QUALITY OF LIFE

IN PANCREAS TRANSPLANTATION

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A Giusi e Franco Mosca, con infinito amore.

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DECLARATION

I declare that, unless otherwise stated, all the work presented in this thesis is my own and that, with a few exceptions approved by all the necessary Regulatory Bodies, all the study procedures were carried on by me. Moreover, I have no conflict of interest to disclose.

ABSTRACT

QUALITY OF LIFE IN PANCREAS TRANSPLANTATION

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DPhil Thesis

Background: Pancreas transplantation is the only therapy capable of restoring long term insulin independence in patients with type 1 diabetes. However, it is still burdened by high rates of perioperative complications: surgical risks must be weighed against clinical benefits and health related quality of life gain (HRQOL).

Aim: The purpose of the DPhil was to assess HRQOL benefits after pancreas transplantation.

Methods: This research is based on two studies: a prospective longitudinal cohort study on patients undergoing pancreas transplantation, and a cross-sectional study on long term HRQOL in an historical group of pancreas transplant recipients. Participants of the prospective study completed patient reported outcome measures (PROMs) at multiple timepoints before and after surgery, while the cross-sectional study only required one set of post-operative PROMs. **Results:** A total of 57 patients undergoing Simultaneous Pancreas-Kidney transplantation were recruited into the prospective study. Baseline HRQOL was below population norms. After transplantation, HRQOL improved quicky and significantly, but, except for mental health, it remained below normative values. Results from the cross-sectional study

on a mixed cohort of 98 pancreas recipient- at approximately of 8.6 years from surgery- depicted a similar scenario.

Conclusions: Successful Simultaneous Pancreas Kidney transplantation (SPK) significantly improves HRQOL, and changes seem sustained in time; however, it doesn't restore patients to their former state before the onset of complications. Current PROMs don't allow us to clarify which obstacles prevent our patients from thriving, despite longstanding euglycemia and freedom from dialysis: there is an urgent need for a bespoke pancreas transplant HRQOL instrument capable of capturing all the intricacies of this population.

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GLOSSARY OF ABBREVIATIONS

BM	Blood Sugar Level
CGM	Continuous Glucose Monitoring
CIT	Cold Ischaemia Time
CRF	Calculated Reaction Frequency
CT	Computerised Tomography Scan
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
DGF	Delayed Graft Function
DKA	Diabetic Ketoacidosis
eGFR	Estimated Glomerular Filtration Rate
ESRF	End-Stage Renal Failure
FDA	Food and Drug Administration
Hb	Haemoglobin
HbA1c	Glycated Haemoglobin
HD	Haemodialysis
HES	Hospital Episodes Statistics
HLA	Human Leukocyte Antigens
HRQOL	Health Related Quality of Life
IAK	Islets After Kidney Transplant
IHD	Ischaemic Heart Disease
IPTR	International Pancreas Transplant Registry
ITA	Islet Transplant Alone

ITU	Intensive Therapy Unit
KTA	Kidney Transplant Alone
KTx	Kidney Transplant All Causes
LDKT	Living Donor Kidney Transplant
LdKTA	Living Donor Kidney Transplant Alone
MCS	Mental Component Summary
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
OGTT	Oral Glucose Tolerance Test
PAK	Pancreas After Kidney Transplant
PASPK	Pancreas After SPK
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PF	Primary Function
PHE	Public Health England
PNF	Primary Non-Function
PT	Solid Organ Pancreas Transplant, type unspecified
PTA	Pancreas Transplant Alone
PTAnfp	Pancreas Transplant Alone, Failed
QOL	Quality of Life
RRT	Renal Replacement Therapy
SD	Standard Deviation
SIK	Simultaneous Islet and Kidney Transplant

SPK	Simultaneous Pancreas Kidney Transplant
SPK-pre	Simultaneous Pancreas Kidney Transplant, Pre-emptive
SPKf	Simultaneous Pancreas Kidney Transplant, Successful
SPKnfb	Simultaneous Pancreas Kidney Transplant, non-functioning both
SPKnfk	Simultaneous Pancreas Kidney Transplant, non-functioning kidney
SPKnfp	Simultaneous Pancreas Kidney Transplant, non-functioning pancreas
UNOS	United Network for Organ Sharing
WHO	World Health Organisation
WL	Waiting List
WLRTC	West London Renal and Transplant Centre

1 CHAPTER 1: INTRODUCTION

1.1 OVERVIEW

Solid organ Pancreas Transplantation (PT) is the only therapy capable of restoring long term endocrine function in a selected cohort of patients with Type 1 Diabetes Mellitus and, when combined with successful kidney transplantation, it can improve life expectancy and chronic complications (Esmeijer, Hoogeveen et al. 2020).

However, PT is still burdened by significant surgical risks, and, unlike liver or heart transplantation, it is not immediately lifesaving. Moreover, patients can be offered other treatment options which, albeit inferior with respect to long-term results, are safer in the short term. Hence, PT specialists agree that surgical risks must be weighed against clinical and quality of life (QOL) gain (White, Shaw et al. 2009).

The trade-offs for an existence free from insulin and renal failure are the high perioperative risks and a lifelong dependence on anti-rejection medications. Immunosuppressants are indeed associated with complications such as infections and cancer and can cause a wide range of severe side effects. Regardless, it is common practice to consider a high QOL as an important outcome of successful pancreas transplantation.

While there is robust evidence supporting long term clinical benefits of this procedure, there is still a degree of uncertainty with regards to its impact on patients' wellbeing. The existing literature seems at times contradictory (Sureshkumar,

Mubin et al. 2002, Sureshkumar, Patel et al. 2006, Smith, Trauer et al. 2010) despite the topic being investigated since the very start of this activity. The reasons for this are likely multifactorial and realistically include the evolving methodology in quantitative/qualitative research throughout the decades and the low pancreas transplant rates of most of PT centres.

However, the assumption that PT recipients perceive an improved QOL seems to be indirectly confirmed by the high re-transplantation rates in large volume centres (Rudolph, Finger et al. 2015). Patients who have lost the transplanted pancreas, sometimes after dramatic post-operative complications, come forward for a second or even third transplant. QOL changes or expectations of QOL improvement might be the driving force behind this phenomenon.

This research aims to investigate QOL outcomes after a pancreas/pancreas-kidney transplant in adult patients with type 1 diabetes suffering from hypoglycaemia unawareness and/or end stage renal failure (ESRF).

The Oxford Transplant Centre has the largest PT program in Europe, with an average of 50-70 transplants per year, approximately one third of the total PT activity in the United Kingdom (Appendix, A1.1, A1.2) (NHS Blood and Transplant 2022). This constitutes the ideal background to perform a single centre analysis on Health-Related Quality of Life (HRQOL) within this population. Equally befitting is the possibility of a collaboration with Nuffield Department of Population Health, University of Oxford, to ensure the application of appropriate quantitative research methodology.

A broader knowledge on this topic could provide a deeper insight into what receiving a PT entails. Consequently, clinicians could offer more informed counselling to

patients when presenting therapeutic choices and alternatives, thus placing each individual at the centre of a complex decision-making pathway. Finally, this research could indirectly highlight areas of care that could be improved to enhance post-transplantation wellbeing.

1.2 THESIS STRUCTURE

- Chapter 1

  The first chapter of this thesis provides an overview on type 1 diabetes, solid organ pancreas transplantation and QOL research and how these three topics are interconnected.

- Chapter 2

  The second chapter is a Systematic Review of the existing literature on HRQOL in Pancreas Transplantation, aimed at identifying and appraising previous work on this topic and clarifying which PROMs have been used to investigate the topic. Comparative data suggests that most patients benefit in the form of an enhanced perception of health and increased vitality scores, but the small numbers of participants, heterogeneity of study designs and occasionally old methodology do not currently allow firm conclusions to be drawn on which domains improve the most.

- Chapter 3

  The third chapter is a description of a Prospective Longitudinal Observational Study on QOL after any form of solid organ Pancreas Transplantation in a cohort of adults with type 1 diabetes undergoing any form of Solid Organ Pancreas Transplantation

at Oxford Transplant Centre. The aim of this study is to evaluate changes in HRQOL up to one year after Pancreas Transplantation.

- Chapter 4

The fourth chapter is a description of a Cross-Sectional Observational Study on Long Term QOL on a historic cohort of individuals who received any form of solid organ Pancreas Transplantation at Oxford Transplant Centre for the treatment of Type 1 Diabetes.

- Chapter 5

The final chapter is a discussion of the research findings as well as its strengths and limitations. It presents possible future academic development based on the output of this DPhil.

1.3 TYPE 1 DIABETES

Individuals affected by type 1 diabetes are no longer able to produce insulin, the hormone responsible for the maintenance of circulating glucose levels within physiological range.

Unlike type 2 diabetes, this condition cannot be prevented by implementing healthy lifestyle choices. The only known way of improving long term outcomes is sustained euglycemia, as demonstrated by the Diabetes Control and Complications Trial. This pivotal research proved the unequivocal impact of tight metabolic control on the progression of chronic complications and their repercussions on QOL (Diabetes Control and Complications Trial Research Group; Nathan D.M. 1993).

However, maintaining appropriate glucose levels is hardly an easy task, and some patients experience asymptomatic and therefore life-threatening hypoglycaemia crises as well as hyperglycaemic peaks and diabetic ketoacidosis, which can be lethal if left untreated. Poor metabolic control also accelerates progression of the disease, mainly secondary to histopathological changes within the arterial tree that lead to severe macro and microvascular complications. Patients affected by type 1 diabetes have a reduced life expectancy (Livingstone, Levin et al. 2015) and their QOL can worsen progressively with time (Jacobson, Braffett et al. 2013).

1.3.1 Epidemiology and pathogenesis

There are approximately 3.8 million people diagnosed with diabetes in the UK. It is reported that 8% of these cases are type 1 diabetes (DiabetesUK 2020).

According to the estimates of the International Diabetes Federation Diabetes Atlas, worldwide incidence and prevalence of type 1 diabetes under 20 years of age were 128.900 and 1.110.100 cases respectively. The distribution of this illness varies across geographical areas as well as socioeconomic statuses (Patterson, Karuranga et al. 2019).

Type 1 diabetes - once referred to as “childhood diabetes”- is generally diagnosed before 40 years of age, but more often during childhood, between 10 and 14 years of age, with a male to female incidence rate ratio of 1.32 (Rogers, Kim et al. 2017). The etiopathogenesis is multifactorial: a combination of genetic and environmental elements leads to quasi-complete loss of insulin production in a relatively short period of time. HLA class II haplotypes have been identified as associated with or

protective of this disease (Noble, Valdes et al. 2010). Furthermore, the association between type 1 diabetes and autoimmune diseases has been well known for more than 50 years (MacCuish, Irvine et al. 1974) and the correlation between HLA class II and co-occurrence of autoimmune diseases has been extensively demonstrated since (Hagopian, Lee et al. 2017). There is an increased risk of diabetes in first grade relatives of patients affected by this disease, with well documented concordance amongst monozygotic twins (Kaprio, Tuomilehto et al. 1992). The degree of this concordance, however, ranges from 30 to 70% (Triolo, Fouts et al. 2019) and therefore genetic identicalness is not synonymous with DM onset. This, in conjunction with the observation of variation in geographic and socioeconomic distribution of the disease, supports the argument that environmental factors must play a role in genetically predisposed individuals.

The most accredited environmental factors for triggering the cascade of events leading to type one diabetes range from early childhood viral infections- in particular enteroviridae infections altering the gut microbiota- early introduction of gluten and cow milk in the diet, and exposure to toxins.

Whatever the triggering factors, it is well established that autoimmunity plays a role in the destruction of pancreatic b cells, with approximately 90% of patients having autoantibodies against b-cells proteins and insulin (McLaughlin, Richardson et al. 2016); hence DM type 1 is considered an autoimmune disease in its own rights.

Clinically, the loss of insulin producing b-cells proceeds undetected until the individual develops indirect signs of hyperglycaemia and acidosis, such as increased thirst, enuresis, weight loss, fatigue, and confusion. In a high proportion of cases clinical diagnosis occurs dramatically, with an acute episode of

ketoacidosis, requiring urgent medical intervention (Dabelea, Rewers et al. 2014) and is a life changing event, for the individuals and their families (Whittemore, Jaser et al. 2012).

1.3.2 Medical Management

The management and prognosis of type 1 diabetes changed abruptly with the introduction of exogenous insulin in clinical practice, approximately one hundred years ago. Children who previously had a 3-year average life expectancy at diagnosis and the prospect of rigorous dietary regimens (Brostoff, Keen et al. 2007), had the chance to reach adulthood. As this previously deadly disease became a chronic condition, clinicians acquired new knowledge on its evolution and long-term complications (Wolfensberger and Hamilton 2001, Cameron 2006), and insulin treatment strategies were refined.

Perhaps the most defining milestones in understanding the implications of adequate glycaemic control are the Diabetes Control and Complication Trial (Diabetes Control and Complications Trial Research Group; Nathan D.M. 1993) and subsequent Epidemiology of Diabetes interventions and Complications (Jacobson, Braffett et al. 1999)

These large multicentre prospective longitudinal randomised studies demonstrated the paramount importance of tight glycaemic control on the onset and progression of secondary complications. Individuals with good metabolic control had a significant reduction in the incidence of cardiovascular events and in the progression of microvascular atherosclerotic disease.

In the context of an illness that mostly affects young people and cannot be prevented, the discovery that there were potential ways of reducing its dreadful consequences inaugurated an era of enthusiasm among clinicians and researchers. New insulin formulations with a bioavailability that could mirror endogenous secretion were developed (Hirsch 2005), new combined regimens were established, and new ways of monitoring glucose circulating levels were invented.

Most patients are prescribed combinations of insulin that differ in onset and duration of effects, with doses adjusted according to intensified intermittent blood glucose sampling. This strategy would theoretically provide a baseline coverage and avoid post-prandial peaks as well as hypoglycaemic spells. Despite the large array of insulin regimens that can be tailored around each patient's needs, it is not uncommon for individuals to fail to reach the target glycosylated haemoglobin (HbA1c) levels or keep glucose levels under control only at the price of increased hypoglycaemic episodes. Current guidelines give a target HbA1c for type 1 diabetes of 48 mmol/mol (6.5%)(NICE 2020).

Continuous glucose monitoring strategies (CGM) have proved useful in improving glycaemic control (Maiorino, Signoriello et al. 2020) and monitoring long term glycaemic control (Danne, Nimri et al. 2017).

However, some individuals never reach the desired targets or incur increased hypoglycaemic episodes when attempting to do so. This group of patients meets the National Institute for Health and Care Excellence (NICE) criteria for insulin pumps: devices that automatically deliver insulin throughout the 24 hours.

The combination of insulin pump and continuous glucose monitoring in closed loop systems or "artificial pancreas" represents the most refined and physiological way

of delivering the drug, as these devices are capable of measuring glucose levels in real time and releasing the appropriate amount of insulin accordingly.

Although these ground-breaking innovations can significantly improve outcomes and survival rates (Lachin, Orchard et al. 2014), population-level results in terms of glucose control are still far from ideal. According to the latest National Paediatric Diabetes Audit Annual Report, only 7.2% of children and young adults in England and Wales reached the target in 2019/18 (Health 2019). Similarly, only 30.9% of all people with type 1 diabetes in England and Wales had HbA1c levels below 58 mol/mol (Digital 2020).

As elegantly demonstrated by the DCCT trial and subsequent work, the consequence of inadequate management of diabetes is the onset of acute and chronic complications and reduced life expectancy as compared to a healthy population (Livingstone, Levin et al. 2015). Hence the ultimate goal of any therapy is the restoration of circulating glucose levels as close to the physiological optimum as possible.

1.3.3 Acute Metabolic Complications

Acute complications of type 1 diabetes are related to uncontrolled blood glucose levels, and they represent the most frequent cause of death in type 1 diabetes patients younger than 40 years (Huo, Harding et al. 2016).

- Hypoglycaemia Unawareness.

Glucose is the body's energy currency and low circulating levels can lead to neuroglycopenic status and death. The human body perceives circulating levels

below 4mmol/L as threatening and responds by mobilising stored energetic sources and proceeds with gluconeogenesis. Hypoglycaemia triggers a contra-regulatory response mediated by glucagon, catecholamines, cortisol and growth hormone which guarantees temporary availability of glucose by decreasing utilisation and increasing production. This is just an emergency pathway and glucose levels would eventually continue to fall unless exogenous glucose is introduced. The same compensatory mechanisms triggered by hypoglycaemia are responsible for a series of clinical symptoms that, if recognised, can prompt sugar consumption or administration.

The cluster of symptoms - tachycardia, sweating, vasoconstriction, paleness, trembling, dizziness, and confusion - are paradigmatic of hypoglycaemia and are so common that patients refer to them as ‘hypos’, as an expression of their underlying familiarity with these phenomena. These alarming clinical changes are essential to self-preservation, and they ensure prompt correction of the hypoglycaemic state, unless the individual is unable to recognise them. Approximately 20-30% of patients with type 1 diabetes patients have lost the ability to generate warning prodromic symptoms of glucose depletion (Geddes, Schopman et al. 2008). Consequently, the onset of neuroglycopenic symptoms and loss of consciousness can be life threatening if they occur when the individual is alone or at night.

- Diabetic Ketoacidosis.

Insulin is the hormone that mediates glucose utilisation by tissues and organs. When it is insufficient - either for decreased release or increased consumption - despite high plasma glucose levels, the body is deprived of its main source of

energy. As a salvage pathway, adipose tissue releases lipidic content that gets metabolised into ketone bodies within the liver's cells. Once released into circulation, ketone bodies enter starving cells and become the substrate of an energy producing pathway within the cell's mitochondria. However, when the hepatic production of ketones is massive and beyond the ability of tissues to utilise them, these molecules accumulate in the blood stream and cause severe acidosis, which is life threatening if left untreated. For this reason, it is the first cause of death amongst children with diabetes (Wasag, Gregory et al. 2018).

Ketoacidosis (DKA) can occur when the individual is not aware of suffering from diabetes, and indeed approximately one third of paediatric diagnoses of type 1 diabetes often follow a ketoacidosis episode (Dabelea, Rewers et al. 2014).

However, DKA can still develop in patients who are already being treated with insulin, for example when infections or strenuous exercise create an abrupt discrepancy between circulating insulin and glucose requirements, or as a result of inadequate dosing or failure of the insulin pump.

1.3.4 Long Term Complications

Inadequate glycaemic control and compensatory metabolic adaptations sustained over time progressively lead to structural changes in the arterial wall of main arteries as well as the microvascular bed. As a result, patients are at substantially increased risk of developing chronic macrovascular (ischaemic heart disease, stroke, peripheral arterial disease) and microvascular (nephropathy, retinopathy,

neuropathy) complications, which have a significant impact on subsequent survival and QOL.

- Cardiovascular Complications.

Ischaemic heart disease and stroke are the leading causes of death in this population. As expected, the immediate risk of cardiovascular complications is relatively low in the initial years following diagnosis at a typical age of 12 years. A key turning point in the incidence of cardiovascular complications is the development of renal failure (Smith, Trauer et al. 2010): by the age of 40 over 40% of patients with renal failure have developed significant coronary disease, against 7% of individuals without nephropathy (Tuomilehto, Borch-Johnsen et al. 1998). Figures from this seminal study might be somewhat dated because of the subsequent widespread adoption of ACE-inhibitors and intensive diabetes treatment strategies, which have proven effective in reducing cardiovascular risk. Nevertheless, it highlighted the direct relationship between longstanding diabetes and high prevalence of cardiovascular morbidity. Subsequent work has confirmed how, even in patients with no associated cardiovascular risk factors other than type 1 diabetes, the excess risk for cardiovascular events and death as compared to the matched general population was above 82% and 30% respectively (Rawshani, Rawshani et al. 2017). Type 1 diabetes is also a well-recognised risk factor for acute cerebrovascular accidents, and a large prospective cohort study conducted in a high-prevalence geographic area has confirmed a direct correlation between the risk of stroke and glycated haemoglobin levels, a surrogate marker of glycaemic control (Ståhl, Lind et al. 2017).

