not present (n=102-121)[1]	Neuropathy/PVD Present (n=51-67)[1]	Difference Between Groups[2]
Total IRQOL Score**	50.70 (32.72, 68.69)	65.50 (47.55, 83.46)	14.80
HUI2 overall utility***	0.79 (0.72, 0.86)	0.71 (0.64, 0.78)	**0.08**
HUI2 SAUS			
Sensation	0.89 (0.83, 0.95)	0.89 (0.83, 0.94)	0
Mobility	0.95 (0.92, 0.98)	0.93 (0.90, 0.96)	0.02
Emotion*	0.86 (0.78, 0.94)	0.79 (0.71. 0.88)	**0.07**
Cognition**	0.96 (0.92, 1.01)	0.92 (0.88, 0.96)	0.04
Self-Care	1.00 (0.96, 1.04)	0.98 (0.94, 1.02)	0.02
Pain*	0.87 (0.79, 0.94)	0.82 (0.74, 0.89)	**0.06**
HUI3 overall utility***	0.69 (0.58, 0.80)	0.55 (0.45, 0.65)	**0.14**
HUI3 SAUS			
Vision	0.95 (0.90, 1.00)	0.95 (0.90, 1.00)	0
Hearing	0.99 (0.94, 1.04)	0.99 (0.94, 1.04)	0
Speech	1.00 (0.98, 1.02)	0.99 (0.98, 1.01)	0.01
Ambulation	0.93 (0.89, 0.97)	0.90 (0.87, 0.94)	0.03
Dexterity	0.95 (0.91, 0.98)	0.93 (0.90, 0.96)	0.02
Emotion	0.83 (0.74, 0.92)	0.78 (0.69, 0.87)	**0.05**
Cognition**	0.96 (0.89, 1.03)	0.90 (0.83, 0.97)	**0.06**
Pain***	0.80 (0.74, 0.87)	0.73 (0.67, 0.80)	**0.07**

[†]**Adjusted for age, sex, education, martial status, income, duration of diabetes and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p \leq 0.001$

[1]n varied depending on number of subjects with missing data for each global and single attribute utility score or covariate

[2] Differences in **bold** can be considered clinically important

4.7 Construct Validity - Interscale Correlations

Observed interscale correlations for the HUI2 and HUI3, IRQOL and RAND-36 are presented in Table 4.24. Overall HUI2 and 3, RAND-36 (i.e., PHC and MHC), and total IRQOL scores were all strongly correlated ($r>0.50$).

Overall, agreement between predicted and observed correlations was 68.2% (229/336). For the HUI2, the agreement was 69.6% (78/112). For the HUI3, the agreement was 50.0% (64/128). For the IRQOL, the agreement was 90.6% (87/96). Agreement was lower in emotional/mental health domains and specific sensation attributes; whereas, the physical functioning domains and overall scores showed better agreement. All disagreements were by only one category (e.g., strong instead of medium or not correlated instead of weak).

Table 4.24 Observed Correlation Matrix

Correlation legend:

S = strongly correlated (> 0.50)

M = moderately correlated (0.35 to 0.50)

W = weakly correlated (0.20 to 0.34)

- = negligible or not correlated (0.00 to 0.19)

Bold observations are congruent with predicted correlations

	IRQOL						RAND-36									
	IRQOL overall	Emotional burden	Life role	Mobility	GI distress	Misc.	PHC	MHC	PF	RP	BP	GH	VT	SF	RE	MH
HUI2-overall	**-0.69**	-0.52	-0.65	**-0.36**	-0.35	-0.39	**0.71**	**0.66**	0.65	0.51	0.68	0.56	0.62	0.59	0.53	0.60
Sensation	**-0.13**	**-0.13**	**-0.26**	**-0.19**	**-0.15**	**-0.13**	0.37	**0.17**	0.31	0.31	0.26	0.27	0.30	0.15	**0.16**	**0.11**
Mobility	-0.16	**-0.19**	**-0.37**	-0.24	**-0.11**	**-0.16**	**0.34**	**0.21**	**0.51**	0.27	0.40	0.20	0.25	0.30	**0.20**	0.19
Emotion	0.57	**-0.62**	-0.47	-0.27	**-0.24**	-0.31	**0.34**	**0.68**	0.29	0.19	0.21	0.41	0.57	0.58	**0.43**	**0.73**
Cognition	-0.48	-0.50	-0.41	-0.19	-0.22	**-0.15**	0.43	**0.48**	0.37	0.33	0.37	0.36	0.50	0.42	0.40	0.40
Self-care	-0.13	**0.02**	0.01	-0.03	0.03	-0.01	0.11	0.03	0.18	0.05	0.15	0.03	0.02	0.42	**0.09**	0.06
Pain/discomfort	**-0.37**	-0.16	-0.44	-0.18	-0.27	-0.26	**0.60**	0.27	0.51	0.45	**0.69**	**0.34**	0.30	0.25	0.28	0.17
HUI3 – overall	**-0.67**	-0.62	-0.61	-0.34	-0.39	**-0.33**	**0.68**	**0.71**	0.61	0.52	0.60	0.56	0.64	0.64	0.54	0.66
Vision	-0.90	**-0.17**	**-0.22**	**-0.14**	**-0.11**	**-0.09**	0.26	0.21	0.25	0.19	**0.15**	**0.23**	**0.15**	0.22	0.23	**0.17**
Ambulation	**-0.39**	-0.21	-0.43	-0.29	-0.17	**-0.18**	**0.40**	**0.28**	0.59	0.31	0.43	0.23	0.29	**0.34**	0.23	0.26
Dexterity	**-0.22**	**-0.13**	**-0.33**	-0.17	**-0.17**	**-0.13**	0.45	0.19	0.42	**0.40**	0.41	**0.24**	0.19	0.12	**0.14**	**0.16**
Pain	-0.33	-0.27	-0.39	-0.20	-0.23	**-0.14**	**0.63**	**0.37**	0.60	**0.47**	**0.74**	**0.41**	**0.27**	0.30	**0.40**	**0.38**
Hearing	**-0.07**	**-0.06**	-0.05	**-0.14**	**-0.07**	**-0.01**	**0.14**	0.03	**0.16**	**0.12**	**0.12**	0.07	**0.09**	-0.02	**-0.04**	**0.03**
Speech	**0.02**	0.02	-0.08	**-0.01**	**-0.04**	**0.01**	**0.16**	0.09	**0.05**	**0.19**	**0.13**	0.11	0.09	0.12	**0.13**	**0.01**
Emotion	**-0.51**	**-0.56**	-0.41	**-0.21**	-0.31	-0.30	0.33	**0.64**	0.27	0.21	0.20	0.42	0.52	0.55	**0.44**	**0.69**
Cognition	-0.50	-0.53	-0.43	-0.19	-0.23	-0.18	0.41	**0.46**	0.32	0.34	0.29	0.31	0.45	0.38	0.37	0.41

IRQOL	RAND-36									
	PF	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**MHC**	**PHC**
Overall	-0.61	-0.46	-0.51	-0.68	-0.68	-0.72	-0.60	-0.65	-0.76	-0.72
Emotional burden	-0.39	-0.37	-0.38	-0.60	-0.68	-0.69	**-0.59**	**-0.77**	**-0.81**	-0.55
Life role/responsibility	-0.66	-0.66	-0.53	-0.53	-0.61	-0.70	-0.51	-0.57	-0.73	-0.68
Mobility	-0.41	-0.24	-0.33	-0.36	**-0.36**	**-0.32**	**-0.25**	**-0.31**	-0.36	-0.40
GI distress	-0.28	**-0.32**	-0.36	**-0.38**	-0.29	-0.36	-0.39	-0.28	-0.36	-0.40
Miscellaneous	-0.33	-0.36	-0.30	-0.40	-0.45	-0.36	-0.42	-0.33	-0.44	-0.43

Chapter 5: Discussion

5.1. Introduction

Diabetes places a substantial burden on individuals with the disease and their families. This burden arises not only from diabetes itself, but also its treatment, the complications, and possible co-morbidities associated with diabetes. The morbidity burden of diabetes can be associated with impairment on many dimensions of health-related quality of life (HRQL), including social, cognitive, role and physical functioning, emotional well-being, general perceptions of health, and pain (Wandell et al., 1997). When measuring HRQL in any condition, it is essential that the instruments used are valid in the population under study.

Previous research with generic preference-based measures in diabetes shows the presence of diabetic complications (particularly microvascular complications), the intensity of diabetes treatment, and the presence of co-morbidities result in larger HRQL burdens (Tabaei et al., 2003; Coffey et al., 2002; Redekop et al., 2002; Koopmanschap et al., 2002; Hahl et al., 2002; UKPDS 37., 1999; Holmes et al., 2000).

While a number of studies have used specific or generic health profiles to assess HRQL in type 1 diabetes, past research exploring preference-based measures is limited, particularly using the Health Utilities Index Mark 2 (HUI2) and the Health Utilities Index Mark 3 (HUI3) (Torrance et al., 1995; Feeny et al., 2002). Previous experience with the HUI2 and HUI3 in diabetes has proven the HUI to be effective in detecting diabetes-related HRQL.