Peripheral arterial disease is another common complication of diabetes. It can cause significant disability, augmented by the effects of diabetic neuropathy. According to a secondary analysis of data from Public Health England, the yearly rate of diabetes related amputations in England between 2011 and 2015 was approximately 7000 cases. One population study conducted on over 30,000 patients affected by type 1 diabetes over a 30-year time span found that individuals older than 65 years had a cumulative probability of nontraumatic lower limb amputation of 11.0% for women and 20.7% for men, significantly higher than the matched healthy controls (Jonasson, Ye et al. 2008).

- Nephropathy.

Diabetic nephropathy affects approximately 30-40% of patients with Type 1 diabetes whereas the overall risk of developing renal failure secondary to diabetes has decreased significantly throughout the decades, because of improved medical management (Hovind, Tarnow et al. 2003). The onset of diabetic nephropathy, however, still represents a turning point in the progress of the disease. Renal impairment correlates positively with progression of cardiovascular disease and negatively with survival (Groop, Thomas et al. 2009). Although renal failure may be viewed simply as the clinical expression of an advanced systemic disease, once it becomes manifest with macroalbuminuria and decreased glomerular filtration rate, the risk of other complications rapidly increases. It has been hypothesised that renal failure itself might contribute to a worsening of dysmetabolic and vascular risk factors such as dyslipidaemia, anaemia, arterial calcification, endothelial dysfunction, and hypertension, all of which contribute to increase the progression rate of the disease (Groop, Thomas et al. 2009).

- Retinopathy.

Although diabetes is no longer the leading cause of blindness amongst individual of working age in the UK (Liew, Michaelides et al. 2014), its incidence worldwide continues to increase. It is estimated that approximately 2.6 million people have developed vision impairment secondary to diabetic retinopathy, with approximately 0.6 million of these registered blind (Flaxman, Bourne et al. 2017).

- Neuropathy.

Diabetic neuropathy results from progressive damage of vasa nervorum. It can be very debilitating and difficult to manage. It predominantly affects the autonomic nervous system and can cause a wide range of clinical repercussions such as postural hypotension, dizziness, hypoglycaemia unawareness, decreased resistance to fatigue, delayed gastric emptying, gastrointestinal dysmotility and genitourinary symptoms. A large prospective population study conducted in the UK has confirmed that up to 66% of type 1 diabetic patients suffer from some form of neuropathy (Dyck, Kratz et al. 1993). Peripheral neuropathy is a frequent complication aggravating approximately 13% of patients with type 1 diabetes (Jeyam, McGurnaghan et al. 2020) and can lead to loss of sensation as well as pain often refractory to common medications (Schreiber, Nones et al. 2015).

1.4 TYPE 1 DIABETES AND TRANSPLANT OPTIONS

Transplant strategies have been essentially developed for two very different cohorts of patients with type 1 diabetes: individuals with ESRF and those who suffer from hypoglycaemia unawareness. In both cases, transplantation is sought to resolve practical matters, such as renal failure, dependence from exogenous insulin and hypoglycaemia crisis. (Details on the treatment algorithm can be found in Appendix, A1.3.). As demonstrated by the DCCT trial, improved glycaemic control is associated with a significantly reduced risk of diabetic retinopathy (76%), nephropathy (50%), neuropathy (60%), cardiovascular disease (30%) and cardiovascular events (32%) (Diabetes Control and Complications Trial Research Group; Nathan D.M. 1993, Jacobson, Braffett et al. 1999). It is reasonable to assume, therefore, that the consistent euglycemic status provided by PT may improve the progression of long-term complications of the disease, (White, Shaw et al. 2009, Jenssen, Hartmann et al. 2017)

1.4.1 Transplantation, Type 1 diabetes, and Renal Failure.

Patients affected by type 1 diabetes with an estimated glomerular filtration rate below 20ml/min or on renal replacement therapy (RRT) are potentially eligible for transplantation of both pancreas and kidney or pancreatic tissue and kidney. Despite recent improvements, the prognosis of diabetic patients on RRT remains poor (Groop, Thomas et al. 2009): in this population transplantation of the kidney is recommendable whenever feasible. Whether the patient will also receive a

simultaneous PT or not depends on a combination of variables, the most relevant being the individual's surgical risk and personal preferences.

- Simultaneous Pancreas Kidney Transplant (SPK).

The history of Pancreas Transplantation began at the University of Minnesota in 1966, with combined segmental pancreas kidney transplant performed by William Kelly and Richard Lillehei on a young diabetic patient with ESRF (Kelly, Lillehei et al. 1967). In the subsequent nearly six decades, over 56000 PT have been performed worldwide (Stratta, Gruessner et al. 2020), with SPK representing over two thirds of the total PT activity (Gruessner and Gruessner 2016). Although established in the mid-20th century, this operation is still the only therapeutic option capable of simultaneously restoring long term euglycemia and renal function and is considered the standard of care in a selected cohort of patients with type 1 diabetes and kidney failure.

The great majority of organs implanted as SPK are from deceased donors. Other combinations, such as simultaneous living donor kidney and deceased donor pancreas transplant or kidney transplant and segmental PT from the same living donor are quite uncommon, although good results have been reported. (Farney, Cho et al. 2000).

Long term results of SPK have demonstrated survival benefit as well as a positive impact on the progression of chronic complications of diabetes (White, Shaw et al. 2009). Pancreas graft survival in the US is >85% at yr., at 73% at yrs. and >56% at 10 years respectively (Gruessner and Gruessner 2016.).

However, this operation is still associated with high perioperative morbidity and mortality. In addition to the surgical risk and often because of surgical complications, post-operative cardiovascular events are frequent, with a peak in cardiovascular deaths within the first three months from surgery (Yiannoullou, Summers et al. 2019): hence individuals with a high pre-operative cardiovascular risk might not be eligible for the double procedure, but may still be eligible for less invasive forms of transplantation as reported below.

- Kidney Transplant Alone (KTA).

KTA was initially reserved for patients who were not fit for an SPK. However, after living donor kidney transplantation has become the gold standard for treatment of ESRF, an increasing number of patients have been offered this option, regardless of their surgical risk factors.

Deceased donor KTA (ddKTA) has worse long-term outcomes compared to SPK. It has been postulated that the survival benefit of SPK over ddKTA could be explained by the relatively younger age of SPK donors and worse general baseline conditions of ddKTA, rather than the addition of a functioning pancreas. Living donor kidney transplantation alone compares favourably with SPK and there is evidence supporting either approach in the medium term (Venkatanarasimhamoorthy and Barlow 2018), although successful SPK might still be the best option in the long term (Morath, Zeier et al. 2008, Weiss, Smits et al. 2009).

- Pancreas after Kidney or SPK Transplant (PAK/PaSPK).

Patients who are not eligible for an SPK might become so after receiving the beneficial effects of kidney transplantation alone. In addition, the surgical burden of the combined operation is considered heavier than a two-step approach. Equally, patients with an available living donor KTA option might prioritise this and proceed with a deceased donor PT at a later stage. Finally, SPK recipients who have lost pancreas function might be eligible for a second pancreas transplant.

- Islets after Kidney Transplant (IAK)/Simultaneous Islet-Kidney Transplant (SIK)

Patients in need of a kidney transplant who experience severe hypoglycaemia unawareness but are not fit for or do not want an SPK, might benefit from Islet of Langerhans and kidney transplantation. Timing of the islet infusion depends on the availability of an adequate number and quality of islets at time of donation, bearing in mind that one procedure might not be sufficient to reach therapeutic goals.

1.4.2 Transplantation, Type 1 diabetes, and Hypoglycaemia Unawareness.

Hypoglycaemia Unawareness can often be managed conservatively, without the added risk of invasive procedures. Transplantation for these individuals is still considered as ultima ratio. The initial approach is therefore medical, with a pathway that starts with intensive diabetes education. Insulin pump and close loop systems are resources that must be attempted whenever education alone is insufficient to guarantee the patient's safety. However, despite the great contribution of new technologies to this problematic issue, there is still a proportion of patients who are refractory to medical management. In this case, any risk associated with invasive

procedures or immunosuppression is likely to outweigh the risk of life-threatening hypoglycaemia spells.

These individuals are advised to opt for either Pancreas or Islet Transplantation Alone, after thorough assessment of their renal function. In fact, allotransplantation has an embedded risk of renal failure caused by immunosuppression and so patients should ideally have an estimated glomerular filtration rate (egfr) >80ml/min/1.73m^2 to proceed with either option.

- Pancreas Transplant Alone (PTA)

PTA is the second most frequent form of solid organ pancreas transplantation. The historical debate around this procedure has concerned the significant surgical risks with little evidence of long-term survival benefit or protective effect against chronic complications of diabetes. However, it is the only established therapy capable of restoring sustained long term insulin independence, with relatively high graft survival rates at 5 years.

Outcomes have been improving through time and evidence now indicates that, after an initial perioperative disadvantage as compared to matched individuals on the waiting list, long term survival rates are similar in the two cohorts (Choi, Jung et al. 2017, Gruessner, Laftavi et al. 2017).

- Islet Transplant Alone (ITA).

Beta-cell replacement in the form of IT is progressively becoming the option of choice for many diabetologists. In fact, albeit long term insulin independence is yet to be achieved, this procedure is effective in treating problematic hypoglycaemia at minimum risk, in a population where high surgical risk is hardly justifiable. For this reason, resolution of hypoglycaemia unawareness rather than insulin independence

is the primary outcome of this procedure. However, multiple infusions from different donors might be necessary to reach the desired targets. Hence patients will be exposed to repeat rounds of induction immunosuppression and might incur in an increased risk of sensitisation. The latter risk might then be detrimental to those who will develop renal failure or persistent hypoglycaemia unawareness and will thereby need further solid organ transplantation.

1.4.3 Clinical Outcomes of Pancreatic Transplantation

Clinical outcomes of PT have been extensively investigated throughout the decades and have been progressively improving. Registry data from the US show excellent medium-term results for SPK, PAK and PTA, with 5-year patient and graft survival rates of 93-91-78% and 73-65-53% respectively. Rejection and death with a functioning pancreas represented the most frequent causes of graft loss (Gruessner and Gruessner 2016.). Whilst data regarding survival is readily available for all these transplants categories, results on long term complications of diabetes are more controversial and are mainly applicable to SPK. Most of the long-term histopathological changes aggravated by sustained hyperglycaemia are already well established at the time of transplantation. However, authors have reported encouraging results for all the secondary complications of diabetes.

- Impact on cardiovascular profile

  Cardiovascular complications are the main cause of death in type 1 diabetic recipients after 40 years of age. At 10 years from transplantation SPK recipients have a survival rate of 68% vs 50% amongst patients who remained on the SPK waiting list. It is intuitive to hypothesise a causal relationship between euglycemia-

improved cardiovascular profile and reduced mortality. Normal endothelial function, reduction of atherosclerotic risk factors and reversal of left ventricular dysfunction have been demonstrated (Fiorina, La Rocca et al. 2001). In addition, long term reduction in progression of macrovascular disease has been reported, as compared to KTA recipients (Biesenbach, Königsrainer et al. 2005).

- Impact on Diabetic Retinopathy

Improvement of diabetic retinopathy after transplantation is somewhat controversial. The literature is scarce, and results are contradictory. Some authors have reported an increased risk of early haemorrhage in patients with established retinopathy at transplantation (Chow, Pai et al. 1999). Others have documented downgrading or stabilisation of non-proliferative retinal disease as little as 2 years after PTA, with significant reduction of lesions in proliferative retinopathy, albeit a smaller proportion of patients showed progression of the disease (Giannarelli, Coppelli et al. 2006).

- Impact on Diabetic Neuropathy

The DCCT trial follow up studies demonstrated how intensive insulin management was associated with a statistically significant reduction of cardiac autonomic neuropathy and peripheric neuropathy at 10 years from the intervention (Martin, Albers et al. 2014). Equally, neurological improvement after PT requires many years of sustained euglycemia. Quantifiable improvements in cardiac autonomic function as well as peripheric neuropathy have been recorded, although it is difficult to document meaningful improvements in patients' symptoms. However, some research has shown improved perception of gastrointestinal symptoms after

transplantation (Martins, Outerelo et al. 2015) and correlation between improved autonomic function and QOL gain (Hathaway, Wicks et al. 2000).

- Impact on Diabetic Nephropathy

Approximately 12% of PTA recipients on Tacrolimus will develop native kidney failure at 5 years from transplantation (Gruessner, Sutherland et al. 2008). This is likely a combination of pre-existing diabetic nephropathy and well documented Calcineurin inhibitor's toxicity (Nankivell, Borrows et al. 2004). However, post transplantation clinical and histopathological regression of nephrological damage has been demonstrated. Successful PTA can slow or reverse micro and macro albuminuria (Coppelli, Giannarelli et al. 2005) after just one year from surgery. In a pivotal study conducted on a small group of pancreas transplant recipients, 10 years of euglycemia determined biopsy proven histopathological improvement of glomerulopathy and mesangiopathy. (Fioretto, Steffes et al. 1998).

1.5 QUALITY OF LIFE RESEARCH

1.5.1 Brief History of Quality-of-Life Studies

The history of quality-of-life studies can be traced back to the pioneering work on US rural communities in the aftermath of Second World War. Population researchers developed the first indexes of social well-being or "level-of-living-indexes" and applied statistics to sociology to compare living conditions among different geographic areas, through time (Land, Michalos et al. 2011). Social sciences applied to agricultural economics became increasingly important throughout the "Great Depression" and were instrumental in the development of

agricultural reforms within the “New Deal Era” (Baldwin 1968, Gillespie and McMillen 2015).

However, the real coming to age for QOL studies came with the establishment of welfare states and the widespread social awakening of the 1960-70s (Wood-Dauphinee 1999).

In modern times, WHO defines QOL as “individual’s perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept, incorporating in a complex way a person’s physical health, psychological state, level of independence, social relationships, personal beliefs, and relationship to salient features of the environment”.

This multifaceted description is purposely inclusive, and it reflects the complexity of the concept “Quality of Life”. For this reason, it is now common practice to utilise the term of “Health Related Quality of Life” when specifically addressing health aspects of QOL (Kaplan and Bush 1982).

1.5.2 Health Related Quality of Life (HRQOL)

Medical innovations of the past century and improved general sanitary conditions have changed the natural history of many diseases: life threatening conditions have become chronic illnesses. Hence, we have witnessed a partial shift in evaluating the validity of treatments from “quantity of life” to “quality of life”.

HRQOL studies, by providing information on an individual’s and/or population’s preferences, also provide the tools to evaluate clinical interventions. For this

purpose, outcome researchers have developed preference-based measures to quantify “the health of an individual or population at a particular point in time against identifiable standards” (WHO: Quality of Life Assessment Group 1996).

1.5.3 Patient Reported Outcome Measures (PROMs)

Based on the paradigm that data collected is only as good as the questions asked, when the importance of HRQOL studies became increasingly manifest, researchers recognised the need to develop instruments that could yield reliable results and criteria to appraise these instruments (**Appendix A 1.4**).

Patient Reported Outcome Measures (PROMs) is a general term that includes any measurement of a “patient’s health condition that comes directly from the patient without the interpretation of the patient’s responses by a physician or anyone else” (Food and Drug-Adminstration. 2009). When PROMs meet adequate psychometric standards, they can be validated to be adopted in clinical and research settings.

However, as the interest in QOL started before the development of this framework, much of the existing early literature on HRQOL is based on non-validated, “ad hoc” instruments.

Currently, PROMs used in health care fall into two main categories: generic instruments and disease specific ones. The choice of PROMs is determined by the type of information required and the populations under investigation. Most HRQOL literature is based on the utilisation of combinations of both.

- Generic PROMs

Generic PROMs are designed to capture HRQOL and compare results across groups. Some of these instruments are suitable both for diseased and healthy individuals (Ware and Sherbourne 1992). Both health status measures and utility indexes belong to this subgroup.

Generic PROMs assess an individual's subjective perception of health status (Karimi and Brazier 2016) and they can be used by clinicians as a complement to objective data collection. These instruments allow to score patient's responses and quantify the repercussions of illness on one or more of the core dimensions of quality of life: physical, psychological, and social wellbeing. Generic PROMs may greatly vary based on the domains investigated, however they all aim to provide a measure of the constraints associated with health conditions. They can, therefore, be useful in identifying areas of care that require implementing. Moreover, they can be used longitudinally to evaluate the effects of treatment on such constraints or the repercussions of therapeutic interventions on HRQOL. In other words, they can be used to measure both the consequences of illnesses and the impact of treatment on HRQOL.

Preference-based measures go further in also aiming to assign a valuation or weight to each health state: as the basis for this valuation is an attempt to derive preferences for different health states by estimating the value or utility which an individual may derive from being in a particular health state, these measures are often referred to as preference-based or utility indexes. By combining duration of different QOL levels with survival time, it is possible to derive Quality Adjusted Life Years or QALYs, which is a measure that appeals to health economists interested in evaluating and comparing interventions, as they permit comparison across

interventions and conditions whether they primarily affect QOL, survival, or some combination of both. Many countries have adopted QALYs for decision making in resource allocation. In the UK the National Institute for Health and Clinical Excellence (NICE) has adopted the QALY framework to develop national guidelines and evaluate interventions to assess their value for money to the National Health Service.

- Disease Specific PROMs

As HRQOL studies became more regimented and widely applied, clinical researchers identified the intrinsic limitation of generic measures: the inability to capture significant health related variables specific to a particular disease. While generic instruments provide insight across different populations, disease specific ones allow for a deeper analysis within a discrete group of people who share the condition of interest. They often have a multidimensional construct aimed at investigating a wide array of disease-specific domains, ranging from symptoms and their burden to satisfaction with treatment and psychosocial well-being. As these instruments are able to quantify very specific aspects related to diseases, they can be very sensitive to change and detect even small variations in quality of life (Wood-Dauphinee 1999).

In conclusion, generic and disease specific PROMs provide complementary information on patient's perception of health and HRQOL. For this reason, the use of a combination of both type of instruments has been recommended (Gibbons and Fitzpatrick 2010).

1.6 CONCLUSIONS

Acute and chronic complications of type 1 diabetes are an often an inevitable consequence of erratic blood glucose levels sustained over time. This has been confirmed by the DCCT trial, which demonstrated how euglycemia reduces the progression of macrovascular and microvascular disease. However, it also demonstrated the difficulty of maintaining optimal glucose levels without an increase in hypoglycaemia crises.

Pancreas transplantation is the only therapy capable of restoring long-term insulin independence, however the risks associated with surgery are still high.

Clinical outcomes of pancreas transplantation have significantly improved throughout the decades, but so has the medical management of the disease and less invasive options are often considered a valid compromise between risks and benefits.

Although the history of QOL in pancreas transplantation is possibly as old as the procedure itself, assumptions about its positive impact are often based on clinicians' perceptions and derived from occasional patient's feedback, rather than from well-designed prospective studies.

This degree of uncertainty might be due to a great proportion of studies being conducted in an era when QOL research methodology was still rudimentary.

The following chapter will therefore provide a systematic review of the literature on QOL after solid organ pancreas transplantation.

2 CHAPTER 2: SYSTEMATIC REVIEW OF THE LITERATURE ON QUALITY OF LIFE AFTER PANCREAS TRANSPLANTATION

2.1 RATIONALE

The first medical specialty to acknowledge the importance of health-related quality of life (HRQOL) studies was oncology. Clinicians, in administering burdensome therapies with uncertain clinical gain, realised that the optimum treatment for advanced cancer couldn't prescind from patient's experiences and wishes. Patient reported outcome measures (PROMs) became instrumental in bridging the gap between quantification of survival and quality of survival. The U.S. Food and Drug Administration has included HRQOL gain amongst the endpoints of cancer pharmaceutical research ever since 1996 (Beitz, Gnecco et al. 1996).

Although QOL studies in transplantation are not as embedded in the matrix of the discipline as in the oncological field, clinician interest has been there from the start, as documented by a structured review of the literature conducted in 1997: Dew and colleagues identified a total of 218 independent studies from 1965 to 1996 addressing HRQOL/QOL outcomes across transplant specialities (Dew, Switzer et al. 1997).

The two most relevant literature reviews specific to HRQOL/QOL after Pancreas Transplantation (PT) were published in 1998 and 2003 respectively (Gross, Limwattananon et al. 1998, Joseph, Baines et al. 2003). After a meticulous analysis of published manuscripts, Gross and colleagues found that, despite favourable evidence of HRQOL/QOL improvements after PT, outcomes seemed similar to those of patients with type 1 diabetes undergoing Kidney Transplant Alone (KTA).

The authors concluded that further studies based on more stringent methodological criteria were needed.

Joseph and colleagues presented data on kidney and pancreas/pancreas-kidney transplantation and argued that prospective HRQOL and mental health should be routinely investigated with validated instruments. Again, the issue of methodological limitations was highlighted, and the authors proposed a “consensus conference on QOL issues after organ transplantation”(Joseph, Baines et al. 2003).

Another review, mainly focused on HRQOL/QOL after Islet Transplantation (IT) was conducted a decade later, and only three out of twelve articles involved solid organ PT. The authors hypothesised that results were severely impacted by use of inadequate instruments and non-inclusion of domains potentially relevant to this population. Equally, they did not identify any qualitative research that could clarify such domains (Speight, Reaney et al. 2010).

More recently, Hanlon and colleagues looked at previous reviews and appraised four studies on HRQOL/QOL after PT. They concluded that, because of the evolution of surgical techniques and medical management, new prospective research was needed. (Hanlon, Cooper et al. 2019)

The discrepancy between the number of studies included by Gross in 1998 (37) and those reported by Hanlon approximately 30 years later (4) highlighted the need of a further systematic review of the literature aimed at investigating, organising, and interpreting the existing evidence on the topic.

2.2 METHODS

2.2.1 Framing the question and Search Strategy

This review was conducted following a pre-established protocol, registered on PROSPERO (International Prospective register of systematic review, National Institute for Health Research, Registration Number: CRD42017073968) and reported according to the most recent PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (Page, McKenzie et al. 2021) to ensure transparency and replicability of the results. Search terms were developed and expanded in MEDLINE® (Ovid) to identify Medical Subject Headings (MeSH) terms (Appendix A2.1). The search strategy initially developed was then adapted for EMBASE (Ovid), Transplant Library (Ovid) and Cochrane Library (Appendix AA2.2.). Previous Systematic Reviews' article reference lists were assessed as a potential source of additional studies. Eligible studies were: Primary Studies, Cohort Studies, Randomized Control Studies, Case Series and Systematic Reviews, published and e-pub ahead of print, up to 12 October 2020. Conference Abstracts were also considered. All languages were accepted. The domain being studied was type 1 diabetes with or without renal failure.

The population included consisted of adult patients (>18 years of age) with type 1 diabetes with or without renal failure requiring treatment.

The interventions were: all forms of solid organ Pancreas Transplantation and/or Kidney Transplantation, and Islet Transplantation.

The comparators were "no transplant" or "different transplant types."

The primary outcome of the search was to investigate QOL post transplantation in patients with type 1 diabetes.

Secondary objectives were understanding which forms of PT provided a higher QOL gain, if any, and identifying which validated PROMs have been considered most suitable to assess HRQOL in this population.

2.2.2 Study Selection

References identified were imported into Endnote® reference manager. After automated and manual duplicate removal, titles and abstracts were checked against the protocol's inclusion criteria by two separate investigators. All the references that met the inclusion criteria and articles whose abstract didn't allow for a clear choice underwent full article review. Differences amongst authors were solved by discussion. For studies with multiple publications, only the principal manuscript was selected unless further work included new and/or more updated results. In this case even conference abstracts were included.

2.2.3 Data Extraction and synthesis

Data was extracted by a single researcher and reviewed by a second investigator, with no major disagreements. Data extracted was inclusive of -but not limited to- pre-established parameters such as: study general Information, country, language, type of transplant, number of cases, demographics, PROMs used, follow-up timing, outcomes, risk of bias. (Appendix A2.5). Data was recorded on Microsoft Excel and

subsequently analysed with Microsoft SPSS. Results were interpreted and reported with a narrative approach.

2.2.4 Risk of Bias and Quality of Evidence

Quality of the included studies was assessed to evaluate the strength of the evidence accrued and not as a tool for study exclusion. In manuscripts reporting both clinical and HRQOL/QOL outcomes, the risk of bias and quality assessment refers exclusively to the QOL aspects of the study.

No instrument was identified to specifically address the risk of bias in observational studies on HRQOL. Hence risk of bias was assessed with the simplified Downs and Black checklist, chosen for its suitability for both randomized and non-randomized trials (Downs and Black 1998).

The Downs and Black checklist (Appendix A2.3) is an instrument developed to assess risk of bias in quantitative studies in health care setting. It covers 5 areas of potential bias, for a total of 27 questions:

1. Study Quality
2. External Validity
3. Study Bias
4. Confounding and selection bias
5. Power of the study

The scoring system allows for individual summary scores of each sub-section and a final grading of total risk of bias (ranging 0 to 25 for non-randomised studies). The quality of studies can then be ranked according to the total risk of bias as excellent

(26-28 points for randomised studies only), good (20-25 points), fair (15-19 points) and poor (< 14 points)(Hooper, Jutai et al. 2008).

While the methodology to assess the quality of psychometric properties of PROMs is well established (Mokkink, Terwee et al. 2010), evaluating the quality of quality-of-life studies is still a topic of debate. Gill and Feinstein developed a set of 10 investigator- and instrument-related criteria (**Table 1**) aimed at addressing the question of "face validity" of these manuscripts (Gill T.M. and Feinstein AR, 1994). To our knowledge, there is no other recent guideline addressing this issue. As described by Gill and Feinstein, articles were scored with one point for each criterion met. The sum of the points obtained was then divided by the number of criteria applicable to the specific article, and the result multiplied by 100. Applying this strategy to each article provided a Summary Score for compliance with the criteria.

Table 1 Gill and Feinstein's Criteria (Gill and Feinstein 1994)

	GILL AND FEINSTEIN CRITERIA		
	Investigator Specific		
1	*Meaning of quality of life*	yes 1	no 0
2	*Constituents of quality of life*	yes 1	no 0
3	*Selection of instruments*	yes 1	no 0
4	*Aggregate Score*	yes 1	no 0
	Instrument Specific		
5	*Patient rating*	yes 1	no 0
6	*Distinguish quality of life*	yes 1	no 0
7	*Supplemental responses*	yes 1	no 0
8	*Supplemental responses incorporated*	yes 1	no 0
9	*Rating of importance*	yes 1	no 0
10	*Rating of importance incorporated*	yes 1	no 0

2.3 RESULTS

The search yielded a total of 2399 references. Another manuscript was identified from the bibliography of a review. After duplicate removal the title/abstract of 1534 records were screened and 932 eliminated. The full abstract/text of 602 publications were then assessed against the inclusion criteria and 131 relevant references were selected (Appendix, A2.3). References on Islet Transplantation (31) were not analysed in the context of this DPhil.

After the above-described steps the final number of manuscripts included was 100.

2.3.1 Characteristics of included studies

The references included consisted of 83 manuscripts and 17 conference abstracts. In two circumstances the same article described two separate researches (Zehrer, Cr et al. 1991, Sureshkumar, Patel et al. 2006). Hence, the actual number of studies included is 102 out of 100 by 55 different transplant centres.

The articles were published during approximately 3 decades from 1989 to 2020. Three quarters of the references were published in the first and last decades (38 and 37 references, respectively), whilst there was a slight inflection from 2000 to 2009 (25 references).

The great majority of studies (85%) was based on PROMs. Occasionally authors included a few open-ended questions to complement quantitative outcomes. In 3% of cases “quality of life” reports were based on objective measures, such as employment status (Friedrich, Niebel et al. 1999, Knight and Daly 2004, Gruesser,

Gruessner et al. 2017). Four out of 102 (4%) were qualitative studies or semi-structured interviews (Langenbach, Stippel et al. 2004, Isla Pera, Moncho Vasallo et al. 2012, Jackson, Gleeson et al. 2013, Martell, Rice et al. 2015). Finally, 8/102 manuscripts (8%) were literature reviews (Dew, Switzer et al. 1997, Gross, Limwattananon et al. 1998, Joseph, Baines et al. 2003, Muehrer 2009, Speight, Reaney et al. 2010, Hanlon, Cooper et al. 2019, Mosca, Dumbill et al. 2019, Shahabeddin Parizi, Krabbe et al. 2019)

A relatively small proportion of research (24%) was conducted prospectively. In most cases PROMs were collected after transplantation. A synopsis of the studies' principal characteristics is provided in Appendix A2.5.

Population and comparator.

The median population size was 32 patients (range 3-4476). In 51 manuscripts there was no comparator group. In 1 case it was not specified. In 6 studies PT recipients were part of a broader group of transplant recipients and differences across categories were inadequately documented.

The remaining 36 cross-sectional studies compared PT to:

- Kidney Transplant Alone (KTA): 13
- KTA and other control groups: 8
- patients on the Waiting List (WL) and/or patients with type 1 diabetes not seeking transplantation: 11.
- Renal Transplant for all causes (KTx): 4

A breakdown of comparator's distribution is shown in Appendix A2.6.

2.3.2 PROMs

The total number of studies based on PROMs was 87/102. More than 70 different PROMs were identified (Appendix A2.7).

In 12/87 cases (14%) authors used “ad hoc” questionnaires covering a variety of domains established a priori. In 72/87 (83%) studies PROMs were validated instruments (of these, 4 were modified versions of validated instruments). In three cases the instrument was unavailable (Appendix 2.8)

Generic validated tools were used in 63/87 (72%) studies, alone or in combination with other instruments.

In more than one half of the cases the generic instrument was a Short-Form, usually SF-36 (Ware and Sherbourne 1992).

The other most frequently utilised PROMs were the Spitzer Quality of Life Index (QLI) - Satisfaction with Health and Life (Spitzer, Dobson et al. 1981) and the Karnofsky Index of performance status (Karnofsky and Burchenal 1949).

A single validated instrument was used in 39/87 (45%) studies, whilst in 33/87 (38%) cases multiple tools were utilized.

Disease specific QOL (diabetes and renal failure) was investigated in 20 (23%) and 8 (9%) studies respectively, with either validated instruments or questions developed by the investigators. In 15/87 (17%) manuscripts QOL was studied in relation to specific aspects (e.g., gastrointestinal QOL), mostly with validated instruments.

Finally, in 10/87 (11.5%) studies investigators explicitly mentioned transplant related items, in two cases (2.3%) elicited with validated questionnaires.

The use of preference-based measures was extremely rare. Only three manuscripts reported data elicited with EQ-5D instruments. However, only 30 of the PROM-based studies included in the research were published in Europe after the development of EQ-5D in 1990 (Devlin and Brooks 2017), making this finding perhaps less surprising. No PROMS specifically designed for PT were identified, consistent with data reported by Shahabeddin Parizi and colleagues in a scoping review of the literature on PROMs used in transplantation (Shahabeddin Parizi, Krabbe et al. 2019).

2.3.3 Risk of Bias-Quality of Evidence

Conference abstracts, reviews and qualitative studies were excluded from the risk of bias and Quality of Evidence assessment.

- Downs and Black Checklist

The median Downs and Black score was 12. Approximately 23% of manuscripts scored between 18 and 19, the rest below 14. Risk of bias was high in over two thirds of the cases. “Statistical power”-the likelihood of measuring a true effect when rejecting a null hypothesis- had the highest risk of bias, possibly because of relatively small transplant numbers in many centres. In other words, the lack of randomisation, the use of non-validated PROMs and sample attrition seemed to be at the core of a high “selection bias” risk. Conversely, “reporting” bias was the

lowest, possibly because of similarities in presenting clinical and quantitative research. (Appendix A2.9)

- Gill and Feinstein Outcomes

The summary score for compliance with the criteria was overall medium/low, with nearly two-thirds of the of studies scoring below 50 (Appendix A2.10). More precisely, 1.6% did not meet any criteria, 15.6% scored 12.5 (1 out of 8 criteria met), 37.5% scored 25 (2 out of 8 criteria met), 1.6% scored 33 (3/9 criteria met) 17.2% scored 37.5 (3 out of 8 criteria met), 12.5% scored 50 (4 out of 8 criteria met), 7.8% scored 56 (5 out of 9 criteria met), 1.6% scored 62.5 (5 out of 8 criteria met) and 4.7% scored 67 (6 out of 9 criteria met) (Appendix 2.11).

The mean overall summary score was approximately 33 and the median 25 (range 0-67). The most frequently met criterion was “specification of the domains of QoL investigated,” reported by approximately 90% of the authors. However, less than 30% of the investigators provided a clear definition of QOL and only 12% overtly distinguished QOL from HRQOL.

In about one half of the studies QOL was reported as an aggregate score. PROMs selection was explained in approximately 42% of studies. The lowest scores were instrument specific and the great majority of investigators didn’t offer the option to provide supplemental responses or weight the importance of the individual problems. Investigator Related Criteria were met fourfold more frequently than Instrument Related Criteria (Appendix, A2.12). Again, the issue of inadequate PROMs seemed to recur.

2.3.4 Summary of Evidence

The most striking finding of this review is the heterogeneity of methodology and results. Studies differed in populations (PT, SPK, pre-emptive SPK, PTA, PT enteric drained, PT bladder drained, all transplants) and control groups (KTA, K Tx for all causes, WL, WL patients not on dialysis, WL patients on dialysis, patients with type 1 diabetes not seeking transplantation, patients with type 1 diabetes with no renal failure, patients with type 1 diabetes with advanced disease, patients on HD without type 1 diabetes, healthy controls, patients with other chronic diseases, population norms). Some authors exclusively looked at results of successful PT, while others stratified HRQOL outcomes on pancreas and kidney functional status.

Over 70 different validated tools were used either alone or as a combination of multiple instruments, adding a further layer of inter-study variability. A few authors used non validated instruments designed for the purpose of a specific project.

Data collection time-points were controlled in approximately 26% of the studies: in the rest of the sample, they were either random, unadjusted for cohort differences or unspecified.

Statistical tests were clearly described in 59% of the eligible studies and in approximately 50% of the cases they were deemed appropriate to the data.

Interestingly, in approximately 45% of all references, quality of life was assessed by the transplant team, without the guidance of experts on quantitative research or psychometric data interpretation.

Differences in study rationale, design, population, comparator, PROMs utilized, follow-up modality/duration, and occasionally the lack of detailed reporting did not

allow for a meaningful metanalysis of the information accrued. Hence studies were synthesised narratively. References were grouped and reviewed by type (quantitative, qualitative) and, within the quantitative group, by population and comparator (SPK vs KTA, PT vs WL/type 1 diabetes, PTA). A small contingent of articles on specific aspects of HRQOL/QOL was analysed separately. Finally, some manuscripts were difficult to place in a pre-determined category: after discussion amongst reviewers, they were included within the group deemed conceptually more suitable. In the attempt to organise findings and, possibly, extrapolate some comparative data, the manuscripts included were grouped as follows:

Quantitative Studies

- Manuscripts using objective parameters as indicators of HRQOL/QOL
- Manuscripts comparing HRQOL outcomes in SPK and KTA
- Manuscripts reporting HRQOL outcome in PT exclusively or against not transplanted patients with type 1 diabetes.
    - Cross-sectional Studies
    - Prospective Longitudinal Studies
- Manuscripts investigating HRQOL in PTA
- Manuscripts investigating specific aspects of HRQOL
    - Sleep
    - Gastrointestinal and Autonomic Function
    - Sexual Function
    -

Qualitative Studies

Wherever possible, PROMs utilised in each study were specified in brackets in the context of the review. A comprehensive list can be found in Appendix A2.7

Quantitative Studies

- Manuscripts using objective parameters as indicators of HRQOL/QOL

The earliest studies on QOL after PT are often briefly mentioned in manuscripts describing much more detailed clinical outcomes. These historical reports often lack information regarding methodology and results are summarised in a few lines. The concept of QOL is seldom defined and conclusions are often derived by indirect markers such as, for example, employment rates, rehabilitation, marital status, pregnancies. In most cases the little information reported is suggestive of significant bias and the number of cases studied is extremely small.

Brons was amongst the first authors to report nonclinical outcomes in a cohort of 13 patients with type 1 diabetes, stratified by intervention (SPK vs KTA) and transplant functional status. He actually presented objective results, such as household management, independence, pregnancy, and employment rates, all higher in successful SPK recipients (Brons, Calne et al. 1989). Similarly, Friedrich reported how 10 out of 17 SPK patients were able to resume work as evidence of improved QOL, with no issues related to immunosuppression and tethering with transplant centre (Friedrich, Niebel et al. 1999).

Nakache and colleagues compared HRQOL/QOL, social and occupational outcomes of SPK and KTA at 5- and 7-years post transplantation and documented

how, with longer follow up, employment rates continued to improve in SPK and declined in KTA (Nakache, Tyden et al. 1994).

According to Stratta, pre-emptive SPK and PTA recipients had better pre-transplant social and employment rates and quicker post-transplant recovery than SPK recipients on dialysis at transplantation, underlying how that the presence of renal failure weighted negatively on post-operative outcomes (Stratta, Taylor et al. 1994). In another manuscript, they documented adequate levels of rehabilitation at 5 years for both PTA and PAK recipients. This seems to confirm how the presence of adequate renal function, native or not, contributes to good outcomes in the medium term (Stratta, Weide et al. 1997). Findings from a registry analysis of 4476 pancreas transplants performed in the USA between 2010 and 2014 seem to support this theory, with highest pre- and post-transplant employment rates in patients with preserved renal function (Gruesser, Gruessner et al. 2017). Bendtal found no difference in rehabilitation and ability to work between 11 successful SPK transplant recipients and 16 SPK with a failed pancreatic graft and functioning kidney (Bentdal, Fauchald et al. 1991). Piehleimer, reported that “the vocational situation seems not to improve substantially after successful (pancreas) transplantation” (Piehlmeier, Bullinger et al. 1991).

Interestingly, a high proportion of patients within Stratta’s first study seemed to be unemployed after surgery for reasons other than medical. This is per se suggestive that objective measures such as ability to work might not mirror subjective measures such as fulfilment of one’s vocational aspirations or one’s attitude to employment. Esmatjes and colleagues had noticed how higher HRQOL/QOL in SPK recipients, when compared to KTA and type 1 diabetes on HD, did not lead to higher “socio-labour” (Esmatjes, Ricart et al. 1994). Equally, Gross and colleagues noted how,

despite net superiority of SPK over KTA recipients and patients with type 1 diabetes not seeking transplantation, there was a discrepancy between ability to work and actual employment rates (Gross, Limwattananon et al. 2000).