HRQL norms and patterns of treatment, complication, and co-morbidity effects are available for type 2 diabetes or combined type 1 and type 2 diabetes populations; however, literature is lacking for generic preference-based HRQL measures in type 1

diabetes. The first objective of this study was to generate evidence of cross-sectional construct validity of the Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) in adults with type 1 diabetes.

Next, this study set out to evaluate the IRQOL as a measure of HRQL. As per our experience in HRQL assessments of IT patients, we hypothesized that this measure would perform similar to the generic health measures employed. The HUI2, HUI3 and RAND-36 were be used as benchmark generic measures in order for comparison.

Lastly, this study set out to provide local norms for the battery of generic HRQL measures (HUI2, HUI3, RAND-36) in patients who have type 1 diabetes. This will allow us to compare HRQL differences between adults with type 1 diabetes who have undergone either islet or whole pancreas transplants with those who are currently using standard insulin therapy in future studies.

In this chapter, the results of each of these objectives will be discussed in turn. In addition, through the completion of meeting these objectives, an interesting aspect of the interpretation of generic HRQL scores arose, which will also be discussed.

5.2 Construct Validity of the Health Utilities Index Mark 2 and Mark 3

5.2.1. Known Group Comparisons of HUI Scores

Interpretation of our results would generally support the conclusion that both the HUI2 and HUI2 have validity in discriminating the HRQL burden of the known groups considered in this study.

While HRQL measures can be interpreted based on statistical significance of HRQL differences, statistical significance does not imply clinical importance. Statistical significance between groups only reveals if the differences can be attributed to chance. A significant p-value (typically < 0.05) merely indicates that there likely is a *real* difference

between groups that cannot be explained by chance alone. A clinically important difference is not based on statistical significance and incorporates clinical and patient perspective into interpretations (Fayers, 2000).

Clinically important differences (CID) tend to be less well known because they require previous research and experience with a measure in a specific population. A minimally clinically important difference (MCID) takes into account the clinical changes between patient groups as well as patient and clinician opinions and values (Fayers, 2000). This evidence may not be available for all clinicians, when looking to interpret a measure; however, it is an important consideration when looking to translate research into practice (Fayers, 2000).

Previous research with the HU2 and HUI3 in diabetes has shown that differences greater than 0.03 on the HUI2 and HUI3 overall scores can be considered clinically important (Grootendorst et al., 2000; Drummond et al., 2001); differences greater than 0.05 on the HUI2 and HUI3 single attribute utility scores (SAUS) can be considered to be clinically important (HUI, 2004; Maddigan et al., 2004).

Using these previously established criteria, this study shows clinically important and statistically significant differences between evaluated subgroups. These differences are similar to those shown in type 2 diabetes, where individuals with more advanced disease (i.e., the presence of complications and longer duration of diabetes) and co-morbidities to have clinically larger HRQL impairments (Maddigan et al., 2004). Also consistent with previous research using other generic preference-based measures, microvascular complications such as nephropathy and peripheral vascular disease (PVD),

are associated with clinically larger HRQL impairments than macrovascular complications such as cardiovascular disease (Holmes et al., 2000).

Although cardiovascular disease, a macrovascular complication of diabetes, can be termed a 'silent killer' because it is usually symptom-free, previous research has shown individuals with hypertension (i.e., receiving one or more anti-hypertensive medication(s)) have larger HRQL impairments than those without hypertension (Erickson et al., 2004). In addition, the inclusion of subjects in the subgroup for cardiovascular disease with stroke, who have been shown to have substantially lower HUI3 scores than the general population (Grootendorst et al., 2000), may lower the overall utility scores of those with cardiovascular disease. As there are only two subjects with stroke in our sample, however, it is unlikely that they account for the entire burden shown by those with cardiovascular disease.

For many of the known group comparisons, only few SAUS proved clinically important. The majority of differences in overall HU2 and HUI3 scores were however, clinically important. This is likely a result of small HRQL impairments in various aspects of an individual's health and lifestyle which sum to have an overall clinically important impact on an individual's HRQL (i.e., overall HRQL burden appears not to be the result of large impact in one attribute, but the net result of small impairments on many attributes).

In particular, individuals with nephropathy showed large overall HRQL differences versus those without nephropathy (differences of 0.10-0.15). This is likely a result of the burden of nephropathy treatment, where individuals receiving dialysis have

slightly lower HUI overall scores and SAUS than those receiving medication for nephropathy, thus, creating a larger difference between subgroups.

Evidence was also generated for the validity of SAUS in this patient population. The HUI SAUS for emotion and pain consistently showed clinically important differences, particularly the HUI3. This supports previous research in type 2 diabetes that the differences in the HUI2 and HUI3 system for these attributes may be more sensitive to HRQL impairments (Maddigan et al., 2003; Maddigan et al., 2004). This is likely a result of the difference in measurement of these attributes between the HUI2 and HUI3 systems.

The pain attribute of the HUI2 focuses on achievement of pain relief through medications; whereas, the HUI3 focuses on the disruption of daily activities due to pain. For this reason, the HUI2 may underestimate true HRQL deficits associated with diabetes in individuals with moderate to severe impairment, who may already be on pain medicine.

This trend was less apparent in our study data, where both the HUI2 and HUI3 SAUS for pain tended to show equal HRQL burdens. However, the comparison of individuals with co-morbidities versus those without co-morbidities showed a clinically important difference between groups on the HUI3 SAUS for Pain, whereas, the HUI2 SAUS did not show a clinically important difference. This may also be a result a number of the co-morbidities, particularly arthritis. The high prevalence of arthritis (16.8%) in this sample, where pain would be likely to be the largest impacted attribute of the HUI, may account for some of the differences in pain between groups. Grootendorst and colleagues have shown arthritis and stroke subjects tend to have larger pain HRQL

impairments than a reference population, with arthritis subjects having slightly larger pain impairments than subjects with stroke (Grootendorst et al., 2000).

The emotion attribute of the HUI2 focuses on worry and anxiety; whereas, the HUI3 focuses on happiness versus depression. This difference in content may be of particular importance for individuals with type 1 diabetes, as they may have more anxiety associated with more frequent hypoglycemic events than individuals with type 2 diabetes. This was not supported by the data, where HUI3 SAUS emotion scores consistently showed equal or greater HRQL impairment than did the HUI2 SAUS emotion scores. Regardless, the emotional HRQL burden of advanced disease or presence of complications was apparent in all comparisons. This highlights the importance of mental health issues in this patient population.

Lastly, it was anticipated that neuropathy and myopathy may affect the pain and discomfort attribute of the HUI2 and HUI3 and the dexterity attribute of the HUI3. Our data support the idea that the SAUS for pain are affected by neuropathy; however, the SAUS3 for dexterity did not show a difference between groups for the presence of peripheral vascular disease.

It was also anticipated that retinopathy may affect the vision attribute of the HUI3 and the sensation attribute of the HUI (Maddigan et al., 2004). Although our data did not show statistical or clinical differences between subgroups for the presence of retinopathy on these attributes, it is important to note that our sample is representative of a general population of people with type 1 diabetes. These attributes may only be affected in individuals with advanced retinopathy (i.e., partial or complete blindness), which were not present in our sample and are rather rare in a sample of the general population.

5.2.2. Correlational Evidence of HUI Construct Validity

In addition to the discriminative evidence of construct validity of the HUI2 and HUI3 in type 1 diabetes, our data provides correlational evidence of construct validity. Overall HUI2 and HUI3 were found to be strongly correlated ($r>0.50$) to the physical health component (PHC) and mental health component (MHC) scores of the RAND-36 Health Status Inventory. Mental health domains of the HUI tended to be strongly correlated to mental health domains of the RAND-36. This trend was also shown with physical health domains. In comparison, mental health domains tended to show moderate correlation ($r=0.35$-0.50) with physical health domains.

5.2.3 Comparison to other Type 2 Diabetes Literature

Whether or not criteria are in place for interpretation of HRQL scores for the study population, comparing scores to a reference population (of a similar disease or the general population) provides perspective into the burden (or lack of) reflected by the generated HRQL scores. Previously reported average overall HUI2 and HUI3 scores in type 2 diabetes reveal a larger HRQL burden than those found in our study for individuals with type 1 diabetes (Maddigan et al., 2003); however, there was a similar trend of the HUI3 showing a larger burden than did the HUI2. Differences in sample characteristics may attribute to these differences between scores, where those in the reference type 2 diabetes population were older (mean age 62.3y ± 12.5), of lower socioeconomic status and less educated than those of our study population (Maddigan et al., 2003). Our study sample's diabetes was more advanced (i.e., longer duration of disease and higher prevalence of diabetic complications) tha

n this reference population; our population has a mean age of diagnosis of 16.6 years, in comparison to an median duration of diabetes of 5.0 years with an average age

of 62.3 years in the reference type 2 diabetes population (Maddigan et al., 2003). However, lifestyle adaptation may account for the differences in HRQL burden. Individuals with type 2 diabetes may feel more "burdened" by the disease as they are usually diagnosed at middle-age, versus individuals with type 1 diabetes who generally have had diabetes since adolescence.

When comparing our overall HUI3 study scores to a those of the general population or 'population norms', the burden of type 1 diabetes becomes evident, where individuals with type 1 diabetes in our sample show an overall HUI3 score of 0.78, in comparison to those of the general population norm of 0.90 (Maddigan, 04-01). It is also interesting to note that consideration of the distribution of the overall HUI3 scores in our study shows a distribution skewed to the left, where a large number of subject scores cluster around the general population norm of 0.90. The overall HUI3 mean for our sample is lowered by individuals with very high burden. This is reinforced by our sample's median overall HUI3 score of 0.85. This may suggest that the HRQL burden associated with type 1 diabetes for middle-age, working-class adults is not as low as suggested by the observed HUI3 overall score in this study. It is the development of diabetic complications and co-morbidities in later years which results in an increase in diabetes-related HRQL burden.

5.3 Construct Validity of the IRQOL Survey

Interpretation of the Memphis Immunosuppressant-related Quality of Life (IRQOL) Survey can be difficult due to the lack of literature surrounding this measure. Overall, the total IRQOL score shows the sample to have moderately high IRQOL burden, based on a-priori IRQOL interpretation criteria (Winsett, 2001). These criteria

were established for patients who had undergone whole organ transplants and may not necessarily directly translate into appropriate IRQOL burden criteria for this sample. Unfortunately, reference IRQOL scores, such as those of the general population or an appropriate disease comparison population, are not available. Despite the limitation surrounding interpretation of this measure, it is evident that the IRQOL is showing a quality of life burden in this sample. The issue remains as to whether or not this burden is in fact specific for immunosuppressant-related HRQL.

Statistical interpretation of the IRQOL known group analysis shows that total IRQOL scores were statistically different between subgroups for the presence of diabetic complications; however, total IRQOL scores were not significantly different between subgroups for the duration of diabetes and the presence of co-morbidities. In summary, the IRQOL performed much like the generic HUI2 and HUI3 measures in this sample.

Previous literature has not provided a clinically important difference for the IRQOL, which limits our interpretation of the IRQOL known group analysis. However, comparison of total IRQOL score differences to overall HUI score differences reveals that a 5-10 IRQOL score differences tends to parallel ~0.05 changes in overall HUI scores. As 0.03 or greater differences in HUI overall scores can be considered a clinically important change (Grootendorst et al., 2000; Drummond, 2001), this may be interpreted to mean that a difference of ~5.0 on IRQOL total scores could be a considered clinically important in this population.

In addition to similarities between the performance of HUI and IRQOL in the known group analysis, total IRQOL scores were found to be strongly correlated to those of generic measures employed (i.e., overall HUI2 and HUI3 scores; RAND-36 PHC and

MHC)(r>0.68-0.78). This shows that the IRQOL is reflecting a similar HRQL burden to that shown by generic measures, which may question it's specificity for measuring immunosuppressant-related quality of life.

Based on previous research in islet transplant (IT) patients (Johnson et al., 2002) and our data, we can conclude that the IRQOL does not act as an immunosuppressant-specific HRQL measure in this population. This limits its construct validity in the IT population.

In addition, the IRQOL was plagued with problems of missing data and respondent interpretation (where subjects were confused with the format of the questionnaire). These limitations further limit the content (or face) validity of this measure in these applications. Despite these limitations, it must be recognized that the IRQOL was designed and validated for individuals undergoing whole organ transplant, who are receiving an immunosuppressant regimen including glucocorticoids. The IRQOL may be effective in detecting immunosuppressant-specific quality of life in the latter population; however, in a general population of adults with type 1 diabetes and in patients with labile type 1 diabetes undergoing IT with the Edmonton Protocol, it has shown to act similar to that of a generic HRQL measure.

5.4 Score Interpretations

Interpretation of health-related quality of life (HRQL) scores and differences between subgroups can be hampered due to various interpretation methods/criteria, differences between measure development and scoring, and differing perspectives (individual versus population). HRQL scores can be interpreted statistically or clinically. While statistical interpretation is rather straightforward, clinical interpretation can be

more problematic as *a priori* criteria for these interpretations may be limited or vague at best, if present at all. Also, various operational definitions of scoring and interpretation (e.g., norm or distribution-based versus anchor-based) can lead to difficulties when comparing HRQL scores results between studies. Last, a researcher's perspective of interpretation of HRQL scores may focus more on population norms, whereas a clinician may be more interested in individual or patient burden (Lydick et al., 1993). Therefore, explicit methods for interpreting HRQL differences can help illuminate the strengths and limitations of the measures used.

5.4.1. Anchor-based versus Distribution-based Scoring

Operational definitions of clinical meaningfulness can be divided into two broad categories: anchor-based and distribution-based (Lydick et al., 1993). Anchor-based interpretations represent instances were the differences seen in HRQL measures are compared, or anchored, to other clinical differences. Anchor-based interpretations have two requirements: the anchor must be interpretable and there must be a sensible relationship between the target and the anchor (Guyatt et al., 2002).

In many respects, assessments of construct validity provide valuable information for the interpretation of HRQL scores. Known group comparisons may be viewed, in some respects, as an anchor-based approach to the validation and interpretation. For example, this study utilizes an anchor-based interpretation of HRQL differences between subgroups of individuals anticipated to differ in HRQL (i.e., based on the presence of a diabetic complication, co-morbidities, or the duration of diabetes). Using subgroups anticipated to differ in HRQL is felt to be appropriate as these subgroups are clinically sensible and differences can be anticipated to be due to the basis of subgroup

determination. Furthermore, correlations amoung HUI, IRQOL and RAND-36 scores support the construct validity of those measures. Our anchor-based interpretations also incorporate clinically important differences (CID), which will be discussed later.

Distribution-based interpretations are based upon assumed normal distributions, where means and standard deviations in the study sample are compared to means and standard deviations of a reference population (such as the general population) (Lydick et al., 1993). In comparison to an anchor-based interpretation approach, which anchors measure scores to some 'external reference', a distribution-based interpretation approach allows for internal comparison of scores. For example, the norm-based scoring of the SF-36 (or RAND-36) summary scores is based on T-scores, relative to the general US population. Using this normed-based approach, observed scores (individual or sample means) are interpreted relative to the general US population, whose mean and standard deviation are arbitrarily set at 50.0 and 10.0, respectively.

Distribution-based interpretation of RAND-36 scores are challenging in this study. RAND-36 PHC and MHC scores of 58.2 and 56.9, respectively, appear to be 'better than the norm'. This is troublesome, as our anchor-based interpretation of HUI scores show HRQL in adults with type 1 diabetes to be lower than that of the general population (It should be noted that U.S. norms are used for the RAND-36, while Canadian norms are used for the HUI3). Further analysis of the distribution of HUI and RAND-36 scores provides evidence that, in fact, scores for all measures were not normally distributed, with substantial skew to the left, nonetheless a distributional-based approach assumes scores to be normally distributed. In this case, distributional-based interpretation of RAND-36 scores may lead to misinterpretation of HRQL burden

associated with type 1 diabetes, as clinical evidence and other HRQL measures would suggest HRQL is lower than in the general population.

This is illustrated in our study by the known group comparisons for the physical health (PHC) and mental health (MHC) composite scores of the RAND-36. Here, all PHC and MHC scores were above the mean of the reference population (i.e., 50.0), even those subjects with reported co-morbidities and complications (Appendix F). After adjusting for age, sex, education, marital status, duration of diabetes and the presence of co-morbidities, the mean PHC and MHC were lower; however, the majority of these scores remained above the reference population. It would seem odd that, for example, patients with kidney damage or peripheral vascular disease would have health status near or above the mean of the general population. Further, when considered relative to the HUI2 and HUI3 in this study, because of the strong correlations between overall summary scores, it appears that the RAND-36 summary scores have skewed the interpretation of the HRQL burden by imposing a normal distribution on non-normally distributed data. These results call into question this validity of norm-based scoring in such situations.

5.5 Study Limitations

It should be recognized that all data and comparisons were cross-sectional. Longitudinal assessments of the HUI and IRQOL are required in order to further investigate reliability and responsiveness, in this study population. Despite this design limitation, study objectives did not require a longitudinal assessment of the measures. This study has effectively generated evidence of the cross-sectional construct validity and population norms of the HUI2 and HUI3 in adults with type 1 diabetes.

It should also be recognized that all clinical and known groups data were based on patient self-report. However, it should be expected that respondents were motivated to provide valid answers on information about aspects of their lives which are of high personal relevance to them (Knäuper et al., 2003). This supports the accuracy of study results. Also, the collection of the presence of co-morbidities was based on a previously used and reliable self-report source, the National Population Health Survey (NPHS) of Statistics Canada.