Other authors have continued to regard work status as a relevant aspect of HRQOL/QOL even in more recent years. Martins and Colleagues considered net increase in post-SPK employment rates as a surrogate marker of improved QOL (Martins, Outerelo et al. 2015). Barama reported better vocational, domestic, and social adjustment in SPK vs KTA. At ten years from transplantation only 24% of KTA recipients had a paying job, approximately a half of the SPK cohort (Barama 2009). When prospectively comparing 33 successful SPK and 15 KTA, Knight and colleagues found that the strongest predictors of post transplantation employment rates were pre-transplant work status and presence of a functioning pancreas. However, the two groups were not matched for number of comorbidities or progression of diabetes complications (Knight and Daly 2004)

- Manuscripts comparing HRQOL/QOL outcomes in SPK and KTA

Long term benefits of successful SPK transplantation on survival and chronic complications are now well documented (Navarro, Sutherland et al. 1997, Larsen, Colling et al. 2004, Coppelli, Giannarelli et al. 2005, van Dellen, Worthington et al. 2013, Lindahl, Reinholt et al. 2014). However, this was not the case in the early years of PT. Perioperative morbidity and mortality were significant, whilst long term clinical benefits were unknown. Clinicians, possibly driven by personal perceptions of patient's improved QOL, started to compare SPK - the most frequent form of PT- (Gruessner and Gruessner 2016) and less invasive approaches. For this reason,

many studies on HRQOL after SPK included KTA or PAK recipients as a comparator, especially in the early eras. However, most of the manuscripts do not document adjustment for baseline differences across groups.

Despite methodological limitations, investigators seem to concur that SPK is associated with better QOL/HRQOL than KTA. The magnitude of this finding varies considerably across studies with some authors reporting modest differences, while others documented significantly superior results for SPK recipients in multiple items and/or domains.

The spectrum of possible outcomes is particularly broad for results obtained with generic health status instruments and there is little agreement on which domains are most affected by the addition of a pancreatic transplant.

Some authors suggest that the divide in generic HRQOL between patients with successful transplantation, regardless of the type, and patients with graft loss might be deeper than the gap between SPK and KTA. Kiebert (ad hoc, multidimensional instrument) found similar results in both KTA and SPK recipients, the latter superior only in mobility. Failure of one or both organs, though, determined lower scores in all the dimensions and a smaller perceived improvement than in patients who had met their transplant goals (Kiebert, van Oosterhout et al. 1994). This could suggest that recalled HRQOL/QOL might be transplant outcome dependent, as asserted a few years later by Adang (Adang, Kootstra et al. 1998). However, it could also be the result of a tumultuous post-operative course that is difficult to overcome. Corry and Zehr used 11 validated questionnaires (Karnofsky, Pearson, Myers, Parfrey, Gill, Walston, Beck, Multiple Affect Adjective Checklist, Simmon, Campbell, Cantril) and were able to show how successful SPK and KTA reported higher HRQOL/QOL

levels and higher expectations of future health than patients whose pancreas had failed. The authors concluded that meeting one's transplant goal was the most important predicting factor of QOL, but it is unclear whether the reduced scores in patients who lost pancreatic function were secondary to the return to insulin per se or to the process that led to it. (Corry and Zehr 1990, Zehr, Milde et al. 1991, Zehr, Milde et al. 1992, Zehr, Milde et al. 1994)

Anderson (SF-36), Esmatjes (QLI, Karnofsky, Index of integration to normal life) and Nakache (RNL, QLI, interview) found limited differences across the two groups, with the exception of superior physical domains/disability scores in SPK (Esmatjes, Ricart et al. 1994, Nakache, Tyden et al. 1994, Anderson, Hart et al. 2011). Equally Gross, who spent nearly a decade investigating this topic with multiple instruments (SF-20, SF-36, Karnofsky, CES-D, IWB, life, health, and diabetes satisfaction items, transplant specific items, employment rates), reported how at three years from surgery KTA recipients performed significantly better in the mental components, and SPK recipients in the physical components, albeit below US norms. The addition of a pancreas represented a predictive factor for satisfaction. Longer term results, though, were affected by marked sample attrition, therefore some of the findings might be difficult to generalise (Gross, Limwattananon et al. 2000). And in fact, other authors have described the exact contrary: Sureshkumar, by using generic and diabetes specific PROMs (SF-36, DQOL, QWB), reported worsening mental health and quality of wellbeing in KTA at longer follow up, while Secchi attributed higher HRQOL/QOL after SPK to improved psychological wellbeing: better mood, general affect, social well-being, life satisfaction and treatment satisfaction (Secchi, Martinenghi et al. 1998, Sureshkumar, Patel et al. 2006).

It is important to underline how the instrument used by Secchi was a validated tool developed for patients with renal failure, integrated with diabetes and transplant specific items (Simmons, Abress et al. 1988). Indeed, it was authors who used disease specific instruments who reported the most meaningful differences in HRQOL/QOL between SPK and KTA.

Koznarova (SF-36, Muthny modified), Nathan (DQOL), Nyumura (SF-36v2 , PAID) and Sureshkumar detected significant differences with particular regards to treatment satisfaction, diet restrictions (Nathan, Fogel et al. 1991, Sureshkumar, Mubin et al. 2002), diabetes related stress (Nyumura, Babazono et al. 2017), but also higher global HRQOL/QOL, superior general health score and better emotions (Koznarova 2001). However, they did not identify marked differences with generic PROMs, except for higher perceived general health in SPK, as reported also by Esmatjes, Matas and Zehr (Esmatjes, Ricart et al. 1994, Zehr, Milde et al. 1994, Matas, McHugh et al. 1998).

Furthermore, authors who have explored specific aspects, such as sexual function or gastrointestinal QOL, found better scores in SPK recipients than KTA (Voruganti and Sells 1989, Esmatjes, Ricart et al. 1994, Hathaway, Hartwig et al. 1994, Salonia, D'Addio et al. 2011).

A few investigators - Bozek, Gross, Nakache and Sureshkumar - observed how the divide between SPK and KTA recipients deepens with time, although the evidence doesn’t allow us to understand whether it is due to an upwards trend of the first or a downwards trend of the latter.

Bozek and colleagues were amongst the few authors who adopted a renal disease specific validated measure which includes generic health status domains (KDQOL-

SF). The prospective data collection with longitudinal follow up after over one year, showed that the presence of a functioning pancreatic graft yielded to higher Physical Component Summary scores (PCS) as well as 12 out of 20 subscales. Past cardiovascular episodes were the factor with highest impact on HRQOL/QOL (Bozek-Pajak, Ziaja et al. 2016), as confirmed by our own analysis of prospectively collected EQ-5D-3L data from 200 PT recipients (Mosca, Mittal et al. 2018). Other important prognostic factors were lack of insulin independence, duration of diabetes, cardiovascular disease, age and BMI of recipient, history of toe amputation and presence of hypertension.

According to Gross all transplant categories, when successful, demonstrated an increased HRQOL at one year. Most of the domains returned to baseline at 3 years, however differences between SPK and KTA became more manifest with time (Gross, Limwattananon et al. 2000). Nakache and colleagues retrospectively compared SPK at a minimum of two years from surgery to a control group inclusive of deceased donor KTA recipients, living donor KTA recipients and SPK patients with a failed pancreatic transplant. They suggested that successful SPK recipients had possibly better QOL and better rehabilitation scores despite longer post-operative course (Nakache, Tyden et al. 1989). Differences were more pronounced at 7 years from transplantation with SPK becoming superior in most of the domains except for the global QOL index (Nakache, Tyden et al. 1994). Sureshkumar reported a widening gap between SPK and KTA with longer follow-up, with KTA recipients progressively scoring worse in some of the diabetes related domains, in general wellbeing and in general and mental health (Sureshkumar, Patel et al. 2006).

Finally, as previously discussed, SPK seems associated with higher employment rates than KTA (Knight and Daly 2004, Barama 2009, Nyumura, Babazono et al. 2017).

- Manuscripts reporting HRQOL outcomes in PT or against not-transplanted patients with type 1 diabetes.

Many QOL researchers have looked at PT recipients per se or compared them to either patients on the waiting list (WL) or patients with type 1 diabetes not seeking transplantation, controlling for baseline differences.

Most of the early studies were cross-sectional, while most prospective longitudinal cohort studies were relatively recent, possibly because of the concomitant evolution in QOL research methodology.

- Cross-sectional Studies

These studies aimed to investigate post-operative HRQOL. However, there was no pre-operative baseline data to link results to. In some cases, patients were asked to compare their current state to their recalled pre-transplant one. Outcomes collected in such fashion are anything but reliable, and, as underlined by Coughlin, “the extent of inaccurate recall in retrospective studies is determined by characteristics of the exposure of interest including the degree of detail, significance to the respondent, social acceptance and time period.” (Coughlin 1990).

Adang and colleagues demonstrated discrepancies between pre-transplant baseline outcomes and “recalled” baseline ones. Successful SPK recipients retrospectively re-scored their pre transplant QOL as worse than they did before the

intervention. The authors suggested that this might be due to a degree of adaption of patients to chronic diseases (Adang, Kootstra et al. 1998).

This additional source of bias poses further doubts on reliability of results.

A few studies are cross-sectional, although potential clinical confounders were infrequently considered. It is, therefore, impossible to confidently establish whether the reported differences across groups were ascribable to PT or not.

In other circumstances the data provided is insufficient to comment on results at all. For example, Sansalone (SF-36) reported high HRQOL after SPK. Unfortunately, the manuscript doesn't provide any description of methodology or results (Sansalone, Aseni et al. 2003).

When comparing successful SPK recipients with those who were back on insulin, a few authors, such as Satterly, Bendtal and Piehlmeier in his early work, didn't identify significant differences. Satterly looked at post-transplant "life activities" and found that patients with successful transplantation reported fewer symptoms, however they did not improve significantly from a recalled baseline status (Satterly, Cox et al. 1991). According to Piehlmeier results from the two cohorts were quite similar, even using multi-dimensional instruments (Muthny Modified, SF-36, VAS) at a mean follow-up of approximately 6 years (Piehlmeier, Bullinger et al. 1994). Bendtal (interview) reported analogous ability to work and rehabilitation at approximately 5 years from surgery. However, as acknowledged by the authors, no measures of emotional or psychological well-being were used (Bentdal, Fauchald et al. 1991).

Most of these works were based on a handful of patients and it is no surprise that other studies, even by the same teams, reached opposite conclusions. Comparison between a large cohort of successful SPK recipients, patients who had lost one or both organs and patients on the waiting list, highlighted how graft loss had a negative impact on general health perception and vitality. The worst ratings were from not-transplanted patients and those with failure of both transplants (Piehlmeier, Bullinger et al. 1994, Piehlmeier, Bullinger et al. 1996).

Consistently with these findings, Alharbi (SF-36) reported worse physical health, social and vocational activities in SPK recipients who had returned to insulin, but not energy and emotions (Alharbi, Aquil et al. 2017). However, when Kansal and colleagues integrated generic PROMs with specific validated instruments finalised at framing psychosocial aspects (QOL Bref, Core-10, HADS, GAD7, RMDQ-A and WSAS), in addition to higher disability they also found higher psychological distress related to loss of pancreatic graft function (Kansal, Johnson et al. 2013).

Others have found return to dialysis most detrimental. Drognitz (SF-36) and Schareck (ad hoc instrument and interviews) showed lower general health, physical and social function ratings in SPK recipients with failed renal transplant, while patients with preserved function of both organs achieved HRQOL scores within 95% interval confidence from matched German population. The authors acknowledged how missing data of non-responders could have potentially skewed results (Schareck, Hopt et al. 1994, Drognitz, Benz et al. 2004). Finally, according to Scheurmann (SF-36), loss of either graft was a predictor factor for worse HRQOL, especially in physical domains (Scheuermann, Rademacher et al. 2020).

Although the level of evidence accrued with retrospective studies and small case series is considered low, it is difficult to ignore data when it seems to converge towards similar conclusions. This is the case of most outcomes derived by comparing HRQOL/QOL of patients PT recipients and patients on the PT waiting list.

Many investigators including Posseger, Sugitani, Bolesta, Gibbons have consistently reported superior scores after transplantation, although the domains deemed more relevant varied across studies. This apparent discordance could be suggestive of a variegated realm of potential benefits. Posegger and colleagues analysed both generic, renal and diabetes related HRQOL in 103 SPK recipients and 57 WL patients (KDQOL-SF, PAID). Many of the generic domains, as well as burden and effects of kidney disease were better after transplantation at a relatively early stage. Furthermore, when controlling for a failed pancreas transplant, SPK recipients progressively showed lower diabetes associated distress. (Posegger, Linhares et al. 2020). Sugitani (SF-36) found that 9 functioning SPK recipients performed significantly better than 26 WL patients in all domains analysed, approaching Japanese normative values (Sugitani and Yoshida 2011). Bolesta and Kühn (SF-36) reported how SPK was associated with higher mental and physical component summary scores (MCS and PCS), with net superiority in physical functioning, general health, social functioning, vitality, and mental health. Biological male gender and more recent transplantation were associated with better outcomes. However, successful SPK recipients only reached levels comparable to a decade older German population (Bolesta, Kuhn et al. 2016). Gibbons and colleagues conducted a composite research study merging results from a retrospective, a prospective and a qualitative study (ADDQOL, RDQOL, DTSQS,

DTSQSc, RTSQS, RTSQSc, QOL-w-BQ12, EQ-5D-5L and interviews). In the retrospective data collection from 95 SPK recipients and 41 patients on the WL, SPK patients scored better than WL in generic HRQOL, total wellbeing, health status and satisfaction with renal treatment. However, the two groups were similar in areas related to diabetes and health utilities (Gibbons, Cinnirella et al. 2020). Most recently, though, Nijhoff and colleagues, who explored the relationship between psychological wellbeing and HRQOL in SPK, WL and patients with non-advanced type 1 diabetes (SF-36), reported divergent results: SPK recipients' modest advantage over WL patients wasn't sustained in time. Equally, the two groups had similar levels of psychological symptoms, with non-advanced type 1 diabetes patients scoring higher in all the domains investigated. Negative predictive factors for HRQOL were higher psychological distress scores, malignancies other than melanoma, dialysis, retinopathy, and previous vascular episodes (Nijhoff, Hovens et al. 2020). In other words, based on this group's findings, diabetes-related complications rather than diabetes itself were responsible for HRQOL. Rather than discouraging, these results could support those who believe in an early timing of PT transplantation. In addition, it is important to underline how Kwiatkowski (non-validated questionnaire) had reported how, despite nearly 50% of successful SPK recipient complained of low mood and fear of graft loss, the totality of the sample expressed increased life satisfaction and enjoyment after transplantation (Kwiatkowski, Michalak et al. 2005). Furthermore, other authors who have studied larger cohorts of functioning SPK recipients have registered normal levels of psychosocial adjustment and HRQOL (Bruce, Newell et al. 1996) and better mood and general affect (Secchi, Martinenghi et al. 1998).

In other words, once the damages inflicted by the disease become well established, PT seems to be the option offering higher HRQOL, as the evidence accrued by Isla-Pera, and Kessler seem to suggest.

According to Isla-Pera (SF-36), who compared SPK recipients to patients with type 1 diabetes and renal failure, transplantation was associated with superior HRQOL, however both groups scored below the Spanish population norm. Intra-group analysis revealed how pancreas transplantation, older age, biological male gender, more recent transplant, shorter duration of diabetes and RRT were associated with higher HRQOL (Isla Pera, Moncho Vasallo et al. 2009). Kessler (DQOL), who used a group of patients with advanced type 1 diabetes managed with optimized glucose therapy as a control, reported similar diabetes related concerns across cohorts, however SPK recipients more often would rate their health status as good and had a higher level of life and treatment satisfaction (Kessler, Boudjema et al. 1996).

Some authors have investigated specific pre-transplant/transplant variables, reporting interesting findings. Scheuermann and colleagues found that patients previously on PD had better post-transplant HRQOL than patients with a history of HD (Scheuermann, Rademacher et al. 2020). Hathaway, Gaber, and colleagues (SIP, QLI, ASIS) demonstrated no difference in quality-of-life outcomes between SPK recipients with enteric and bladder exocrine drainage, with significant improvement of almost all the scales analysed in both cohorts (Lo, Stratta et al. 2001).

Humar (SF-36, CES-D), in a large study clinical and HRQOL/QOL outcomes of SPK and PAK, reported that the combined operation didn’t seem to be more burdensome

than the two stages approach, offering further insight on the possible timing of the procedures (Humar, Ramcharan et al. 2001).

Prospective Longitudinal Studies

Prospective research on HRQOL/QOL after PT represents approximately one quarter of the manuscripts reviewed. Prospective, comparative studies on SPK versus KTA focused on specific topics such as sexuality, autonomic dysfunction, employment rates as well as qualitative studies are discussed elsewhere.

Our knowledge on longitudinal changes in HRQOL/QOL after PT is based on a handful of studies, with a median population of 26 participants (range 7-618).

Interestingly, a statistically higher proportion of prospective studies (72%) was conducted either by specialists in quantitative research or with their contribution, compared to 47% of cross-sectional manuscripts. Yet, in a few instances it was not possible to establish the strength of the evidence presented. For example, Kinkhabwala, in the context of an article describing general outcomes of PT, reported remarkable HRQOL/QOL after SPK (Kinkhabwala, Wilkinson et al. 1996). Similarly, Johnson and colleagues reported how “no patient considered their lives normal” in the face of an overall improvement of performance status (Johnson, Schellberg et al. 1990). Ultimately, findings seem to align with what was reported by most, but, unfortunately, neither manuscript provide detailed description of methodology or results.

In a pivotal manuscript describing clinical outcomes on over 1000 pancreas transplants, Sutherland included a prospective longitudinal study of performance

status (Karnofsky) in a mixed cohort of 618 PT recipients (SPK, PAK and PTA). All transplant categories had improvements both at 1 and 2 years from surgery. PAK candidates were the least impaired at baseline, whilst PTA recipients reached the highest scores after transplantation. Again, this data seems to suggest the relevance of renal function on HRQOL. However, the authors then documented how loss of pancreatic function had a detrimental effect on performance status, unlike loss of kidney function (Sutherland, Gruessner et al. 2001). The analysis of a smaller cohort of 14 successful PT up to 17 years of follow-up, showed how approximately two thirds had little performance limitation and were very or fairly satisfied with life. The totality of the sample agreed that immunosuppression side effects were preferable to diabetes (Najarian, Gruessner et al. 1998).

Hashizume, Ito, Kenmochi, and Suzuki studied HRQOL on 16 living donor segmental pancreas kidney recipients up to 3 years after transplantation (SF-36). Both PCS and MCS, below the Japanese population norm before surgery, continued to increase progressively afterwards (Suzuki, Kenmochi et al. 2008, Suzuki, Kenmochi et al. 2012). They observed similar results on a smaller cohort of ABO incompatible segmental pancreas kidney recipients (Kenmochi T et al. , 2010). Tai and colleagues undertook a similar study on 7 SPK recipients and documented a statistically significant improvement in all domains at 2 years from surgery, reaching similar levels of the Chinese SF-36 population norm (Tai, He et al. 2010).