Also, all self-report co-morbidities were based on a dichotomous response of yes/no therefore, we were not able to capture the severity of reported co-morbidities and complications. This is likely to attenuate differences between our known groups. However, as we did observe statistically significant and clinically important differences on overall HUI2 and HUI3 scores, this is less of a concern. The ability to assess degree of severity of co-morbidities and complications would be most helpful for assessments of the SAUS. We did consider differences in severity of some complications, such as the nature of treatment for nephropathy, but the sizes of the relevant subgroups were too small to make meaningful comparisons on severity. Such information would strengthen the evidence of construct validity for all measures.

As with all mail-out self-report questionnaires, the issue of responder bias is an important consideration. It is unknown if non-responders were significantly different from responders; therefore, measurement of responder bias in this study was not possible. However, based on collected respondent demographics and clinical characteristics, it is felt that this population effectively represents that of a general population of adults with type 1 diabetes. Although this sample likely excludes individuals in hospital or nursing

homes (with highly advanced disease), it is also likely that individuals with few problems associated with their diabetes (i.e., young adults), were less likely to complete the questionnaire as they may feel they are not burdened by their disease or were not at a fixed address (e.g. students).

Lastly, it is unclear how missing data affected these study results. Missing data was rather minimal for the HUI and the RAND-36 therefore, it is not anticipated that these study results would differ. Although missing data was a larger issue for the IRQOL, previous issues of missing data and validity were reasons for investigating this measure in this study. Also, imputation of IRQOL data (when possible) was performed, thus reducing the effects of the missing data on the overall study results. In fact, the very issue of missing data in an important outcome of validation and interpretation studies, and speaks to the feasibility of applying these measures in future studies.

5.6 Implications for future research

This study has generated evidence for the construct validity of the HUI2 and HUI3 in adults with type 1 diabetes, as well as provided information on HUI2 and HUI3 norms for this population. This evidence allows for future comparisons between adults with type 1 diabetes and those with type 2 diabetes, other disease states, or comparison to the general population. Comparisons such as these will provide researchers and clinicians with further information on the overall HRQL burden of type 1 diabetes. This information will be useful in the development of future studies and ideally, affect clinical decisions.

The generated population norms also provide a comparison for the Islet Transplant (IT) Program Study participants. Comparison of these scores will provide

information on the success and impact of this future treatment to those with type 1 diabetes. Also, these generated utility scores can be used for a cost-utility analysis for the IT program. This analysis will be highly influential for health resource and policy decision makers.

Lastly, this study has provided further evidence that the IRQOL does not act as an immunosuppressant-specific HRQL instrument in this population. Although this measure may be applicable for those with whole organ transplants (receiving glucocorticoids), it is likely not providing valuable information for the IT Program Study. It is suggested that an IT-specific HRQL measure be generated or an alternate measure be employed, in order to effectively measure the HRQL burden resulting from post-transplant immunosuppressant therapy.

As noted earlier, this cross-sectional study only provides evidence of discriminative and correlational construct validity of the included measures. Future longitudinal assessments of these measures are encouraged to investigate the reliability and responsiveness of these measures in this study population.

5.7 Study Conclusions

When measuring HRQL in any condition, it is essential that the instruments used are valid in the population under study. Construct validity can be defined as the extent to which an instrument measures the property it is intended to measure (Hays et al., 1993). Construct validation cannot be proven definitively, it is a result of a continuing process and accumulation of evidence. Although there is a wealth of information available regarding the validity of health profile measures in type 1 and type 2 diabetes, literature regarding the use of preference-based index measure in type 1 diabetes is rather limited.

This study effectively provides further evidence of the construct validity of the Health Utilities Index Mark 2 and Mark 3 (a generic preference-based index measure) in type 1 diabetes. In this study, the HUI2 and HUI3 were shown to have discriminative validity in detecting HRQL differences between groups anticipated to differ in HRQL, based on the duration of diabetes and the presence of diabetic complications and co-morbidities. The majority of these differences proved to be statistically significant and clinically importantly different. Further, this study provided evidence of correlational construct validity, where overall scores of employed generic preference based measures were found to be strongly correlated.

Similar HRQL trends were found to those previously reported in type 2 diabetes (Maddigan et al., 2004). It is evident from these study results that type 1 diabetes can be associated with HRQL impairments, particularly impairments associated with emotion and pain. The HRQL impairments related to pain and emotion may be of particular interest to clinicians, as they are commonly overlooked in practice settings.

In addition to providing evidence of construct validity, this study generated reference scores for the generic measures employed (i.e., the HUI2, HUI3, and RAND-36). This evidence allows for future comparisons between adults with type 1 diabetes and those with type 2 diabetes, other disease states, or the general population. Also, comparison of these scores to those of patients of the IT program will provide information on the success and impact of this future treatment to those with type 1 diabetes.

A second objective of this study was to evaluate the IRQOL as a measure of HRQL. IRQOL scores were found to be strongly correlated to those of other generic

measures employed and were similar in detecting group differences. This shows that the IRQOL is reflecting a similar HRQL burden to that shown by generic measures, which may question it's specificity for measuring immunosuppressant-related quality of life. Based on previous research in islet transplant (IT) patients (Johnson et al., 2002) and our data, we can conclude that the IRQOL does not act as an immunosuppressant-specific HRQL measure in this population, thus limiting its construct validity in this population.

In addition, the IRQOL was plagued with problems of missing data and respondent interpretation (where subjects were confused with the format of the questionnaire). These limitations further limit the content (or face) validity of this measure. Despite our study findings, it must be recognized that the IRQOL was designed and validated for individuals undergoing whole organ transplant, who are receiving an immunosuppressant regimen including glucocorticoids, for whom this instrument may be valid.

Lastly, in addition to outlined study objectives, further investigation of study data revealed an interesting discrepancy between the HRQL scores observed in the HUI and the RAND-36. In this case, distributional-based interpretation of RAND-36 scores may lead to misinterpretation of HRQL burden associated with type 1 diabetes, as clinical evidence and other HRQL measures, such as the HUI, would suggest this population's HRQL is lower than that of the general population. Further analysis of the distribution of HUI and RAND-36 scores provides evidence that, in fact, scores were not normally distributed, with substantial skew to the left, while a distributional-based approach assumes scores to be normally distributed. This raises the interesting issue of whether

norm-based scoring approaches are appropriate for measuring HRQL in populations, where it can be argued that 'health' is unlikely to be normally distributed.

Further research in this area should focus on the longitudinal construct validity of the HUI2 and HUI3 in this population, to provide evidence towards the responsiveness and reliability of this measure in adults with type 1 diabetes. Also, researchers and clinicians of the IT program should consider investigating alternative HRQL measures or means of capturing immunosuppressant-related HRQL as the IRQOL does not appear to be effectively capturing HRQL associated with this treatment in this population. Lastly, a comparison of preference-based index scores and norm-based scores reveal that a norm-based scoring approach may not be appropriate in populations which are not normally distributed.

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Appendix A
Questionnaire Package

Health-Related Quality of Life Assessment

in Type 1 Diabetes

University of Alberta

CONFIDENTIAL (when completed)

Please answer the following questions:

ABOUT YOU...

The following questions are about you. Please answer the questions as best as you can. You do not have to answer questions if you don't want to. The information you do provide will help us to describe the results of our research, and compare results between different groups of people.

1. **What is your current age?** _____

2. **Are you:** ___ **male** ___ **female**

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

Less than high school	1	☐
High school graduate	2	☐
Some college/technical school	3	☐
College degree/technical diploma	4	☐
Some university	5	☐
University degree	6	☐
Graduate school	7	☐

4. **Are you currently:**

Single	1	☐
Married/In a partnership	2	☐
Separated/Divorced	3	☐
Widowed	4	☐

5. **During the past 12 months, what best describes your <u>main</u> activity? Were you mainly...**

Working at a job or business?	1	☐
Looking for work?	2	☐
Keeping house?	3	☐
A student?	4	☐
Unemployed due to disability?	5	☐
Retired?	6	☐

Please answer the following questions:

6. **Which of the following categories includes your total household income (before taxes) in the last tax year?**

Under $10,000	1	☐
$10,000 - $29,999	2	☐
$30,000 - $49,999	3	☐
$50,000 - $69,999	4	☐
$70,000 and above	5	☐

ABOUT YOUR DIABETES....

7. **How many years have you had diabetes? _____ years**

8. **How old were you when your diabetes was first diagnosed? _____ years**

9. **When you were diagnosed, were you:**

____ Underweight

____ Normal Weight

____ Overweight

10. **Did you start using insulin within 3 months after your diagnosis of diabetes?**

___ Yes ___ No

11. **How many times each day do you take insulin?**

___ None
___ One
___ Two
___ Three
___ Four or More
___ I use an insulin pump

Please answer the following questions:

12. **How would you rate your overall diabetes control?**

___ Excellent (5)
___ Very Good (4)
___ Good (3)
___ Fair (2)
___ Poor (1)

13. **a) When was your HbA_{1c} (hemoglobin) measured last?**

___ During the last 4 weeks
___ 1-3 months ago
___ 4-6 months ago
___ Over 6 months ago
___ Don't know

13. **b) What was your last HbA_{1c} (hemoglobin) value (for example, 0.085 or 8.5%)?**

_____ ____ Don't know

14. **How many diabetes - related visits to the emergency room did you make over the last 3 months?** _____ **visits**

15. **How many days of work did you miss over the last 3 months due to diabetes?**

_____ **days**

16. **How many diabetes – related overnight hospital stays did you make over the last 3 months?** _____ **stays**

Please answer the following questions:

17. **In the last 3 months, have you experienced low blood sugars that:**

... you were able to treat yourself without help?

___ Yes ___ No

... you needed help from another person or you went to the hospital for treatment?

___ Yes ___ No

17. **Have you been told you have retinal damage (vision problems) due to your diabetes?** ___ Yes ___ No

18. **Has your vision deteriorated because of diabetes-related retinal changes?**

___ Yes ___ No

19. **Have you been told you have cataracts due to your diabetes?**

___ Yes ___ No

20. **Have you been told your kidneys have been damaged due to your diabetes?**

___ Yes ___ No

21. **Has the kidney damage been treated or is it being treated now?**

___ Yes ___ No ___ Not Applicable

22. **How is your kidney damage being treated?**

___ Medication ___ Peritoneal Dialysis ___ Hemodialysis

___ Kidney Transplantation ___ Not Applicable

23. **Do you have any pain or numbness in your legs/feet?**

___ Yes No ___

24. **Have you had any wounds in your legs/feet?**

___ Yes No ___

Please answer the following questions:

25. **Do you have any blood circulation problems in your legs/feet?**

___ Yes No ___

26. **Have you had surgical operation of your leg because of diabetes? (for example, having a toe removed)** ___ Yes No ___

27. **Have you ever had diabetic ketoacidosis?**

___ Yes No ___ Don't know ____

We are also interested in "long-term conditions" that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional.

28. **Have you ever been told by a health professional that you have:**

a. Asthma	___ Yes	No ___
b. Arthritis or rheumatism	___ Yes	No ___
c. Back problems, excluding arthritis	___ Yes	No ___
d. High blood pressure	___ Yes	No ___
e. Migraine headaches	___ Yes	No ___
f. Chronic bronchitis or emphysema	___ Yes	No ___
g. Sinusitis	___ Yes	No ___
h. Epilepsy	___ Yes	No ___
i. Heart disease or had a heart attack	___ Yes	No ___
j. Stroke	___ Yes	No ___
k. Cancer	___ Yes	No ___
l. Stomach or intestinal ulcers	___ Yes	No ___

Please answer the following questions:

m. Urinary incontinence	___ Yes	No ___
n. A bowel disorder (Crohn's or colitis)	___ Yes	No ___
o. Glaucoma	___ Yes	No ___
p. A thyroid condition	___ Yes	No ___
q. Other, please specify:		

29. If you checked yes to any of the conditions listed in question 28:

How do they impact your everyday life?

___ No impact (1)

___ Mild impact (2)

___ Moderate impact (3)

___ Large impact (4)

___ Makes life extremely difficult (5)

Thank you for this information. The remainder of the questionnaire contains sets of questions which ask about various aspects of your health.

Please go to the next page and follow the instructions for the remainder of the questionnaire.

Instructions:
This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day-to-day basis, during the past 4 weeks. To define the past 4 week period, please think about the date this time last month and recall the major events that you have experienced during this period. Please focus your answers on your overall abilities, disabilities and how you felt during the past 4 weeks.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Please read each question and consider your answers carefully. For each question, please select one answer that best describes your level of ability or disability during the past 4 weeks. Please indicate the selected answer by circling the letter (a,b,c,...) beside the answer.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

---

1. Which one of the following best describes your ability, during the past 4 weeks, to see well enough to read ordinary newsprint?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

2. Which one of the following best describes your ability, during the past 4 weeks, to see well enough to recognize a friend on the other side of the street?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

3. Which one of the following best describes your ability, during the past 4 weeks, to hear what was said in a group conversation with at least three other people?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

4. Which one of the following best describes your ability, during the past 4 weeks, to hear what was said in a conversation with one other person in a quiet room?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

5. Which one of the following best describes your ability, during the past 4 weeks, to be understood when speaking your own language with people who do not know you?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

6. Which one of the following best describes your ability, during the past 4 weeks, to be understood when speaking with people who know you well?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

7. Which one of the following best describes how you have been feeling during the past 4 weeks?

   a. Happy and interested in life.

   b. Somewhat happy.

   c. Somewhat unhappy.

   d. Very unhappy.

   e. So unhappy that life was not worthwhile.

8. Which one of the following best describes the pain and discomfort you have experienced during the past 4 weeks?

   a. Free of pain and discomfort.

   b. Mild to moderate pain or discomfort that prevented no activities.

   c. Moderate pain or discomfort that prevented a few activities.

   d. Moderate to severe pain or discomfort that prevented some activities.

   e. Severe pain or discomfort that prevented most activities.

9. Which one of the following best describes your ability, during the past 4 weeks, to walk?
Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

a. Able to walk around the neighbourhood without difficulty, and without walking equipment.

b. Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.

c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.

d. Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.

e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.

f. Unable to walk at all.

10. Which one of the following best describes your ability, during the past 4 weeks, to use your hands and fingers?
Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

a. Full use of two hands and ten fingers.

b. Limitations in the use of hands or fingers, but did not require special tools or the help of another person.

c. Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).

d. Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools).

e. Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools).

f. Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools).

11. Which one of the following best describes your ability, during the past 4 weeks, to remember things?

    a. Able to remember most things.

    b. Somewhat forgetful.

    c. Very forgetful.

    d. Unable to remember anything at all.

12. Which one of the following best describes your ability, during the past 4 weeks, to think and solve day to day problems?

    a. Able to think clearly and solve day to day problems.

    b. Had a little difficulty when trying to think and solve day to day problems.

    c. Had some difficulty when trying to think and solve day to day problems.

    d. Had great difficulty when trying to think and solve day to day problems.

    e. Unable to think or solve day to day problems.

13. Which one of the following best describes your ability, during the past 4 weeks, to perform basic activities?

    a. Eat, bathe, dress and use the toilet normally.

    b. Eat, bathe, dress or use the toilet independently with difficulty.

    c. Required mechanical equipment to eat, bathe, dress or use the toilet independently.

    d. Required the help of another person to eat, bathe, dress or use the toilet.

14. Which one of the following best describes how you have been feeling during the past 4 weeks?

    a. Generally happy and free from worry.

    b. Occasionally fretful, angry, irritable, anxious or depressed.

    c. Often fretful, angry, irritable, anxious or depressed.

    d. Almost always fretful, angry, irritable, anxious or depressed.

    e. Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15. Which one of the following best describes the pain or discomfort you have experienced during the past 4 weeks?

    a. Free of pain and discomfort.

    b. Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.

    c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.

    d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.

    e. Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.

16. Overall, how would you rate your health during the past 4 weeks?

    a. Excellent.

    b. Very good.

    c. Good.

    d. Fair.

e. Poor.

This next section asks for your views about your health. This information will help tell us how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

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

(circle one)

Excellent.....1
Very good.....2
Good.....3
Fair.....4
Poor.....5

17. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago.....1
Somewhat better now than one year ago.....2
About the same as one year ago.....3
Somewhat worse now than one year ago.....4
Much worse now than one year ago.....5

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

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile/kilometre**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

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

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

20. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

22. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

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

(circle one)

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

24. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks –

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

26. How TRUE or FALSE is each of the following statements for you?

(circle one)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

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

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile/kilometre**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

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

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

20. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

22. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

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

(circle one)

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

24. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks –

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

26. How TRUE or FALSE is each of the following statements for you?

(circle one)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

In this next section, there is a list of things people with diabetes do in order to AVOID low blood sugar. After each thing, you are to say how often you do that thing: Never, Rarely, Sometimes, Often or Always.

Remember there are no right or wrong answers. Please give the answer that best describes how often you do these things during your daily routine to AVOID low blood sugar.

[Please read each item carefully. Circle one number for each item.]

How often do you...

	Never	Rarely	Sometimes	Often	Always
1. Eat large snacks at bedtime	0	1	2	3	4
2. Avoid being alone when your sugar is likely to be low	0	1	2	3	4
3. When testing blood glucose, run a little high to be on the safe side	0	1	2	3	4
4. Keep your sugar high when you will be alone for awhile	0	1	2	3	4
5. Eat something as soon as you feel the first sign of low blood sugar	0	1	2	3	4
6. Reduce your insulin when you think your sugar is low	0	1	2	3	4
7. Keep your sugar high when you plan to be in a long meeting or at a party	0	1	2	3	4
8. Carry fast-acting sugar with you	0	1	2	3	4
9. Avoid exercise when you think your sugar is low	0	1	2	3	4
10. Check your sugar often when you plan to be in a long meeting or out to a party	0	1	2	3	4

Next is a list of concerns or worries people with diabetes sometimes have. Please say how often you WORRY about each item because of low blood sugar. Again, the categories are Never, Rarely, Sometimes, Often or Always.

[Please read each item carefully. Circle one number for each item.]

How often do you worry about.....