In the prospective arm of their study, Gibbons and colleagues noticed how SPK recipients reported improvement in generic HRQOL/QOL, wellbeing, health status and renal treatment satisfaction, with lower negative impact of renal condition. Pre-emptive SPK candidates had the highest baseline scores and improved the least

after surgery, perhaps because of an overall superior health status to start with and some degree of ceiling effect. However, unlike results reported by Kessler, Secchi, Gross and Sureshkumar, diabetes specific items didn't show a significant difference (Kessler, Boudjema et al. 1996, Secchi, Martinenghi et al. 1998, Gross, Limwattananon et al. 2000, Sureshkumar, Mubin et al. 2002, Sureshkumar, Patel et al. 2006). Interestingly, when participants were asked to compare their current treatment for diabetes (hence the transplant) with their previous one (hence insulin), by using a questionnaire designed to capture changes in treatment satisfaction in relation to changes in treatment, (DTSQc)., SPK reached higher levels after transplantation. This was an interesting finding, albeit probably not generalisable because of significant sample attrition (from 22 to 14 responders). However, the investigators provided invaluable information on QOL after SPK with the "qualitative" arm of their research. Patients reported increased energy levels, improved social function and freedom of diet, but also fear of rejection and difficulties to adapt to the new identity/habits. The perception that diabetes related organ damage was irreversible and the discrepancy between expectations and reality were a source of significant distress (Gibbons, Cinnirella et al. 2020).

And indeed, this dichotomy is indirectly suggested elsewhere. Smith and colleagues (SF-36, DSM-IV) found that many SPK recipients experienced a steep and relatively early improvement in MCS, approaching population norms. PCS continued to increase in time, but they reached lower values. However, a significant proportion of patients scored worse after the procedure. The authors identified pre-transplant psychiatric disorder diagnosis and female gender as negative predictor factors of HRQOL (Smith, Trauer et al. 2010).

- Manuscripts investigating HRQOL in Pancreas Transplant Alone

Unlike patients undergoing SPK and PAK, PTA recipients have preserved renal function and seek transplantation as a last resort for hypoglycaemic unawareness. Essentially PT and IT candidates belong to the same category: they often have few if any chronic symptoms caused by diabetes and they are generally at a less advanced stage of type 1 diabetes than patients with end-stage renal failure. Hence it is reasonable to imagine that their HRQOL might depend on different variables than patients with multiple chronic complications of diabetes.

However, because of the surgical nature of the intervention, results are often reported along those of other solid organ PT recipients. Moreover, PTA represents less than 10% of the totality of PT (Gruessner and Gruessner 2016.), hence in many centres numbers might not be big enough to analyse PTA separately. Most of our knowledge of HRQOL after PTA comes from high volume centres such as the University of Minnesota (Stratta, Weide et al. 1997, Sutherland, Gruessner et al. 2001, Scalea, Pettinato et al. 2018).

Sutherland and colleagues (Karnofsky) showed that, despite fewer chronic complications, PTA candidates had pre transplant baseline scores significantly lower than PAK ones. However, they were the ones benefitting the most from transplantation both in the short and in the medium term (Sutherland, Gruessner et al. 2001). Another team who focused on PTA outcomes was from the University of Pisa. Vistoli and colleagues presented their data on 187 consecutive PT. However, whilst clinical outcomes were described separately for each transplant category,

QOL results were defined as “improved” and similar to general population, but no cross-sectional details were provided (Vistoli, Croce et al. 2010). Further work focused on 37 PTA recipients (SF-12, IPAQ_SHORT) showed how patients with preserved insulin independence had higher scores in psychological well-being and physical performance domains, but not in physical activity (Triscornia, Nardi et al. 2017).

It is relevant to underline, though, that patients who come forward for Pancreas Transplant Alone do so because of unmanageable diabetic hypoglycaemia. Hence, any study aimed at clarifying HRQOL/QOL in this cohort needs to include domains that investigate these aspects. Notably, when Scalea and colleagues from the University of Maryland used an “ad hoc” instrument inclusive of hypoglycaemia fear items, they were able to document differences between PTA recipients with a functioning and a failed graft(Scalea, Pettinato et al. 2018).

- Manuscripts investigating specific aspects of HRQOL.

Chronic complications of diabetes can have a significant impact on everyday activities. Hence, a few authors have sought to understand how PT might impact on specific aspects of HRQOL/QOL.

Sleep.

Reilly-Spong and colleagues researched the relationship between transplantation and sleep (PSQI, SF-36 v2, CES-D, STAI). They reported poor sleep and poor sleep HRQOL/HRQOL/QOL for approximately 41% of transplant recipients, with no

differences across specialties (Reilly-Spong, Park et al. 2013). Others have investigated the relationship between PT and autonomic, gastrointestinal, and sexual function.

Autonomic and gastrointestinal function.

In a series of studies on SPK and KTA Hathaway and colleagues were able to demonstrate statistically significant correlation between objective measures of autonomic and gastric function (heart rate variability and gastric emptying) and subjective measures of HRQOL/QOL (SIP, QLI, ASOS). While both cohorts experienced post-transplant improvements, in SPK recipients there was a stronger relationship between biological data and PROMs (Gaber, Hathaway et al. 1994, Hathaway, Hartwig et al. 1994, Hathaway, Wicks et al. 2000). Ben-Youssef reported improvements in subjective ratings of HRQOL/QOL in three patients after intra-pyloric injection of Botulinum Toxin and improvement of gastric dysmotility (Ben-Youssef, Baron et al. 2006).

Vergani and colleagues detected objective improvement of diabetic enteropathy (rectal manometry, histopathology of rectal mucosal biopsies) and concordance with better gastrointestinal QOL (Gastrointestinal Symptom Rating Scales) in SPK but not in KTA recipients (Vergani, Orsenigo et al. 2011). Equally, Martins and colleagues found a correlation between reduction of gastrointestinal symptoms (GIGLI) and increase of HRQOL/QOL (EQ-5D-5L and VAS) in the medium term follow up. Results were based on recalled baselines; however, the authors also conducted a small prospective study with similar findings and used this escamotage to validate their data. Despite methodological predicaments, their outcomes are consistent with findings from Vergani (Martins, Outerelo et al. 2015).

- HRQOL and sexual function.

Most PT recipients in the US are aged between 35 and 55 years (Kandaswamy PG et al, 2021) while in the UK the average age at transplantation is 41 years (NHSBT 2020). Both diabetes and renal failure are known causes of impaired sexual function (Jonasson, Ye et al. 2008, Ramesh, James et al. 2017).

Unsurprisingly, authors have been inclined to clarify whether the resolution of both conditions could improve sexual function and HRQOL/QOL and many - Matas, Hart, Mueherer, Martell - reported lack of specific pre-transplant education as a potential area of improvement.

Hart and colleagues investigated the frequency and impact of sexual dysfunction on a mixed population of 768 adult transplant recipients. Over 60% of the sample reported satisfaction in sexual relationships, with no major differences in multidimensional HRQOL across groups (Hart, Milde et al. 1997).

As demonstrated by Hathaway, physiological parameters and HRQOL in SPK recipients are closely related. This seems to be supported by Jürgensen's observations: individuals without erectile dysfunction (II-EF) - albeit just 20% of the study population - had the highest HRQOL scores (SF-36, QWB), just slightly below the norm (Jurgensen, Ulrich et al. 2008). Whether this was the direct consequence of a lesser systemic microvascular/neurological impairment is difficult to establish. Sexual competence is the result of a finely tuned endocrine axis regulated by both psychological and physiological elements. Salonia and colleagues evaluated both aspects in a cohort of 10 SPK recipients, 20 KTA recipients and 11 healthy controls, correlating results to sexual wellbeing. The two transplant categories were similar in Beck's inventory for depression scores, superior to not-transplanted participants

and inferior to healthy controls. On the contrary, sexual function (II-EF) and steroid profile in SPK recipients was closer to the healthy control than the other two groups. The small sample size could explain the discrepancy between psychometric profiles and physiological outcomes (Salonia, D'Addio et al. 2011).

Mueherer found no correlation between chronic complications and sexual functioning in female SPK recipients albeit a possible selection bias secondary to low return rates. Participants showed an acceptable level of sexual self-esteem (ASEX, Sexual Self-Esteem Scale, Open-ended questions). However, ultimately the proportions of responders who rated the transplant as beneficial or detrimental were similar (Muehrer, Keller et al. 2006).

Approximately a decade later, their longitudinal study on 145 SPK recipients (SF-12, QOL uniscale, SCQ) did not highlight any significant benefit of pancreas transplantation on sexual function, with twice as many items deteriorating as improving. Concerns regarding quality of sexual life were associated with significantly lower HRQOL (Muehrer, Brown et al. 2013). However, pancreas function and possible confounders such as time from transplantation were not specified.

Further insight on the topic is provided in a qualitative study by Martell and colleagues. Recurrent themes were the detrimental effect of medications, difficulty to share sexual concerns with the care team, specific worries about reproduction, negative repercussions of change in appearances on self-esteem and relationship with partners (Martell, Rice et al. 2015).

- Qualitative Studies

One of the advantages of quantitative methodology is the possibility of transforming subjective experiences in numeric language, which allows for longitudinal or cross-sectional comparisons. However, in populations where the boundaries between “existence” and “disease” are extremely blurred, qualitative research might elicit themes that would otherwise go unaccounted for. Although investigators seemed to acknowledge PT recipients’ complexity, manuscripts entirely based on qualitative methodology represented less than 5% of the studies included.

Isla-Pera sought to integrate their quantitative study with qualitative methodology. The main pre-transplant themes identified were `’guilt”, as if progression of complications was somewhat related to the individual’s behaviour, “loneliness”, and “fear of the procedure”. SPK transplant was seen as the chance to recover health and independence: the trade-off for the long-sought change of life was deemed acceptable. After the procedure patients referred to transplantation as a “new life” and the opportunity to experience a “normal” existence, to enjoy life and no longer feel ill. However, themes such as “fear for graft loss”, “articulate feelings towards the deceased donor”, “tethering with the medical team” and new “complex perception of self” ultimately dampened enthusiasm for some. The authors concluded that the prevailing biomedical approach to patients represents a missed opportunity to deliver high quality care (Isla Pera, Moncho Vasallo et al. 2009). This is indirectly confirmed by Stonnington and colleagues, who investigated the effects of mindfulness techniques on psychological wellbeing (Perceived Stress Scale, GAD-7, PHQ-9, Connor-Davidson Resilience scale, PANAS positive, PANAS negative, MAAS, SF-36) of a group of mixed transplant candidates, recipients and

their carers. They found significant improvements in perceived stress, positive and negative affect, depression, and anxiety. Although there was no distinction across different transplant categories, they demonstrated how a holistic approach can bring forward quantifiable improvements in patient's perception of health (Stonnington, Darby et al. 2016).

"Regained freedom", "control" and "normality" were identified by Hathaway as important post-SPK themes (Hathaway, Hartwig et al. 1995). As described by Langenbach in a course of interviews on 8 SPK recipients, transplantation was associated with reaffirmation of identity of self, gratitude, and fantasies regarding the donor (Langenbach, Stippel et al. 2004). However, others described disappointment arising from the acknowledgment that no longer "being diabetic" wouldn't easily erase the long-lasting damage caused by the disease (Gibbons A et al. , 2020). As described by Jackson, patients return to a condition of "normality" they cannot relate to because they have not experienced it in their adulthood (Jackson, Gleeson et al. 2013).

2.3.5 Normative Values

Many authors who have compared Short Form 36 outcomes against population norms, showed how successful PT recipients have the potential to reach the normal range in either PCS or MCS or both (Drognitz, Benz et al. 2004, Jurgensen, Ulrich et al. 2008, Smith, Trauer et al. 2010, Tai, He et al. 2010, Anderson, Hart et al. 2011, Sugitani and Yoshida 2011). A list of the manuscripts reporting on this specific topic is provided in **Appendix 2.13**.

In other studies, based on relatively big populations but with unclear follow-up strategy, scores remained below population norms despite post-operative improvements (Matas, McHugh et al. 1998, Isla Pera, Moncho Vasallo et al. 2009, Bolesta, Kuhn et al. 2016).

2.3.6 Predictor Factors

“Advanced cardiovascular complications” were the most recurrent predictor factor of poor HRQOL. “Loss of both grafts”, “return to dialysis or insulin” were also repeatedly as associated with worse HRQOL. Gender differences seemed to suggest higher post-transplantation scores in males, with the exception of Rajkumar and colleagues. However, their study was conducted on a mixed population of 18 SPK and 57 KTA and results were presented for the totality of the study population, without controlling per transplant type (Rajkumar, Mazid et al. 2019). Martin and colleagues (SF-36, Cincinnati Transplant Questionnaire) found a negative correlation between income and QOL outcomes in a mixed transplant population and apparently no other meaningful predictor factor (Martin 2001). **Appendix 2.14** summarises the most frequent predictors identified.

2.3.7 Cost-effectiveness evaluation

Very little information is available on utility-based measures in pancreas transplantation. Cost-effective modelling was performed in USA during the initial era of SPK transplantation and seemed to point in the direction of an advantage of SPK

against KTA and Pancreas after living donor Kidney Transplant (Holohan 1996, Douzdjian, Ferrara et al. 1998, Boyd, Martin et al. 2001). However, this data is over twenty years old and essentially accrued within the boundaries of a private healthcare system. I only identified three recent manuscripts based on EQ-5D-5L and none provided a longitudinal trajectory of EQ-index changes after pancreas transplantation (Martins, Outerelo et al. 2015, Mosca, Mittal et al. 2018, Gibbons, Cinnirella et al. 2020).

2.4 DISCUSSION

This Systematic Review yielded over one hundred studies published over approximately 30 years. The most prolific eras were the turn of the century, when PT was becoming increasingly popular, and the last decade, after a period of international crises in activity rates. A possible explanation could be that, for different reasons, in both eras there was a tendency to compare PT to other therapeutic strategies, hence clinicians sought ways to understand where the balance between risks and benefits might be found. At first, long term outcomes of PT were unknown and KTA was often considered an adequate alternative to SPK, the most frequent form of PT (Gruessner and Gruessner 2016). Lately, innovations in glucose monitoring and insulin formulations/delivery strategies as well as the improvements in IT efficacy, might have reignited interest in HRQOL outcomes.

Interestingly, despite the recurrent need to assess “hidden benefits” of pancreas transplantation, I found little if any data accrued with preference-based measures: there is a surprising knowledge gap on cost-effectiveness of the procedure and its potential alternatives.

Similarly, the continuous and ongoing attempts to characterise HRQOL or HRQOL/QOL after PT suggests that, despite over 30 years of research in the field, the data available is either scant, unclear, or less meaningful. Indeed, the risk of bias within the articles included in this review was medium high and the quality of the evidence only fair, with a few exceptions.

Interestingly, while checking the full text of articles against the protocol's inclusion/exclusion criteria, I found that in many instances authors would list "better quality of life" amongst the benefits of transplantation, without having investigated it. This phenomenon highlights how the first reports of HRQOL after PT were based on very little scientific evidence.

Progressively, clinicians started documenting the potential benefits of PT by looking at objective factors, such as occupational status. The largest studies adopting this approach agreed that PT was indeed associated with increased occupation levels. Patients with good renal function at transplantation seemed to have the highest pre-operative employment rates and best post-operative outcomes (Stratta, Taylor et al. 1994, Gruesser, Gruessner et al. 2017), possibly as a correlation with less advanced disease to start with.

This is *per se* already an important finding in favour of early transplantation, bearing in mind that most pancreas transplant recipients are of working age. Post-transplant employment rates in patients with type 1 diabetes complicated by ESRF were highest amongst SPK recipients when compared to KTA, both in the short and the long term, underlying the importance of stable glucose control for reintegration to normal life. This data was confirmed by further studies throughout the decades.

However, this is very far from a universal phenomenon: from the very start, authors noticed that many patients, potentially fit for a paying job after successful PT and KTA, were still unemployed at follow-up (Stratta, Taylor et al. 1994). It is possible that this discrepancy is in part rooted in an important omission: many of the early studies were based exclusively on objective measures.

As defined by the World Health Organisation, Quality of Life is “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns”(Organization 1946). Although many other definitions have been proposed, the common denominator to most of them is the inclusion of subjective criteria to evaluate QOL itself (Karnofsky and Burchenal 1949).

The initial lack of knowledge in QOL research is also testified by the medium/low Gill and Feinstein scores of many manuscripts (median 25, range 0-67), where 0 and 100 are the lowest and highest possible scores respectively.

Less than 30% of articles provided a definition of “Quality of Life.” This is hardly just a matter of semantics: in fact, this term has been used indiscriminately when looking at global QOL as well as Health Related QOL. In other words, authors might have used the same definition to describe different outcome measures, leading to equivocal and at times contradictory results. In fact, the concept of QOL includes HRQOL, but it is not exclusively influenced by it.

The median risk of bias with Downs and Blacks checklist was 12/27, which can be considered “poor” (Downs and Black 1998). Further uncertainty is probably due to the lack of a risk of bias tool specific for HRQOL/QOL studies. Despite a progressive acknowledgment of the intricacies of QOL research, many studies still had relatively high risk of bias and medium/low Gill and Feinstein summary score (Appendix 2.7-2.8-2.9). In many instances the information provided on the cohorts studied, their baseline differences, follow-up timepoints and statistical approach was insufficient to understand the quality of the evidence accrued. Over 70% of these studies were conducted after transplantation. Data collection occurred at pre-established time

points in approximately 30% of the cases, in the remaining articles follow up was either uncontrolled or unavailable. Timing of data collection seems particularly important in the case of comparing SPK outcomes against KTA. In fact, the two interventions differ significantly in post-operative recovery time, hence unadjusted data collection could interfere with results.

To complicate matters even further, the most striking outcome of the review is the extraordinary heterogeneity in number and combinations of PROMs utilised. This represents one of the biggest obstacles to extract comparative data.

These findings indirectly highlight the real challenge in studying HRQOL after PT: the multifaceted nature of the disease and the uniqueness of the intervention are hardly captured by existing validated instruments. The high variability in PROMs is probably a reflection of this conceptual impasse.

Over two thirds of PT candidates are patients who have developed quite advanced systemic disease. Progressively, diabetes impacts virtually every aspect of everyday life: patients may develop problems with their sight, digestion, bowel movements, bladder function. Standing up and walking might become problematic because of neuropathy and vascular changes; they might incur digital amputations and devastating wound infections due to poor healing. Progressive uraemia brings forward further problems such as pruritus, muscle cramps, anaemia, weakness and frailty, fluid restrictions, swelling, changes of body habitus, loss of bone density and finally the ultimate burden: dialysis. Equally, the mental health impact of growing up with a life changing disease cannot be underestimated.

Regardless of clinical outcomes, PT comes with its own weight. The mere concept of being on a waiting list can be challenging for some. Waiting for a “the call” can

be unnerving for others, and the thought of deceased donation can be a source of uneasiness for most.

Patients choose to leave behind a lifestyle that is as difficult as it is familiar, to venture into the unknown. They face major surgery with the awareness that it may or may not go well and that many of the complications may or may not improve. Finally, they will have to deal with the burden of post-operative recovery, immunosuppressants, fear of rejection and tethering to the transplant centre, even when things go well.

It is not surprising that some investigators attempted to create “ad hoc” instruments and that another 38% chose multiple tools to capture the intricacies of this population. Equally, it is also plausible that some, recognising such a high degree of complexity, opted for single validated PROMs, in the attempt to simplify data collection, outcomes and their interpretation. And indeed, another crucial aspect in QOL research is sample attrition, which occurs when study participants drop out of one or more point of data collection, reducing the final size of the study population.

Very few studies have reported PROMs return rates or the characteristics of “non-responders”. In addition to dampening reliability of outcomes, the lack of this information represented, in our view, a missed opportunity. In fact, by stratifying return rates against PROMs chosen, length of the surveys and follow-up time points I could have gained a clearer picture of what research strategy would best fit this population. Whilst a combination of multiple instruments could potentially cover as many domains as possible, it could also be burdened by low return rates as compared to single/few short instruments with a high face validity. Equally, by comparing return rates at every follow up time point, it could have been possible to

have some information regarding long term attrition, bearing in mind that research on QOL after PT is usually based on small numbers to start with.

In this review, I found that authors have chosen either strategy in similar proportions, leaving the issue pending.

Finally, I found very little data elicited with preference-based instruments. In other words, there is little data available to understand what patients would consider and acceptable trade-off for a life without diabetes and renal failure. This, seems particularly surprising, considering that there are other treatment options available for these cohort of patients.

Even in the face of this significant number of potential confounders some findings seem to recur, however results must be taken “with a pinch of salt”.

2.5 CONCLUSIONS

Data from prospective studies supports the hypothesis that PT increases HRQOL for the great majority of patients. Most investigators reported better post-transplant scores in physical, mental, and psychosocial domains. Comparison with normative values has shown how SPK recipients have the potential to reach general population scores. However, it was the use of disease specific instruments that allowed investigators to capture the biggest improvements.

Equally, when comparing SPK and KTA, generic instruments often captured similarities rather than differences, with SPK recipients showing some degree of superiority in specific domains, such as general health perception, physical well-being, rehabilitation/vocational items. Again, investigators who used disease specific questionnaires were able to document the biggest differences across groups: successful SPK was associated with higher treatment satisfaction, lower diabetes related stress and lesser effects of kidney disease.

Nevertheless, because of the multifaceted nature of type 1 diabetes, even within the realm of disease specific measures there can be marked differences amongst instruments, depending on the specific focus of each. For example, the little evidence available on PTA seems to suggest that these individuals' reach satisfactory HRQOL and more so than other forms of PT. However, the use of instruments that do not address hypoglycaemia may result in inaccurate conclusions. In contrast, in SPK and PAK the burden of chronic complications on HRQOL is of paramount importance. These patients consider diabetes as their

primary illness, the root of all the other problems. However, it is long term symptoms that gradually impoverish their QOL. Hence, when attempting to characterise HRQOL after PT, it would be useful to understand the individual contribution of pancreas and kidney graft function on long term symptoms.

The data accrued doesn't allow us to discern between the weight of the two. Pancreatic graft failure was frequently associated with lower scores, although the strength of this association varied significantly across reports. Equally, return to dialysis was associated with significantly worse outcomes by some investigators and not by others.

Neither comparing SPK versus KTA outcomes nor successful SPK versus SPK with loss of either graft could help clarify this aspect. Currently, most KTA candidates are patients deemed too frail for SPK transplantation, hence the two cohorts are hardly equivalent, and many studies fail to account for baseline differences. Equally, pancreatic graft failure rates of 15% at 1year and 27% at 5years , (Gruessner and Gruessner 2016) in conjunction with study population sizes, would make it difficult to identify statistically significant differences. Furthermore, it would still be challenging to separate the weight of return to insulin or to dialysis from the process that led to graft loss, especially with generic instruments.

This would likely be possible with a prospective longitudinal study based on a validated PROM designed for this population or a combination of different instruments, with long term follow up of a large number of participants. However, this raises the issue of sample attrition. Unfortunately, with a few exceptions, investigators did not provide any information regarding return rates and characteristics of non-responders, hence it is not possible to draw conclusions on

the best approach to design such a study. On one hand excessive simplification could lead to inaccurate findings, on the other lengthy disease specific questionnaires could be perceived as burdensome and jeopardise compliance.

Many studies showed a widening gap in QOL between SPK and KTA recipients with longer follow-up. It is unclear whether this depends on continuous improvement of SPK or progressive deterioration of KTA recipients, or both, with regards to chronic diabetic complications. A few authors have documented a tendency of HRQOL gain after SPK to fade in time, with recent transplantation identified as a positive predictor factor for good outcomes. In this case, the widening gap between SPK and KTA at longer follow up, would most likely be related to progressive worsening of KTA recipients, rather than further improvement in SPK ones.

It would, therefore, be useful to be able to correlate long term HRQOL to clinical evolution of diabetic complications. A few authors have identified pre-transplant predictor factors of QOL outcomes, however the relationship between the long-term trajectory of specific symptoms and HRQOL has not been extensively investigated. Reports of higher psychological well-being and HRQOL in individuals with non-advanced type 1 diabetes when compared to PT recipients and WL patients seem to suggest that the onset of chronic complications is really the turning point in these patients' lives.

Interestingly, the totality of the authors who have studied the association between gastrointestinal/autonomic function and HRQOL concur that the improvement of symptoms has cascade effects on subjective well-being and QOL. This represents further proof of how QOL in PT recipients is not merely determined by freedom from

insulin and dialysis, but possibly by progressive improvement of perceived diabetes complications.

On the contrary, the evidence accrued doesn't seem to suggest significant benefit of PT on sexual aspects of QOL as medications might worsen sexual function in some individuals. The lack of correlation between pre-transplant disease severity, post-operative course, length of follow up as well as and other potential confounders could prevent from an accurate depiction of this relationship. Furthermore, most of the issues highlighted by these studies don't seem to be exclusively related to transplantation of a pancreatic gland, but rather, to transplantation itself. Medications' side-effects, for example, are hardly exclusive to this procedure, as documented by Winsett and colleagues on a sample of 505 kidney, pancreas, liver, and heart recipients. Their data suggests that immunosuppressive drugs are overall well tolerated, with worse symptoms in women and in more recent transplant recipients. However, they found no statistically significant differences across transplant specialities (Winsett, Stratta et al. 2001)

A common denominator of studies addressing sexual QOL after PT is patient's complaint of inadequate pre-transplant education. This indirectly suggests some degree of uncertainty and confusion regarding expectations, and it is in keeping with the principal finding of qualitative studies: patients don't know what to expect from a "normal" life.

The themes of "normality" and "new Identity" seem to recur, perhaps for the often-perceived identity between diabetes and the individual diagnosed with it. Although recent cultural changes have pushed society towards a more conscious definition of illnesses and disabilities (e.g.: "person with a disability" vs "disabled"), patients

whose lives have been defined by type 1 diabetes are often still referred to as “diabetic”. Furthermore, they often define themselves as such. Transplantation, by breaking the bond between the disease and the individual, creates a new reality, which is, however, burdened by chronic symptoms and new concerns. Hence pre- and post- transplant specific education aimed at addressing these issues could help patients to make a smoother transition to their new life.

One of the difficulties in comparing the data reported in the studies reviewed, was the great variety of PROMs utilized. There is a clear need for a pancreas transplant specific HRQOL instrument for this group of patients. In our view, it should include a selection of items regarding diabetes, renal failure and transplantation and it should be used in correlation with clinical data. Longitudinal HRQOL data collection should become the standard of care to accrue long term information on the real impact of this intervention on our patients’ existence.

3 CHAPTER 3: PROSPECTIVE LONGITUDINAL OBSERVATIONAL STUDY ON QUALITY OF LIFE AFTER PANCREAS TRANSPLANTATION

3.1 RATIONALE

Type 1 diabetes is a metabolic disorder that can cause systemic complications. Since the introduction of exogenous insulin in clinical practice, medical management has become more refined, and patient centred. However, the percentage of children and young adults who achieve satisfactory metabolic control is still below 10% for England and Wales (Royal College of Pediatrics and Child Health, 2019). Consequently, many individuals progressively develop early cardiovascular disease as well as deterioration of their sight, renal function, sensory and neurovegetative systems.

Enhanced metabolic control greatly decreases the likelihood of chronic complications (Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al, 1993), however patients might still be burdened by hypoglycaemic crises that can be life-threatening if unheralded. Once patients reach end stage renal failure, the need for dialysis adds a further layer of complexity to their medical management and their existence.

Type one diabetes is a life changing diagnosis, but so are the therapeutic strategies developed to live with it.

Pancreas transplantation (PT) differs from exogenous insulin because it treats the underlying disease, by restoring insulin production and the contra-regulatory hormonal axis that maintains euglycemia. However, by the time patients receive

the intervention, secondary complications are often well established and may or may not improve. A pivotal manuscript on prospective longitudinal Health Related Quality of Life (HRQOL) changes, which observed patients with type 1 diabetes over 23 years, has demonstrated how both poor metabolic control and the onset of chronic complications are detrimental to patients' wellbeing (Jacobson A, 2013). Hence, pancreas transplantation is likely to have a positive impact on some aspects of QOL but not on others.

Nonetheless, clinicians have been considering HRQOL gain as one of the major outputs of pancreas transplantation all along. Many have attempted to investigate this subject, with contradictory results. This lack of homogeneity is likely multifactorial, however our own review of the literature highlights how most studies were conducted on small samples, with significant methodological limitations.

Although the intricacies inherent to this population and the lack of a specific validated HRQOL instrument make it challenging to fill this knowledge gap completely, there is a clear need for further research aimed at providing reliable information on the topic.

A deeper understanding of the impact of pancreas transplantation on HRQOL would serve multiple purposes: it would allow clinicians to better inform potential recipients ahead of surgery, manage their expectations and implement changes in service delivery. Furthermore, it could provide more reliable information regarding changes in utility scores associated with this intervention, and hence inform economic evaluation in this area.

The Oxford Transplant Centre is the ideal setting to investigate this aspect of care: approximately one third of the entire UK pancreas transplant activity takes place at this institution, one of the largest volume pancreas transplant centres worldwide. Moreover, as a University Hospital, it can rely on the multidisciplinary expertise required to obtain reliable data. Hence, in the quest to provide a significant contribution to knowledge in this field, this project was designed as a collaboration between the Oxford Transplant Centre, the University of Oxford Nuffield Department of Surgical Sciences and Nuffield Department of Population Health.

For the purpose of this research, HRQOL was defined as an extrapolation from the World Health Organization definition of health: “A state of complete physical, mental, and social well-being not merely the absence of disease.” Hence the concept was inclusive of any quality-of-life aspect directly or indirectly affected by changes in health status.

3.1.1 Objectives and Outcome Measures

The main aim of this study was to provide validated data on the progression of HRQOL up to one year after pancreas transplantation. As secondary endpoints it seemed crucial to identify predictor factors of post-transplant HRQOL, in other words to identify which were the characteristics of patients who benefit the most (and the least) from the intervention. This latter aspect seemed particularly important as it would provide supplementary information to instruct a tailored, patient-centred therapeutic approach. Further aims were to compare HRQOL, utility

scores and resource use among the different forms of pancreas transplantation and patients waiting for the intervention.

As the main objective was to assess the progression of HRQOL, the primary outcome measures were Patient Reported Outcome Measures (PROMS). Clinical data was also collected to identify potential predictor factors of post-transplant HRQOL.

In consideration of the unprecedented disruption in hospital services utilization due to Covid-19 pandemic, the initial plan to use Hospital Episode Statistics (HES) to quantify resource utilisation in this patient group no longer seemed feasible or meaningful. However, it was still possible to derive utility indices from the PROMs administered throughout the study.

A synopsis of study objectives and outcome measures is provided in **Appendix A3.1**.

3.2 METHODS

3.2.1 Summary of Study Design

Clinical benefits of pancreas transplantation and, more specifically, of simultaneous pancreas/kidney transplantation (SPK) are well established. Hence, there are significant ethical barriers to setting up randomized controlled trials. Inevitably, the design of this study was observational, however data was collected prospectively before and after transplantation.

Any adult patient, fluent in English, with insulin dependent diabetes and active on the Oxford Pancreas Transplant waiting list as of October 2018 was invited to take part in the study.

Individuals who became eligible for transplantation during the recruitment period were invited upon activation on the transplant waiting list. The pool of potential participants was, therefore, dynamic. The list was verified for new entries at least monthly.

Responders were recruited either on occasion of an outpatient appointment, or when called in for a possible transplant. They were requested to complete paper based PROMs before surgery and at pre-established relevant post-operative landmarks: 6 weeks from transplantation, when most patients have recovered from surgery; 6 months from transplantation, when most patients have resumed pre-transplant activities; and 1 year from transplantation, which represents an important psychological milestone and the turning point for incidence of organ rejection and loss (Gruessner AC, 2016). Pre-transplant PROMs were administered in person

upon consenting. After surgery, participants were contacted telephonically at each time point of data collection to verbally confirm their wish to continue with the study. Follow-up questionnaires were then sent by post, completed at home and returned with pre-stamped envelopes provided by the research team. Participants who verbally agreed to return the study PROMs but did not do so within one month, were contacted again (up to two times) and the study documents re-sent if necessary.

3.2.2 PROMs Selection

PROMs can be distinguished into two separate groups: generic health status and disease specific instruments. Most researchers now concur that both kind of tools should be considered in clinical trials (Jacobson AM and The Diabetes Control and Complications Trial Research Team, 2013).

Generic measures quantify the impact of health status on quality of life. They can be used across different populations and conditions and to compare outcomes with population norms. When applied to longitudinal research, this measure can provide insight into HRQOL changes between timepoints of data collection.

A few of these generic instruments allow calculation of preference-based health indexes, which are essential for health economics evaluations.

Disease specific questionnaires represent the other main category of PROMs.

Once the use of generic HRQOL instruments became widespread, researchers and clinicians realised how different conditions were associated with different concerns (Wood-Dauphinee, 1999). Indeed, most chronic diseases have their own footprint

of HRQOL determinants. These factors can in turn be affected by multiple variables, such as medical interventions, time, comorbidities, disease progression to mention a few. Generic instruments would not necessarily capture these changes, hence the need for disease specific PROMs.

A recent scoping review of PROMs in transplantation has highlighted the existence of at least 51 organ-specific instruments and 43 transplant specific questionnaires (Shahabeddin Parizi, Krabbe et al. 2019).

One of the most striking findings of our own systematic review was the absence of a specific validated PROM for pancreas transplant recipients, despite the well-recognized need for such an instrument. Remarkably, but perhaps not surprisingly, a wide array of different tools has been used for this purpose throughout the decades.

Many researchers opted for a combination of PROMs to capture generic and disease specific aspects of HRQOL. Others, perhaps grasping the complexity of the task, opted for “simple” and reliable generic instruments, such as the Short Form 36.

The main obstacle to selecting (and probably to developing) an adequate tool for these patients is the multifaceted nature of their disease. Over two thirds of pancreas transplant candidates have end-stage renal failure and possibly other long-term complications of diabetes. Thus, life quality is inevitably subjected to the burden of diabetes, diabetes complications and renal failure. After transplantation new concerns and clinical changes may arise, in relation to surgery and antirejection therapies. Ideally HRQOL would be best captured by an instrument capable of

encompassing all these aspects, however the potential length of such a tool might not be acceptable, especially for long term studies.

When choosing PROMs for this research, a few key factors were considered. First, they had to be validated and present good psychometric properties. Secondly, because the prospective design and the study's size would likely yield significant results, a broader investigation seemed worthwhile. Thirdly, participant's involvement was limited to one year, hence the risk of sample attrition seemed relatively low, regardless of the length of the instruments chosen.

For these reasons, it was decided to use a combination of generic and disease specific instruments (**Table 2**), designed to accrue information regarding participants' health status, but also aspect of QOL affected by diabetes and renal failure, when appropriate. A copy of each Study PROM can be found in the Appendix **(A3.3-A3.4-A3.5-A3.6)**

Table 2 Study PROMs.

STUDY PROMS	
DQOL (Diabetes Control and Complications Trial Research Group 1988)	Diabetes Quality of Life Measure
KDQOL-SF™ (Hays, Kallich et al. 1994)	Kidney Disease Quality of Life Short Form
SF-12 v2 (Ware, Kosinski et al. 2009)	12-Item Short Form Survey Instrument v.2
EQ-5D-5L® + EQ-VAS (Devlin and Brooks 2017)	EuroQol Five Dimensions Questionnaire Visual Analogue Scale

- Diabetes Quality of Life Measure (DQOL)[1]

The most widespread diabetes specific questionnaire is one of the oldest available. The DQOL questionnaire was developed in 1988 to investigate HRQOL within the Diabetes Control and Complications Trial (DCCT) arms. It was designed to discriminate between patients following standard or intensive insulin treatment. However, as asserted by the developers, its properties made it equally applicable to other categories of patients with diabetes and for change in therapy, such as in the case of pancreatic transplantation (Jacobson AM and The Diabetes Control and Complications Trial Research Team, 2013; Nathan DM et al., 1991).

The adult DQOL includes 46 core items forming three scales targeted at specific diabetes-related areas: satisfaction with treatment, impact of treatment, worry (about future effects of diabetes and about social/vocational issues). The instrument also includes a generic/well-being item, which is not included in the global DQOL score (**Appendix A3.3**).

Each of the 46 items has 5 possible responses on a 5-point Likert scale ranging from 1 (best) to 5 (worst). Outcomes are then reverse scored and transformed into a 100-point scale, where 0 represents the lowest possible QOL and 100 the highest.

In case of missing responses, raw scores ranges are calculated on the number of responses provided. For each or the four subscales predefined numbers of missing responses are considered acceptable (2 for the Diabetes and Social Worry subscales, 3 for the Satisfaction subscale and 4 for the Impact subscale). Beyond these, authors suggest not calculating the subscale at all.

With regards to longitudinal analysis, a global DQOL difference of 5 points was considered a relevant HRQOL change within the DCCT trial (Jacobson A, 2013).

Albeit quite old, this instrument offers a few advantages relevant to our study: versatility, ability to discern between different therapeutic approaches to diabetes, and reliability.

It's psychometric characteristics of reproducibility, internal consistency, acceptability, responsiveness and high content and construct validity, make it rank it amongst the most suitable instruments to capture QoL in diabetic patients (Gibbons E and Fitzpatrick R, 2009).

- Kidney Disease Quality of Life Short Form (KDQOL-SFTM, v 1.3)[2]

This instrument is the most frequently used to evaluate renal-related QOL in SPK recipients and the most adopted disease specific PROM in transplantation (Shahabeddin Parizi, Krabbe et al. 2019).

It was developed for the RAND corporation in 1995 as a shorter version of the Kidney Disease Quality of Life instrument-KDQOL, considered too lengthy for routine clinical practice. Despite this, it is still a relatively long questionnaire made of a combination of 80 distinct items and scales. Perhaps its most attractive feature is that it embeds a disease specific and a generic tool (SF-36^{TM}), allowing for both longitudinal follow up and comparison with other conditions and population norms.

Disease specific items are organised in 9 renal scales, for a total of 38 items, and 3 QOL scales, for a total of 5 items. The 36 generic items are subdivided in 8 scales measuring physical and mental health status. One additional generic scale allows

responders to rate their overall health. A summary of KDQOL-SF™ is provided in **Appendix A3.2.**

Participants score items on a Likert scale. Each possible response corresponds to a pre-coded numeric value. Raw results get transformed into a 0-100 scale, where 0 is the worst possible and 100 the best possible outcome. After the exclusion of missing data, items within the same scale get averaged to calculate the scale scores. Both physical and mental health scales can be scored as Component Scores: “PCS” and “MCS”.

In terms of psychometric properties, KDQOL-SF™ ranks amongst the most reliable for patients with renal failure, with adequate/high internal consistency for the great majority of items (Gibbons E, 2010).

- SF-12v2® [3]

This instrument is a shortened questionnaire derived from the SF-36® by means of regression analysis, and it is associated with high response rates within the renal population. Like SF-36®, the SF-12® allows for calculation of Component Summary Scores, both physical (PCS) and mental (MCS). This instrument was administered as an alternative to KDQOL-SF™ for those with preserved renal function.

- EQ-5D-5L® [4]

EQ-5D-5L® belongs to a group of preference-based measures designed by EuroQoL to evaluate generic HRQOL and derive utility indexes.