	Never	Rarely	Sometimes	Often	Always
11. Not recognizing/realizing you are having low blood sugar	0	1	2	3	4
12. Not having food, fruit, or juice with you.	0	1	2	3	4
13. Passing out in public	0	1	2	3	4
14. Embarrassing yourself or your friends in a social situation	0	1	2	3	4
15. Having a reaction while alone	0	1	2	3	4
16. Appearing stupid or drunk	0	1	2	3	4
17. Losing control	0	1	2	3	4
18. No one being around to help you during a reaction	0	1	2	3	4
19. Having a reaction while driving	0	1	2	3	4
20. Making a mistake or having an accident	0	1	2	3	4
21. Getting a bad evaluation or being criticized	0	1	2	3	4
22. Difficulty thinking clearly when responsible for others	0	1	2	3	4
23. Feeling lightheaded or dizzy	0	1	2	3	4

Below is a list of problems or symptoms that bother some people. For each problem, first indicate how often you have the problem in the past 4 weeks by circling the number in the first set of columns that best describes your

Then, for each item indicate how much the problem has troubled you in the past 4 weeks by circling the number that is the best answer from the set set of responses.

		How often do you have problems with	not at all	very seldom	sometimes	often	all the time	How troubling is it? not at all	very little	somewhat	a lot	extremely
50	Mood changes		1	2	3	4	5	1	2	3	4	5
51	Depression		1	2	3	4	5	1	2	3	4	5
52	Nervousness or anxiety		1	2	3	4	5	1	2	3	4	5
53	Irritability		1	2	3	4	5	1	2	3	4	5
54	Anger		1	2	3	4	5	1	2	3	4	5
55	Keeping a positive attitude		1	2	3	4	5	1	2	3	4	5
56	Feelings of uselessness		1	2	3	4	5	1	2	3	4	5
57	Being worried		1	2	3	4	5	1	2	3	4	5
58	Worthlessness		1	2	3	4	5	1	2	3	4	5
59	Hopelessness		1	2	3	4	5	1	2	3	4	5
60	Ability to concentrate		1	2	3	4	5	1	2	3	4	5
61	Completing daily errands		1	2	3	4	5	1	2	3	4	5
62	Participating in social activities		1	2	3	4	5	1	2	3	4	5
63	Doing housework		1	2	3	4	5	1	2	3	4	5
64	Doing yardwork		1	2	3	4	5	1	2	3	4	5
65	Performing my job		1	2	3	4	5	1	2	3	4	5
66	Participating in physical activities		1	2	3	4	5	1	2	3	4	5
67	Participating in leisure pasttimes		1	2	3	4	5	1	2	3	4	5
68	Driving		1	2	3	4	5	1	2	3	4	5
69	Being independent		1	2	3	4	5	1	2	3	4	5
70	Ability to travel on vacations		1	2	3	4	5	1	2	3	4	5
71	Reading		1	2	3	4	5	1	2	3	4	5

		How often do you have problems with	not at all	very seldom	sometimes	often	all the time	How troubling is it? not at all	very little	somewhat	a lot	extremely
72	Decreased muscle strength		1	2	3	4	5	1	2	3	4	5
73	Climbing stairs		1	2	3	4	5	1	2	3	4	5
74	Walking		1	2	3	4	5	1	2	3	4	5
75	Bone pain		1	2	3	4	5	1	2	3	4	5
76	Stiff joints		1	2	3	4	5	1	2	3	4	5
77	Foot pain		1	2	3	4	5	1	2	3	4	5
78	Hip pain		1	2	3	4	5	1	2	3	4	5
79	Stomach pains		1	2	3	4	5	1	2	3	4	5
80	Nausea		1	2	3	4	5	1	2	3	4	5
81	Diarrhea		1	2	3	4	5	1	2	3	4	5
82	Vomiting		1	2	3	4	5	1	2	3	4	5
83	Stomach gas		1	2	3	4	5	1	2	3	4	5
84	Indigestion		1	2	3	4	5	1	2	3	4	5
85	High blood pressure		1	2	3	4	5	1	2	3	4	5
86	Easy bruising		1	2	3	4	5	1	2	3	4	5
87	Loss of interest in sex		1	2	3	4	5	1	2	3	4	5
88	Sexual performance		1	2	3	4	5	1	2	3	4	5
89	Increased hunger		1	2	3	4	5	1	2	3	4	5
90	Staying asleep		1	2	3	4	5	1	2	3	4	5
91	Weight gain		1	2	3	4	5	1	2	3	4	5
92	Increase hair growth		1	2	3	4	5	1	2	3	4	5
93	Infections		1	2	3	4	5	1	2	3	4	5
94	Trembling hands		1	2	3	4	5	1	2	3	4	5

This next set of questions is about your quality of life and the effects of your diabetes on your quality of life. Your quality of life is how good or bad you feel your life to be.

For each question you are given a choice of answers. Please circle the number which best indicates your response on each scale. Remember that there are no right or wrong answers; we just want to know how you feel about your life now.

For the next statements please consider the effects of your diabetes, its management and any complications you may have.

1.	**If you did not have diabetes, your quality of life would be:**						
	1	2	3	4	5	6	7
	very much better	much better	a little better	the same	a little worse	much worse	very much worse

For each of the next statements, please consider the effects of your diabetes, its management and any complications you may have on the aspect of life described by the statement.

Each question asks how much your diabetes has affected that aspect of your life, and then how important that aspect of you life is to you overall quality of life.

We realize that some statements may not be applicable to all people. Please say "not applicable" if you think that aspect of life does not apply to you.

1a)	**If you did not have diabetes, your working life and work-related opportunities would be:**							
	1	2	3	4	5	6	7	8
	very much better	much better	a little better	the same	a little worse	much worse	very much worse	not applicable
1b)	**This aspect of your life is:**							
		1	2	3	4			
		very important	important	somewhat important	not at all important			

2a)	**If you did not have diabetes, your family life would be:**							
	1 very much better	2 much better	3 a little better	4 the same	5 a little worse	6 much worse	7 very much worse	8 not applicable
2b)	**This aspect of your life is:**							
	1 very important	2 important	3 somewhat important	4 not at all important				

3a)	**If you did not have diabetes, your friendships and social life would be:**						
	1 very much better	2 much better	3 a little better	4 the same	5 a little worse	6 much worse	7 very much worse
3b)	**This aspect of your life is:**						
	1 very important	2 important	3 somewhat important	4 not at all important			

4a)	**If you did not have diabetes, your sex life would be:**							
	1 very much better	2 much better	3 a little better	4 the same	5 a little worse	6 much worse	7 very much worse	8 not applicable
4b)	**This aspect of your life is:**							
	1 very important	2 important	3 somewhat important	4 not at all important				

5a) If you did not have diabetes, your physical appearance would be:

1	2	3	4	5	6	7
very much better	much better	a little better	the same	a little worse	much worse	very much worse

5b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

6a) If you did not have diabetes, the things you could do physically would be:

1	2	3	4	5	6	7
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

6b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

7a) If you did not have diabetes, your holidays or leisure activities would be:

1	2	3	4	5	6	7
very much better	much better	a little better	the same	a little worse	much worse	very much worse

7b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX

8a) If you did not have diabetes, ease of travelling (local or long distance) would be:

1	2	3	4	5	6	7
very much better	much better	a little better	the same	a little worse	much worse	very much worse

8b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

9a) If you did not have diabetes, your confidence in your ability to do things would be:

1	2	3	4	5	6	7
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

9b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

10a) If you did not have diabetes, your motivation to achieve things would be:

1	2	3	4	5	6	7
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

10b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX

11a) If you did not have diabetes, the way society at large reacts to you would be:

1	2	3	4	5	6	7
very much better	much better	a little better	the same	a little worse	much worse	very much worse

11b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

12a) If you did not have diabetes, your worries about the future would be:

1	2	3	4	5	6	7
Very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased

12b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

13a) If you did not have diabetes, your finances would be:

1	2	3	4	5	6	7
very much better	much better	a little better	the same	a little worse	much worse	very much worse

13b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX

17a) If you did not have diabetes, your enjoyment of food would be:

1	2	3	4	5	6	7
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

17b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

18a) If you did not have diabetes, your freedom to drink as you wish (e.g. sweetened hot and cold drinks, fruit juice, alcohol) would be:

1	2	3	4	5	6	7
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

18b) This aspect of your life is:

1	2	3	4
very important	important	somewhat important	not at all important

115. How did you complete the questionnaire? Please select the one answer that best describes your situation.

a. By myself, without any help from anyone else.

b. By myself, except someone else circled the answers on the questionnaire form for me.

c. With the help of someone else.

d. This questionnaire was completed by a family member, without help from the subject or patient.

e. This questionnaire was completed by a nurse or other health professional, without help from the subject or patient.

Please specify type of health professional: _____

f. This questionnaire was completed by another person, without help from the subject or patient.

Please specify relationship to subject or patient: _____

.....

Thank you for completing this questionnaire about your health.

Please return the completed questionnaire in the enclosed envelope.

Appendix B
Cover Letter

September 1, 2003

Dear Patient:

We are asking you to participate in a study of patients with Type 1 diabetes. We are interested in studying the health-related quality of life of people who have Type -1I diabetes. This project will help us to evaluate these questionnaires' effectiveness as a research tool. We are ultimately interested in comparing the quality of life of people like you with the responses from people who have received islet transplants. In order for these comparisons to be successful, we first need to create local norms for these questionnaires (that is, on average, how do people with Type 1 diabetes respond to each of these questionnaires?).

We have put together a series of health quality questions that we will ask you to fill out. On average the entire series of questionnaires takes 30 minutes to complete. There are 6 questionnaires in total. Please take the time to complete the survey to the best of your ability. If you need help completing the questionnaire, you may ask someone to help you. There are no right or wrong answers. We are interested in your descriptions of the quality of your health. Also, please read the information provided at the beginning of each survey and answer the questions accordingly. We have enclosed a self-addressed, pre-paid postage envelope for return of the completed survey.

Please understand that you do not have to participate in this research if you don't want to. Occasionally, health-related questions might be emotionally difficult to answer because they can touch on difficult life experiences. Whether you decide to participate or not, your medical care will not change. If you choose to proceed with the questionnaire, you may leave out any questions you do not wish to answer. The answers to your questions will be kept safe in a locked room, and all data will be accessible only to the research team of Dr. Johnson, Dr. Ryan, and Alison Supina (Research Assistant). All responses are confidential, and any published results will only refer to group, not individual, results. Although the study is not likely to benefit you directly, it may provide information that will help other patients decide whether to receive an islet transplant or simply to stay on their insulin regimen. Furthermore, your participation in this study will help us evaluate health-related quality of life in people who have received islet cell transplants.

Thank you very much for considering this important study. If you should have any questions about this letter, you may contact Dr Ellen Toth (407-6223) or Terri Gammer (Research manager – 407 3671). For questions about the study itself, please contact Dr. Ryan at (780) 407-6011 or Dr. Johnson /Alison Supina at (780) 448-4881.

Sincerely,

Ellen L. Toth, MD
Department of Medicine
University of Alberta
Canada

Jeffrey A. Johnson, PhD
Principle Investigator
Department of Public Health Sciences
University of Alberta
Canada

THIS STUDY HAS BEEN APPROVED BY THE HEALTH RESEARCH ETHICS BOARD AT THE UNIVERSITY OF ALBERTA, AND MEETS THE UNIVERSITY OF ALBERTA STANDARDS FOR THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Appendix C
Reminder Letter

October 02, 2003

Dear Patient:

We are currently running a study on the health-related quality of life in patients with Type I diabetes. We recently sent you a series of questionnaires, along with a postage-paid return envelope. It seems that we have not yet received your completed questionnaires, and we are hoping that you are still interested in participating in this study. If you have not already done so, would you be able to complete the questionnaires and mail them back to us in the envelope provided?

If you require another questionnaire booklet, please feel free to contact **Alison at (780)448-4881** (ext. 257 if you wish to leave a message).

Thank you very much for considering this study.

Sincerely,

Ellen L. Toth, MD
Department of Medicine
University of Alberta
Canada

Jeffrey A. Johnson, PhD
Principle Investigator
Department of Public Health Sciences
University of Alberta
Canada

****If you have already completed and/or returned the survey, please disregard this message. We have either not yet received or processed your returned questionnaire. Thank you for your participation.*

Appendix D
Health Utilities Index Mark 2 Classification System

HUI2 Health State Classification System

Attribute	Level	Utility	Level Description
Sensation	1	1.0	Able to see, hear and speak normally for age
	2	0.87	Requires equipment to see or hear or speak
	3	0.65	Sees, hears or speaks with limitations even with equipment
	4	0.0	Blind, deaf or mute
Mobility	1	1.0	Able to walk, bend, lift, jump, and run normally for age
	2	0.92	Walks, bends, lifts, jumps, or runs with some limitations but does not require help
	3	0.61	Requires mechanical equipment (such as canes, crutches, braces or wheelchair) to walk or get around independently
	4	0.34	Requires the help of another person to walk or get around and requires mechanical equipment as well
	5	0.0	Unable to control or use arms and legs
Emotion	1	1.0	Generally happy and free from worry
	2	0.86	Occasionally fretful, irritable, anxious, depressed, or suffering night terrors
	3	0.60	Often fretful, irritable, anxious, depressed, or suffering night terrors
	4	0.37	Almost always fretful, irritable, anxious or depressed
	5	0.0	Extremely fretful, irritable, anxious or depressed usually requiring hospitalization or psychiatric institutional care
Cognition	1	1.0	Learns and remembers schoolwork normally for age
	2	0.85	Learns and remembers schoolwork more slowly than classmates as judged by parents and/or teachers
	3	0.55	Learns and remembers very slowly and usually requires special educational assistance
	4	0.00	Unable to learn and remember
Self-care	1	1.0	Eats, bathes, dresses, and uses the toilet normally for age
	2	0.85	Eats, bathes, dresses, or uses the toilet independently with difficulty
	3	0.55	Requires mechanical equipment to eat, bathe, dress or use the toilet independently
	4	0.00	Requires the help of another person to eat, bathe, dress or use the toilet
Pain	1	1.0	Free or pain and discomfort
	2	0.95	Occasional pain; discomfort relieved by nonprescription drugs or self-control activity without disruption of normal activities
	3	0.75	Frequent pain; discomfort relieved by oral medicines with occasional disruption of normal activities
	4	0.42	Frequent pain, frequent disruption of normal activities; discomfort requires prescription narcotics for relief
	5	0.00	Severe pain; pain not relieved by drugs and constantly disrupts normal activities

Source: www.healthutilities.com.

Appendix E
Health Utilities Index Mark 3 Classification System

HUI3 Health Status Classification System

Attribute	Level	Utility	Level Description
Vision	1	1.00	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses
	2	0.95	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses
	3	0.73	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses
	4	0.59	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint even with glasses
	5	0.38	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses
	6	0.00	Unable to see at all
Hearing	1	1.00	Able to hear what is said in a group conversation with at least three other people, without a hearing aid
	2	0.86	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at leastthree other people
	3	0.71	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid and able to hear what is said in a group conversation with at least three other people with a hearing aid
	4	0.48	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	5	0.32	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	6	0.00	Unable to hear at all
Speech	1	1.00	Able to be understood completely when speaking with strangers or friends
	2	0.82	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know the respondent well
	3	0.67	Able to be understood partially when speaking with strangers or people who know the respondent well
	4	0.41	Unable to be understood when speaking with strangers but able to be understood partially by people who know the respondent well
	5	0.00	Unable to be understood when speaking to other people (orunable to speak at all)
Ambulation	1	1.00	Able to walk around the neighborhood without difficulty and without walking equipment
	2	0.83	Able to walk around the neighborhood with difficulty, but does not require walking equipment or the help of another person
	3	0.67	Able to walk around the neighborhood with walking equipment, but without the help of another person
	4	0.36	Able to walk only short distances with walking equipment and requires a wheelchair to get around the neighborhood
	5	0.16	Unable to walk alone, even with walking equipment: able to walk short distances with the help of another person, and requires a wheelchair to get around the neighborhood
	6	0.00	Cannot walk at all
Dexterity	1	1.00	Full use of two hands and ten fingers
	2	0.88	Limitations in the use of hands or fingers, but does not require special tools or help of another person
	3	0.73	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person)
	4	0.45	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with the use of special tools)
	5	0.20	Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with the use of special tools)
	6	0.00	Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with the use of special tools)
Emotion	1	1.00	Happy and interested in life
	2	0.91	Somewhat happy
	3	0.73	Somewhat unhappy
	4	0.33	Very unhappy
	5	0.00	So unhappy that life is not worthwhile
Cognition	1	1.00	Able to remember most things, think clearly and solve day to day problems
	2	0.86	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems
	3	0.92	Somewhat forgetful, but able to think clearly and solve day to day problems
	4	0.70	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problms
	5	0.32	Very forgetful, and have great difficulty when trying to think and or solve day to day problems
	6	0.00	Unable to remember anything at all, and unable to think or solve day to day problems
Pain	1	1.00	Free of pain and discomfort
	2	0.92	Mild to moderate pain that prevents no activities
	3	0.77	Moderate pain that prevents a few activities
	4	0.48	Moderate to severe pain that prevents some activities
	5	0.00	Severe pain that prevents most activities

Source: www.healthutilities.com.