It encompasses a descriptive part, made of 5 health status dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression), and a visual

analogue scale (EQ-VAS). The descriptive part can be used to derive health status profiles to which preference scores can be attached: these are numerical representations of the value that society attaches to a specific health condition. The VAS allows patients to quantitatively score their perceived health in a range between 0 (worst imaginable) and 100 (best imaginable).

For each of the 5 descriptive dimensions, responders have a choice of 5 possible levels of severity (1 no problems, 2 slight problems, 3 moderate problems, 4 severe problems, and 5 extreme problems)

The combination of the 5 responses within the 5 dimensions corresponds to a final 5-digit code which is not to be intended as an arithmetic number but rather depicts a specific “health profile” for a total 3125 possible combinations (**Figure 1**).

Moreover, responses can be used to compute a single health index (EQ- index) – the preference or utility score. This is the instrument of choice recommended by the National Institute for Health and Care Excellence (NICE) for economic evaluations of interventions: utility scores can, in fact, be used to calculate Quality Adjusted Life Years (QALY), the building blocks for economic evaluation In the United Kingdom.

VAS scores and EQ-5D indexes can be presented as measures of central tendency and are therefore suitable for longitudinal analysis.

There is evidence in the literature of poor/moderate correlation between SF-36 and similar Short Forms and EQ-5D and its derivates in renal patients (Gerard K et al, 2004; Kularatna S et al, 2019). Although mapping algorithms between KDQOL™ and EQ-5D-5L® have been developed (Yang F, 2019), the latter is a short

instrument, unlikely to increase responder's burden. Hence it was decided to add this instrument to the study portfolio.

EQ-indexes can be calculated with validated value sets, country specific. However, the UK value-set, funded by the National Institute for Health Research's Policy Research Programme and published in 2017 (Devlin NJ, et al. , 2017), has been deemed unsuitable: the most recent NICE recommendations require estimating EQ-indexes by mapping the 5L descriptive data onto the previous version's (EQ-5D-3L®) dataset for tariffs.

The mapping function utilised in this study is the one developed in 2017 by NICE's Decision Support Unit- University of Sheffield- and applied to a dataset collected for this purpose from six countries (Denmark, England, Italy, the Netherlands, Poland and Scotland) under the guidance of Euroqol (Hernández, Wailoo et al. 2012).

In the absence of approved UK normative values for EQ-5D-5L, other populations were used as a reference (Garcia-Gordillo MA et al, 2016; Alberta PROMs & EQ-5D Research & Support Unit (APERSU), 2018; Grochtdreis T et al, 2019 ; Jensen MB et al, 2021). Whenever feasible, results were compared to the neighbouring and possibly similar Irish normative data stratified by age (Hobbins, Barry et al. 2018)

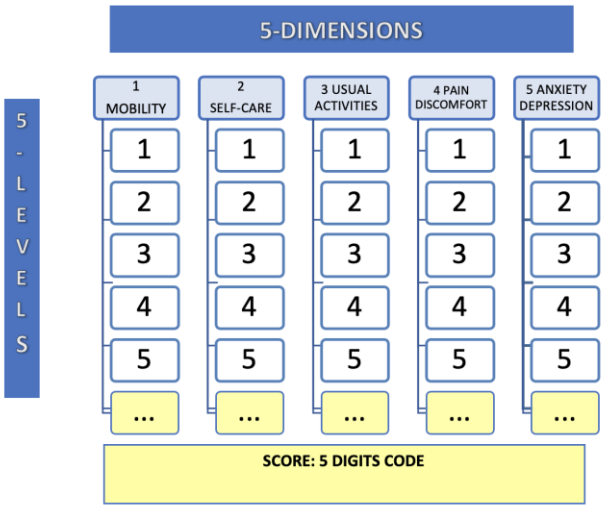


Figure 1 EQ-5D-5L® Diagram of Scoring System

3.2.3 Clinical Data

Pre-operative information seemed of paramount importance to identify potential predictors of HRQOL changes. Would it be people with few if any complications who thrived the most after surgery or perhaps individuals whose entire life had been devastated by the disease? In other words, is the timing of pancreas transplantation in relation to major diabetic complications relevant to HRQOL? According to Jacobson and colleagues, in patients with diabetes, the onset of complications and poor metabolic control are associated with worsening of HRQOL (Jacobson A, 2013). However, there might be other issues impacting on one's perceptions of HRQOL after transplantation, for example ridding oneself of the illness responsible for a challenging existence. Hence pre-transplantation clinical data was collected meticulously from departmental pre-transplant assessment forms, patient's clerking upon admission, electronic patient records, case-notes and directly from participants.

3.2.4 Statistical Analysis

Data was collected in a Microsoft Excel workbook and imported to IBM-SPSS. PROM results, except for Health Statuses obtained with EQ-5D-5L, were expressed as continuous variables. Most potential predictors were recoded into binary variables whenever feasible, in consideration of the small study population.

Descriptive statistics were calculated for all the continuous variables. Confidence interval for means was 95%. Distribution of scores was tested for normality according to Kolmogorov-Smirnov and Shapiro-Wilks. Further information on the distribution of values was obtained by analysing skewness. Results were visualized as boxplots/whiskers and histograms. Frequencies were calculated for all categorical variables and Pearson's Chi-square statistics were used to compare outcomes. Whenever variables had more than 20% of data with a frequency of 5 or less, Fisher exact test was used instead.

Dependent t-test allowed longitudinal pairwise comparison between normally distributed continuous HRQOL at baseline and at each post-operative time-point. Wilcoxon Signed Ranked Test was utilized for non-normally distributed variables. Results were recorded in terms of t and z statistics. A two tailed significance level of 0.05 was considered appropriate for this study. The longitudinal trajectory of HRQOL variables across all timepoint of data collection was investigated by means of one-way ANOVA and Friedman test, as a non-parametric alternative. Moreover, variability in the data was modelled by means of linear mixed models with "time-points of data collection" as fixed variable and each PROM outcome as dependent

variable. This allowed to account for random effects of sampling and to maximise the pool of responses analysed.

Potential predictor factors were identified by univariate analysis. Independent t-test and Mann Whitney U test were used to explore the relationship between binary independent variables and continuous HRQOL outcomes. Whenever the potential predictor was a continuous variable, correlations with HRQOL outcomes were explored with Pearson coefficient or Spearman's RHO, based on normality outcomes. Effect size was calculated to assess the magnitude of the relationship between variables and longitudinal changes within HRQOL scales. Cohen's d was generally used as a measure of effect size. Commonly adopted measures of effect size are reported in **Appendix A3.7**

3.2.5 Impact of Covid-19 on chosen methods

This study started in October 2018, hence the effects of Covid pandemic were manifold. Firstly, pancreas transplantation at our centre was halted from 13/3/2020 to 15/08/2020. Secondly, non-Covid related research at the University of Oxford was stopped with a contingency plan. Permission to resume this study was granted on 26/10/2020. Moreover, outpatient appointments were switched to remote visits whenever feasible, reducing the availability of blood tests results at the pre-established time points of data collection of this study.

- Recruitment

In the context of the time restrictions of a DPhil, no further recruitment occurred when research was restarted. The final number of participants was below the initial expectations.

- Return Rates

At the beginning of March 2020, as other countries were implementing regional or national lockdowns, I made the decision to post questionnaires for participants who were due data collection up to July 2020 ahead of time. Hence, despite research being subsequently halted for many months, it was still possible to collect some HRQOL data. Equally, when research resumed in October, participants who had reached one year mark up to three months before and verbally agreed to continue with the study, were sent the last set of PROMs. This seemed inappropriate the for the time-points based on a shorter follow-up, hence participants who reached “six weeks” and “six-months” from July to October 2020 did not receive the relative questionnaires.

- Clinical Data

The pandemic disrupted the frequency of regular post-transplant outpatient appointments. This resulted in a decreased availability of blood test results and clinical information at the exact time point of data collection. To overcome this, I monitored the schedule of outpatient appointments and collected clinical data from the closest patient’s encounter available.

Footnotes

[1] DQOL was provided by Mapi Research Trust.

[2]KDQOL-SF™, V 1.3 was used with permission from the RAND Corporation. Copyright © the RAND Corporation. Ran’s permission is not an endorsement of the products, services, or other uses in which the survey appears or is applied.

[3]SF-12v2®, was used under a licence agreement with OPTUM™ (Licence Number QM044513). Permission is not an endorsement of the products, services, or other uses in which the survey appears or is applied.

[4]EQ-5D-5L was licensed by EuroQol Research Foundation and utilised as specified in EQ-5D-5L User Guide v. 0.3 © EuroQol Research Foundation 2019.]

3.3 OUTCOMES

3.3.1 Recruitment

The study commenced on 8-10-2018 and finished on 07-10-2021, as initially planned. Recruitment began on 4-11-2018 and ended in March 2020 when pancreas transplantation and all non-Covid research were suspended due to Covid-19 pandemic. Permission to restart research was granted in October 2020. No further recruitment took place, however a proportion of participants who had been recruited prior to this hiatus received the transplant afterwards. The initial estimated population size was 110 participants, based on an average of 75 pancreas transplants per year performed at this institution up to October 2018. During the 16 months of recruitment, 69 patients received the intervention, for an average of 52 patients per year. A total of 80 individuals agreed to take part to the study. One person withdrew consent almost immediately, 62 participants were transplanted within the study period and 17 remained on the waiting-list (**Figure 2**). Of the 62 recipients, 57 completed the study, 1 person died at 11 months from surgery and the others were at an earlier stage of follow-up. Hence, the study population was of 62, 61, 61 and 57 individuals at baseline, 6 weeks, 6 months and one year from transplantation respectively.

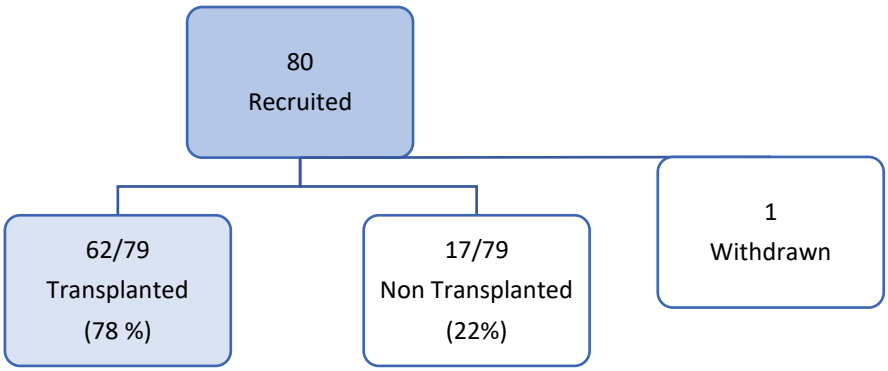


Figure 2 Recruitment Diagram

3.3.2 Return Rates

Baseline return rates were within the desired target (95%). In a few instances, patients who were recruited during the transplant admission, didn't have adequate time to complete all the questionnaires before going to theatre. Hence return rates at baseline did not reach 100%. When stratified for type of PROMs, there was no statistically significant difference at each time point of data collection (**Table 3).**

In contrast, there were inconsistencies in return rates across timepoints (i.e., within the same analysis). The lowest return rates were observed 6 months from transplantation, when less than 50% of participants returned the study questionnaires. This prompted a further sub-analysis to understand if there was a difference in each time points return rates before and after the first "lockdown" (**Table 4)**

Table 3. PROMS return rates stratified by type of PROM.

PROMS RETURN RATES								
	DQOL		**KDQOL+SF12 v2**		**EQ 5D-5L**		**VAS**	
	N	%	N	%	N	%	N	%
Pre-operative	57	92%	56	90%	54	87%	53	85%
1st post-operative	33	54%	33	61%	34	56%	32	52%
2nd post-operative	29	48%	28	46%	29	57%	26	43%
3rd post-operative	40	70%	41	72%	42	74%	40	70%

Results are not significant at $p<0.01$.

Table 4 Breakdown of Return Rates: percentage of participants reaching each time point before in relation to Covid-19 pandemic.

RETURN RATES AND COVID-19 PANDEMIC					
	Before 1/03/2020	**March to July 2020**	**July to October 2020**	**October 2020 onwards**	**TOTAL**
Transplanted Participants who reached 6/52 timepoint	(46/61) 75%	(11/61) 18%	0	(4/61) 7%	61 eligible participants
Return Rates	(31/46) 67%	(3/11) 27%	0	0	(34/61) 56%

	Before 1/03/2020	**March to July 2020**	**July to October 2020**	**October 2020 onwards**	**TOTAL**
Transplanted Participants who reached 6/12 timepoint	(32/61) 52%	(14/61) 23%	(9/61) 15%	(6/61) 10%	61 eligible participants
Return Rates	(24/32) 75%	(5/14) 36%	(1/9) * 11%	0	(30/61) 49%

	Before 1/03/2020	**March to July 2020**	**July to October 2020**	**October 2020 onwards**	**TOTAL**
Transplanted Participants who reached 1 yr. timepoint	(12/57) 21%	(12/57) 21%	(13/57) 23%	(20/57) 35%	57 eligible participants
Return Rates	(10/12) 83%	(9/12) 75%	(11/13) 85%	(11/20) 55%	(44/57) 77%

*One participant spontaneously returned a set of questionnaires he had received at six weeks from transplant (before the onset of the pandemic).

Indeed, return rates at six weeks from transplantation dropped from 67% to 27% from March 2020 and from 75% to 36% for the 6 months timepoint. It is important to underline how patients who reached these two “ad interim” timepoints from July to October never received the corresponding questionnaires.

On the contrary, by the time the great majority of participants had reached the one-year mark, research had resumed. And in fact, return rates at one year had the smallest inflection: from 83% to 76%. Moreover, 12 participants who finished the

study during lockdown, returned the questionnaires later, but did return them within 1-5 months (21%).

Approximately 40% of participants returned all PROMs at all 4 time-points (25 patients: “total-responders”), while one person did not return any (2%), as shown in Appendix **A3.8**. The quota of “full-completers” for KDQOL was smaller (20), because it was not administered to participants without renal failure.

When focusing on post-operative return rates, the proportion of individuals who didn’t return any survey was nearly 23% (14 patients: “non-responders”). As previously stated, patients who reached the 6 weeks and 6 months timepoint from July to October 2020, did not receive the relative questionnaires. Henceforth, the effect of the pandemic added a degree of randomization to post-operative PROMs collection. Regardless, data was analysed to identify potential factors influencing compliance with the study.

Early return to insulin seemed to impact negatively on response rates: none of the participants who had lost pancreatic function in the first few weeks after transplant belonged to the group of “total-responders” ($\chi^2 = 5.262$, $p = .030$, Fisher’s exact test). Moreover, the only statistically significant difference between “non-responders” and the rest of the sample was insulin-independence at one year (Fisher exact test = .009). The paucity of HRQOL data on this sub-group is simultaneously the cause and effect of our inability to comment regarding possible causes.

Poor compliance with the study could derive from difficulties in coping with pancreatic graft loss, or from poor physical conditions. However, it could be due to a degree of reluctance of researchers to approach participants after graft

pancreatectomy or the loss of face validity of the PROMS in the context of a dramatic post-operative course.

Regardless, for the sake of our data analysis, it is relevant to assume that HRQOL results are skewed towards participants with a functioning pancreas graft.

3.3.3 Clinical DATA

- Pre-operative baseline patient characteristics.

Descriptive, clinical and HRQOL data was analysed for pre-operative differences between transplanted and not transplanted individuals, as displayed in **Appendix A3.9.**

Overall, the two cohorts were quite similar, with a few differences in ethnicity, history of cigarette smoking, frequency of hypoglycaemic crisis, number of comorbidities and sexual function, albeit at least 40% of not-transplanted responders did not disclose this information.

Of the 62 transplanted participants, female to male ratio was 1. The mean age at transplantation was 43.19 (± 9.06) years and approximately 80% of the sample was Caucasian. The second most prevalent ethnicity was Black, which represented 10% of the study population. Participants' average BMI was within the healthy spectrum.

Approximately 20% of participants were smokers, 27% ex-smokers and more than 50% had never smoked. Regarding alcohol consumption, slightly fewer people were teetotal than were social drinkers. In 8% of cases this information was not disclosed.

Working status fell essentially into two main categories: individuals unable to work due to poor health and full-time workers, that is individuals with a paid job and house-workers. Part-time workers represented 5% of the sample and two people were unemployed by choice. The remaining 8% of the sample included other conditions such as full-time students, carers, and retired individuals.

DM type 1 (98%) was diagnosed at approximately 15.5 (± 9.4) years of age. The mean duration of the disease was 27.93 (± 10.05) years, with a coefficient of variation of 0.36. Insulin requirement ranged from 2 to 110 daily units, for an average of 42.35 (± 17.46) units. The mean time on the waiting list was 464 (± 248) days. Mean sensitisation expressed as Calculated Reaction Frequency (CRF) was 32.9 (± 30.2).

The great majority of patients were at their first transplant Ice (87%) and in need of both a pancreas and a kidney transplant (89%). Of these individuals undergoing SPK, 22% were transplanted pre-emptively, while the great majority were already on either Haemodialysis (53%) or Peritoneal Dialysis (25%). The mean duration of dialysis before transplantation was 617.6 (± 350.9) days.

Patients who received the sole pancreas transplant (11%) were either patients who had previously received a kidney transplant (or a pancreas/kidney transplant with subsequent loss of pancreatic function/graft) or patients who had preserved native renal function but suffered from life threatening hypoglycaemia unawareness. This latter category – which differs from the others for transplant indications – represented 3% of the entire study population. With regards to diabetes complications, a small proportion of patients had a history of ischaemic heart disease or previous cardiovascular events such as Myocardial Infarction or Stroke

(7%). Claudication and amputation were relatively less frequent (6 and 15%, respectively).

Retinopathy, on the contrary, was present in more than 90% of patients, with 13% of individuals registered blind. Many patients presented some degree of neuropathy (53%) or gastrointestinal/autonomic symptoms (39%).

Brittle diabetes with hypoglycaemic spells was present in approximately 50% of the cases, however only 22 (35.5%) of participants suffered from hypoglycaemia unawareness, with no statistical correlation across transplant categories.

The mean number of chronic complication pro capita was 3.6 ± 1.34. Overall, 79% of the sample had three or more chronic complications, while the remaining 21% one to two. A large proportion of patients suffered from other comorbidities (87%). With a few exceptions, most patients required antihypertensive medications and nearly one half of the sample had either history of a psychiatric illness and/or was on treatment for common mental disorders (CMD).

A summary of participants characteristics can be found in **Appendix A3.9**

- Transplant Data

Over two thirds of organs were from donation after brainstem death (DBD). The average donor's age was 32.71 (± 13.35) and a slightly higher proportion of donors was of female biological gender (53%).

Pancreas allografts were implanted with a systemic venous drainage and all but three received an enteric exocrine reconstruction. Out of 62 transplanted participants, 6.5% had received a forearm vascularised donor skin flap (a technique used for immunological monitoring).

Surgery was uneventful for 77% patients, while in 23% of cases intraoperative issues arose. Nearly 75% of recipients received at least one blood transfusion during their transplant admission. The mean ITU stay was 1.96 (± 2.26) days, while the overall duration of hospital stay was 20.13 (± 32.09) days.

A summary of the main transplant variables is provided in **Appendix A3.10**

- Early Post-operative course.

Almost 70% of patients required at least one abdominal CT angiogram after surgery and in about 25% of cases no significant complication was identified (**Appendix A3.11-A3.12**). Intra-abdominal fluid collections were the most frequent pathological CT finding (39%). Approximately 13% of patients developed radiological evidence of post-operative pancreatitis. Partial pancreatic venous thrombosis was present in 29.3% of CT angiograms, while there was complete lack of perfusion in 4.9% of cases (3.2% of the study population). Vascular complications were less frequent in kidney allografts, with generalised hypoperfusion or focal areas of infarction being present in 19% of the scans. Bowel anastomotic leak occurred in 2.1% of patients.