Appendix F
Study Results for the RAND-36 Health Status Inventory

Comparison of RAND-36 Domain Scores between subgroups

	n	PH	RLP	PA	GH	EWB	RLE	SF	EF
Duration of Diabetes									
≤ 20 years	116	91.30***	82.18**	82.61**	59.41	74.44	72.36	82.05	60.21
		(17.11)	(28.38)	(19.22)	(22.53)	(17.14)	(37.47)	(22.41)	(20.15)
> 20 years	93	82.70	70.30	75.26	54.04	73.69	68.23	80.54	56.76
		(21.31)	(37.20)	(24.75)	(24.16)	(20.34)	(40.33)	(23.52)	(24.38)
Presence of Co morbidities									
No co morbidities	119	88.96	80.60	82.84**	59.79	75.60	70.62	82.52	60.46
		(18.31)	(31.29)	(20.74)	(22.86)	(18.15)	(39.50)	(22.42)	(22.54)
≥1 co morbidity	67	85.65	72.54	75.26	53.79	72.45	70.66	80.15	56.65
		(20.86)	(34.70)	(23.17)	(23.69)	(19.10)	(37.91)	(23.44)	(21.62)
Presence of Complications									
Cardiovascular disease	111	81.45***	66.83**	76.01	46.59***	70.18*	62.89*	75.68**	53.55**
		(22.27)	(36.96)	(24.50)	(24.97)	(20.87)	(41.68)	(26.62)	(25.40)
No cardiovascular disease	52	92.35	84.83	82.79	64.73	77.18	77.53	86.26	63.21
		(15.25)	(26.52)	(19.04)	(20.64)	(16.28)	(34.57)	(19.80)	(20.04)
Nephropathy	172	72.50***	64.64**	69.81**	39.88***	66.60**	51.75***	71.56**	49.00**
		(27.10)	(37.45)	(27.41)	(22.57)	(23.17)	(42.94)	(28.31)	(25.78)
No nephropathy	37	91.00	80.06	81.83	61.07	75.91	75.14	83.91	60.97
		(15.51)	(31.02)	(20.08)	(21.83)	(17.06)	(35.26)	(20.77)	(20.77)
Neuropathy/Peripheral Vascular Disease (PVD)	137	75.35***	62.21***	65.58***	43.97***	68.49***	53.52***	70.72***	47.95***
		(25.48)	(39.36)	(24.12)	(22.99)	(21.07)	(43.82)	(25.36)	(23.57)
No neuropathy/PVD	70	93.64	84.12	86.52	64.20	77.26	79.17	87.23	64.39
		(11.64)	(26.66)	(17.33)	(20.55)	(16.67)	(32.92)	(19.24)	(19.44)
Retinopathy	124	77.60***	63.73***	69.29***	46.39***	68.77***	57.36***	72.02***	50.56***
		(24.85)	(37.48)	(26.03)	(24.07)	(21.40)	(41.11)	(25.64)	(23.54)
No retinopathy	84	94.54	86.09	86.63	64.72	78.06	80.03	88.20	64.80
		(10.00)	(26.24)	(15.67)	(19.60)	(15.49)	(33.86)	(17.91)	(19.05)

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Comparison of MHC and PHC scores between subgroups

	n	Mean (SD) MHC	Mean (SD) PHC
Duration of Diabetes			
≤ 20 years	116	58.66 (10.83)	58.58 (7.99)**
> 20 years	93	57.54 (12.83)	54.79 (10.31)
Presence of Co morbidities			
No co morbidities	66	61.51 (10.53)	61.02 (6.39)**
≥1 co morbidity	96	57.24 (11.95)	55.05 (9.80)
Presence of Complications			
No cardiovascular disease	111	60.56 (10.44)*	59.55 (7.87)***
Cardiovascular disease	52	55.76 (12.96)	53.49 (10.07)
No nephropathy	172	59.41 (11.02)**	58.36 (8.43)***
Nephropathy	37	52.97 (13.71)	50.76 (10.23)
No neuropathy/PVD	137	61.04 (10.23)***	60.12 (7.07)***
Neuropathy/PVD	70	52.81 (12.87)	50.63 (10.00)
No retinopathy	124	61.48 (10.00)***	60.33 (6.76)***
Retinopathy	84	53.66 (12.58)	52.02 (9.26)

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Comparison of RAND-36 Domain Scores between subgroups: Mean (95%CI)[†]

	n	PH	RLP	PA	GH	EWB	RLE	SF	EF
Duration of Diabetes									
≤ 20 years	106	82.26 (74.3,90.3)	71.67 (57.0,86.3)	77.09 (67.59,86.6)	51.95 (41.3,62.6)	66.57 (58.4,74.7)	68.49 (50.5,86.5)	77.31 (67.2,87.4)	50.00 (40.3,59.7)
> 20 years	89	83.38 (74.9,91.9)	67.43 (52.0,82.9)	73.56 (63.5,83.6)	53.87 (42.6,65.2)	66.06 (57.4,74.7)	68.22 (49.12,87.3)	74.66 (64.0,85.4)	51.56 (41.3,61.8)
Presence of Co morbidities									
No co morbidities	104	83.30 (75.9,90.7)	71.82 (58.4,85.3)	78.35* (69.7,87.0)	55.31 (45.6,65.0)	67.72 (60.2,75.2)	68.11 (51.5,84.7)	76.25 (66.9,85.6)	51.33 (42.4,60.2)
≥1 co morbidity	91	82.17 (74.7,89.7)	67.52 (54.0,81.1)	72.36 (63.6,81.1)	50.07 (40.2,59.9)	64.8 (57.3,72.4)	68.7 (51.9,85.4)	75.96 (66.6,85.4)	50.01 (41.0,59.0)
Presence of Complications									
Cardiovascular disease	47	79.64* (69.9,89.4)	59.89** (43.9,75.9)	74.98 (64.1,85.8)	42.82*** (30.3,55.4)	63.20* (53.5,72.9)	74.75* (53.9,95.6)	69.46** (57.6,81.4)	48.88** (37.2,60.6)
No cardiovascular disease	100	87.66 (78.4,97.0)	76.50 (61.3,91.8)	78.87 (68.5,89.3)	61.81 (49.9,73.8)	70.91 (61.7,80.2)	91.07 (71.2,110.9)	82.40 (71.1,93.7)	60.97 (49.8,72.1)
Nephropathy	39	70.24*** (61.9,78.6)	59.6 (43.6,75.7)	66.85** (56.6,77.1)	38.00** (26.8,49.2)	61.35 (52.4,70.3)	52.09** (32.5,71.7)	67.56* (56.6,78.5)	41.7** (31.2,52.2)
No nephropathy	155	85.73 (79.1,92.4)	71.7 (59.0,84.4)	77.37 (69.1,85.6)	56.25 (47.3,65.2)	67.53 (60.4,74.7)	71.5 (55.9,87.0)	77.86 (69.1,86.6)	52.8 (44.4,61.2)
Neuropathy	68	76.11*** (68.4,83.9)	61.97* (47.4,76.5)	64.50*** (55.6,73.3)	41.80*** (31.8,51.8)	61.83* (53.8,69.9)	51.55*** (34.1,69.0)	67.17*** (57.5,76.8)	40.77*** (31.5,50.0)
No neuropathy	124	86.83 (79.7,94.0)	73.95 (60.7,87.2)	82.48 (74.4,90.6)	60.18 (50.9,69.4)	69.26 (51.9,76.7)	76.92 (61.0,92.8)	82.32 (73.5,91.2)	56.50 (48.0,65.0)
Retinopathy	81	77.82** (70.5,85.2)	62.48** (48.8,76.2)	69.38*** (60.5,78.2)	44.12*** (34.5,53.7)	62.35* (54.7,70.0)	56.23*** (39.7,72.7)	56.23*** (39.7,72.7)	44.39*** (35.5,53.3)
No retinopathy	112	87.10 (79.9,94.3)	76.06 (62.7,89.4)	80.79 (72.2,89.4)	60.43 (51.1,69.8)	69.79 (62.3,77.3)	78.88 (62.8,95.0)	78.88 (62.8,95.0)	56.25 (47.5,65.0)

[†]**Adjusted for age, sex, education, marital status, duration of diabetes, income, and the presence of co-morbidities**

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Comparison of MHC and PHC scores between subgroups†

	n	Mean (95%CI) MHC	Mean (95%CI) PHC
Duration of Diabetes			
≤ 20 years	104	54.34 (49.19, 59.48)	54.90 (51.01,58.79)
> 20 years	85	53.85 (48.42, 59.28)	54.15 (50.01, 58.29)
Presence of Co morbidities			
No co morbidities	90	54.64 (49.93, 59.36)	55.77*(52.23, 59.31)
≥1 co morbidity	102	53.54 (48.78, 59.36)	53.24 (49.67, 56.82)
Presence of Complications			
Cardiovascular disease	47	52.86** (46.83, 58.88)	52.02 *** (47.58, 56.45)
No cardiovascular disease	100	58.67 (42.93, 64.42)	57.49 (53.25, 61.72)
Nephropathy	154	46.98 (40.58, 53.38)	45.10*** (40.64, 49.56)
No nephropathy	37	50.90 (45.24, 56.55)	50.08 (46.16, 54.01)
Neuropathy/PVD	123	49.61***(44.64, 54.59)	46.89*** (42.81, 51.00)
No neuropathy/PVD	66	56.88(52.35, 61.42)	51.65 (47.47, 55.82)
Retinopathy	79	47.88 ** (42.31, 53.44)	47.43**(43.50, 55.30)
No retinopathy	111	53.18 (47.32, 59.05)	51.17 (47.04, 44.30)

†Adjusted for age, sex, education, marital status, income, duration of diabetes and the presence of co-morbidities

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$