Post-operative morbidity was relatively high, with nearly 66% of individuals experiencing a complicated post-operative course. Medical and surgical complications occurred in similar proportions, approximately 43% of cases.

Urological problems, including urinary retention and early ureteric strictures, occurred in 5% of the sample.

About 61% of the surgical complications required some form of intervention (endoscopic, radiological, or surgical) and were life-threatening in 10% of cases (**Appendix: A3.13**).

Overall, 25% of study participants required further surgical intervention and a small proportion returned to theatre multiple times (6.5%). Radiological procedures were the treatment of choice in 5% of cases.

Intra-abdominal collections, due to graft pancreatitis, and post-operative bleeding were the main reasons for further surgery (60%), as shown in **Figure 3.**

The second most frequent reason for reintervention (19%) was complications of the donor's sentinel skin flap: 75% of skin flap recipients received further surgery for localised complications, resulting in skin flap removal in two out of four cases.

Early post-operative graft pancreatectomy was necessary for two patients, while no graft nephrectomy was performed.

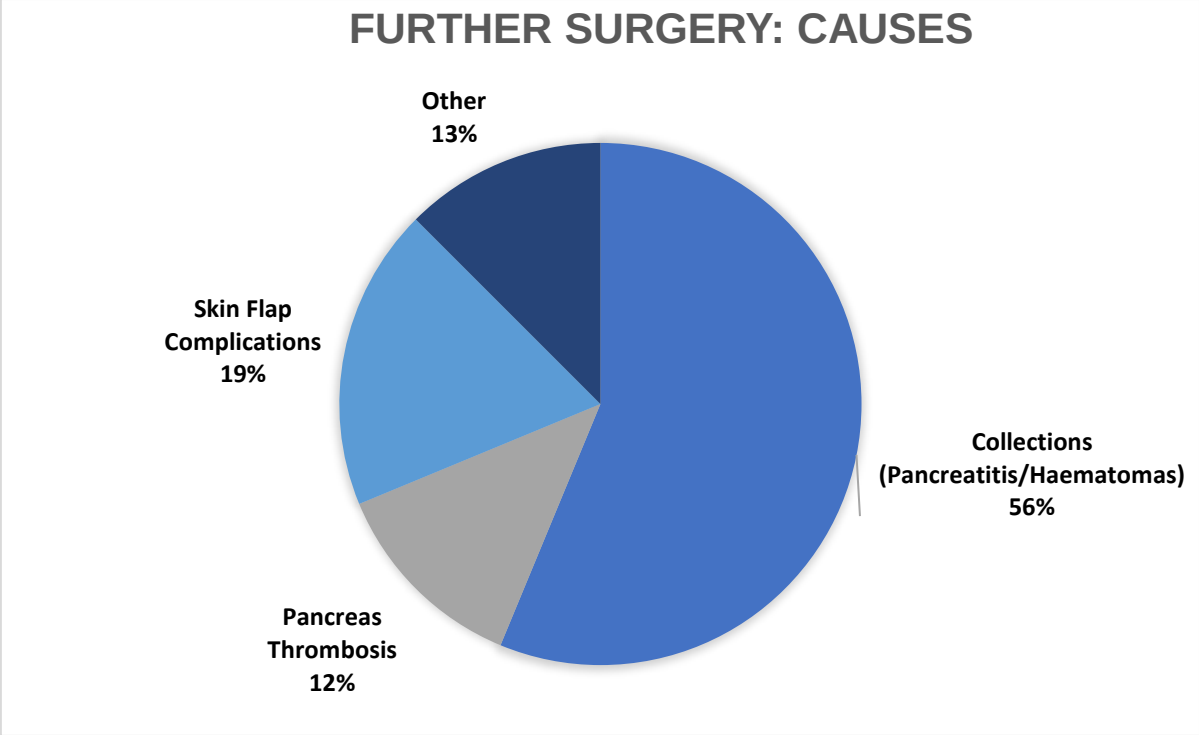


Figure 3 Early Return to Theatre: causes

The pancreatic graft had “primary function” (PF) in most of the cases (95%) and no “primary non-function” (PNF, organ never functioning) occurred (data censored for graft pancreatectomy). Approximately one fourth of kidney grafts had “delayed graft function” (DGF) and one patient (2%) experienced PNF. Two patients were empirically treated for possible pancreas and kidney rejection.

Patients were discharged with a functioning pancreas (93.5%) and kidney (96.7%). A little over half the patients responded well to glucose tolerance tests, while 30% of patients had pathological/sub-optimal results. In 20% of cases no test was performed during the admission. Mean creatinine level was 162 (± 132.27) umol/L and values of haemoglobin ranged from 67 to 112 g/L, with an average of 86.29 (± 11.42).

A summary of post-operative data and main post-operative blood results is provided in **Appendices A3.14-A3.15**

- Six weeks from Transplantation

At six weeks from transplantation all participants were alive. Pancreas and renal function were preserved (i.e., patients independent of insulin and dialysis) in 89.8% and 93.2% of patients, respectively.

Approximately 8% of participants were still inpatients, with one additional graft pancreatectomy having been performed, bringing the total to 3 (5%).

The percentage of surgical complications declined to 14.5% and further surgery or IR procedures occurred in 3.2 % of the cases. Medical complication rates fell less sharply to approximately 23%.

Mean glycated haemoglobin levels were normal (HbA1c < 42 mmol/mol or 6%) and renal function continued to improve for most, with an average creatinine level of 108 (± 34.77) umol/L. One patient was treated for kidney rejection.

- Six months from Transplantation

At six months from transplantation all participants were alive. Pancreas and renal function were preserved in 86% and 90.7% of patients, respectively. Two more patients had undergone graft pancreatectomy, bringing the total to 5 (8%). No graft nephrectomy had been performed. As per protocol, post-operative clinical data was primarily collected on occasion of outpatients' appointment and sourced from electronic patient records. However, at the height of the pandemic, outpatient appointments were switched to remote consultations whenever possible. For this

reason, six months blood test results and detailed information on pancreas and kidney function were missing for approximately 35% of participants.

Known complication rates was 43%. Available data is suggestive of higher prevalence of medical problems (41.9%) as compared to surgical (11.3%) complications. One patient was treated for kidney transplant rejection and one for likely concordant rejection of both allografts. Glycated haemoglobin and creatinine mean levels were 5.103% (± 0.4231) and 121.84 (± 99.7) umol/L.

- One year from Transplantation

At one year from transplantation patient survival was 98.4%. One person died a few months after graft pancreatectomy and loss of kidney function to rejection, with a Covid 19 positive test. After a protracted and complex course, this patient had requested withdrawal of treatment.

Pancreas and renal function were preserved in 84% and 90.7% of participants, respectively. No further graft pancreatectomies occurred, but one patient returned to insulin for rejection. No graft nephrectomy was performed. The mean glycated haemoglobin level was 5.358% (± 0.9784), while the average creatinine was 112.93 (± 38.737)

- Summary

In summary, during the study period patient survival was 98.4%, while pancreatic and renal graft survival was 84% and 90.7%, respectively. All pancreases had primary function, while almost 25% of renal allografts had delayed graft function

and, in one case, primary non-function. Graft pancreatectomy was necessary for 5 patients (8%). No renal graft was explanted during the study period.

Over 91% of patients experienced some degree of complications. As expected, surgical complications were highest in the early post-operative course, dropped by six weeks from surgery and were nearly absent by one year. In contrast the rate of decrease in medical issues was less pronounced. By the end of the study approximately 73% of participants had developed some medical problem.

Figure 4 illustrates the trajectory of complications within the first year from transplantation, stratified by type.

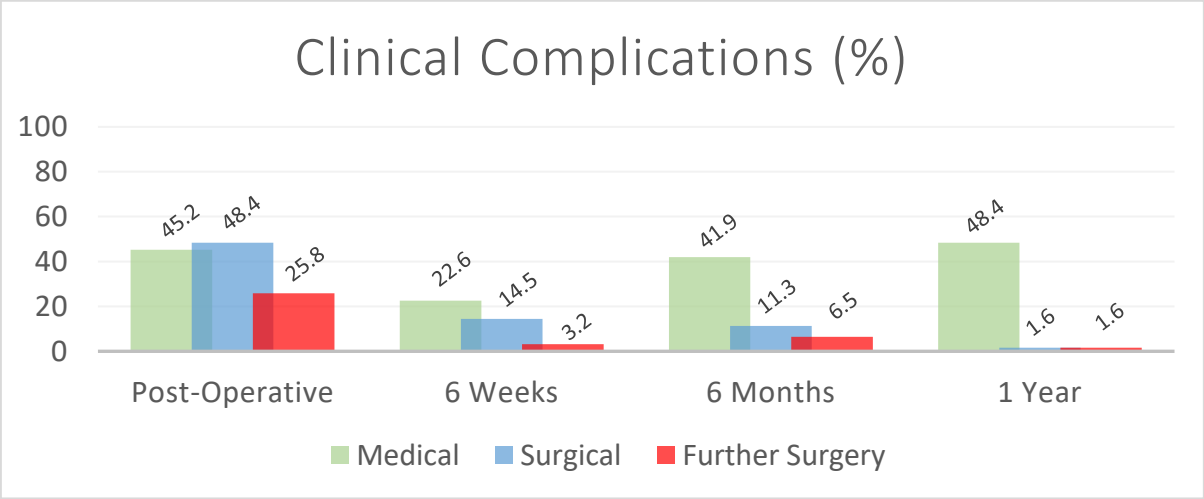


Figure 4 Complications' distribution during the first-year post-surgery.

3.3.4 Patient Reported Outcomes

For each time point, individual scales and summary scores were analysed and compared to pre-transplant outcomes. Equally, the trajectory of EQ-indexes before and up to one year after transplantation was defined.

Longitudinal analysis clarified which changes occurred relatively early, which became relevant at a later date, and which were sustained in time.

Effect sizes were used as a marker of importance to rank which aspect of HRQOL had improved the most/least at each timepoint of data collection.

In addition, SF-36 and EQ-5D-5L results were compared against population norms.

The compromise in sample size imposed by Covid-19 interfered with a few secondary objectives: firstly, it was not possible to stratify HRQOL based on the kind of pancreas transplant received (SPK, PTA, PAK, PASPK), due to the very low numbers of non-SPK transplants. Equally, the predictive value of pre- and post-transplant variables with a low frequency was unattainable. Hence there are aspects of HRQOL conceptually important or that had been found relevant by previous research (Mosca I, et al, 2019) - such as limb amputation, previous stroke/MI, or transplant pancreatectomy, to mention a few - that don't reach the threshold for statistical analysis, let alone significance.

With this relevant limitation, it was still possible to identify several predictor factors of HRQOL before and after transplantation.

- Pre-operative data

Disease Specific Quality of Life

Results of the KDQOL-SF™ can be presented into three summary scales: a renal Summary Scale (KDQOL), a Physical Component Summary Scale (PCS) and a Mental Component Summary Scale (MCS). In addition, the questionnaire includes a single item to rate perceived overall health ("Overall health" rating).

Once raw data is transformed, values are expressed from 0 - (lowest possible) to 100 (highest possible).

Renal QOL results are presented within the "disease specific QOL" paragraph, while PCS, MCS and "Overall Health" outcomes are presented further down, when describing generic HRQOL findings.

DQOL includes three scales that determine a global diabetes related HRQOL outcome: Satisfaction, Impact and Worry. Data is scored on a 5-point Likert scale and processed to cover a range from 0 (worse possible outcome) to 100 (best possible outcome). The questionnaire also includes a single item designed to enquire about general health, scored in the same way, described with the other generic health PROMs.

Renal QOL

Before transplantation the global KDQOL mean score was 56.40 ± 12.55.

Participants showed a high degree of satisfaction with their dialysis care, social support, and well-preserved cognitive function, while the most troublesome areas were “burden” of kidney disease, “employment status” and “ability to work”.

Just about 25% of responders declared themselves as sexually active. Hence, “sexual function” scores were disregarded, as they were not representative of the whole sample. Pre-transplantation KDQOL-SF^{TM} scores are reported in **Table 5**

Table 5 KDQOL-SF:TM pre-transplant scores

BASELINE KDQOL-SF™					
	Scale	Mean	Median	Stan. Dev.	n
RENAL SCALES	Symptom/problem list	62.62	61.36	17.73	51
	Effects of kidney disease	46.08	46.88	22.98	51
	Burden of kidney disease	20.34	12.50	23.48	51
	Work status	31.37	0.00	42.38	51
	Cognitive function	67.97	66.67	23.47	51
	Quality of social interaction	64.25	66.67	20.75	51
	Sexual function	71.15	62.50	21.28	13
	Sleep	52.60	52.50	24.44	51
	Social support	66.01	66.67	26.24	51
	Dialysis staff encouragement	79.38	75.00	19.52	40
GENERIC SCALES	Patient satisfaction	78.03	83.33	19.94	44
	Physical functioning	42.83	45.00	24.85	51
	Role limitations-physical	23.53	0.00	35.15	51
	Pain	54.71	55.00	27.60	51
	General health	23.63	20.00	18.87	51
	Emotional well-being	56.45	60.00	22.91	51
	Role limitations--emotional	63.33	66.67	40.55	50
	Social function	42.89	37.50	31.15	51
	Energy/fatigue	27.29	20.00	22.18	51
	Overall health rating	**35.49**	**40.00**	**19.63**	**51**
SUMMARY SCALES	**KDQOL**	**56.40**	**54.35**	**12.55**	**51**
	PCS	**31.82**	**30.03**	**9.74**	**44**
	MCS	**41.41**	**39.63**	**12.34**	**44**

Diabetes QOL

Although it is not possible to compare our study to the DCCT trial, it was useful to review such data to provide some context to our own findings.

Both arms of the DCCT trial consisted of individuals with a mean age of 27 ± 0.3 years, with a relatively short history of type 1 diabetes and little if any chronic complications. Results from this controlled group can be interpreted as overall diabetes related HRQOL before the onset of chronic complications. Baseline mean scores for both arms of the study were identical, with a global DQOL rating of 78 ± 8 and no obvious difference amongst the individual scales.

Participants to our study were older, with a long history of diabetes and an average of three/four chronic complications each: their diabetes related QOL was far from findings of the DCCT trial.

Global DQOL was 51.74 ± 16.38. Impact, Worry and Satisfaction Scales scores were 53.15 ± 18.32, 49.64 ± 24.49 and 49.03 ± 17.48 respectively. The difference among the scales was not statistically significant: overall, all aspects of living with diabetes were equally burdensome before transplantation.

Pre-transplantation Diabetes-QOL scores are reported in **Table 6**

Table 6 DQOL: Pre-Transplant Scores

BASELINE DQOL				
Scale	Mean	Median	Stan. Dev.	n
Satisfaction	49.03	45.00	17.48	54
Impact	53.15	52.50	18.32	55
Worry	49.64	45.45	24.49	52
TOTAL DQOL	51.73	49.33	16.38	56
Generic Health Item	12.24	.	10.85	49

Generic Health Related Quality of Life

SF-36

Generic HRQOL outcomes were even lower: baseline PCS and MCS mean values were 31.82 ± 9.74 and 41.41 ± 12.34 respectively. In this scenario of overall low HRQOL results, there seemed to be a dichotomy between scales related to physical and mental wellbeing. Indeed, the scales with the lowest mean values were “Physical Role Limitations”, “Energy/Fatigue” and “General Health”. On the contrary, scales such as “Emotional Role Limitations”, and “Satisfaction” scored the highest.

EQ-5D-5L Health States

Looking at Health Status distribution, just 3% of responders had no problems in any of the five dimensions; this compared quite poorly with findings from the general population “Health Survey for England 2018”, in which over 40% of adults and 20% of senior citizens (older than 75 years) had the best possible health status (1-1-1-1-1) (Lifestyles Team, NHS Digital, 2019).

In consideration of the small sample size, data collected across the 5 Levels of severity was dichotomized into “no or slight problems” (levels 1-2) and “moderate/severe/extreme problems” (levels 3-4-5), in a bid to increase the likelihood of statistically meaningful outcomes.

As mentioned in the methods section, in the absence of valid UK normative data, results were compared to Irish population norm. For each of the five domains, the percentage of study responders with little if any problems at baseline was statistically lower than Irish normative data for the same age group (35-44), as shown in **Table 7** This difference was most striking for domains of physical health: “mobility”, “pain”, and “activity”. And indeed, the proportion of individuals with a mobility level of 1-2 before transplantation was statistically lower than the Irish population norms up to four decades older (75 + years).

“Self-care” was the best scoring domain. Interestingly, the second-best domain in our study population was anxiety, which ranks fourth in age matched general population.

Health States distribution seems to confirm the discrepancy between mental and physical health already highlighted by SF-36. And indeed, the difference between severity level 1-2 frequency in Anxiety and Activity was statistically significant (χ^2= 10.70 p = 0.001), as shown in appendix A 3.16.

Table 7 EQ-5D-5L: Frequency of participants reporting severity level 1-2 problems before transplantation and Irish population norm.

LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 35-44*	96.4%	100%	96.8%	90.1%	96.8%
Pre-transplant	54%	80%	37%	51%	68%
Difference	42.4%	20%	59.8	39.1	23.9
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

DQOL Generic Health Item, KDQOL Overall Health Item and EQ-VAS

In keeping with the above findings, general health perception was extremely low. The mean DQOL Single Health Item score was 12.24 ±10.85, while KDQOL Overall Health Item was 35.49 ± 19.63, which corresponds to a position between 3 and 4 on a 10-point Likert scale, where 0 represents the worst possible health (as bas or worse than being dead), 5 half-way between worst and best and 10 best possible health.

Mean VAS 42.66 ± 23.41, approximately half the Irish normative values for the same age group (M 81.6 ± 13.1). Values below 80 were reported by 95% of participants vs 34% of the Irish general population.

EQ-5D-5L Index

Before transplantation, the mean value of EQ-5D-5L Index was 0.559 ± 0.276.

Aiming to better comprehend how far from “normal” our study participants scored before transplantation, I looked at a few other countries normative values for similar age groups. I found that the mean EQ-index values across different countries were all equal or higher than 0.9, which I will continue to use as a reference throughout the study, fully aware of inevitable differences in methodology and populations. Details of this data can be found in Appendix Table **A3.17.**

Pre-operative summary

Before transplantation, HRQOL was severely impacted by diabetes and chronic complications, both in its generic and disease specific declinations. The apparent difference between mean DQOL and KDQOL (50.23 ± 16.85 and 56.40 ± 12.54 respectively) was not statistically significant: diabetes and renal failure had a similar impact on HRQOL before surgery. Disease specific QOL, though, was statistically better than generic HRQOL. In other words, participants seemed to deal better with the constrictions of diabetes and renal failure per se, rather than with their repercussions on general mental and physical health.

Interestingly, the difference between mean Mental Component Summary Scales (41.41 ± 12.3) and Physical Component Summary Scales (31.82 ± 9.74) was statistically significant and suggested a degree of psychological adaptation to the burden of chronic complications. Similar findings were highlighted by EQ-5D-5L:

“anxiety/depression” had the highest frequency of severity level 1-2 (no/minor problems) and the difference with “activity” was statistically significant.

Consistently with these results, overall perceived health as captured by single health items and EQ-VAS was low, as well as the mean EQ-5D-index.

- Six Weeks from Transplantation

Disease Specific Quality of Life

Renal QOL

After six weeks from surgery, KDQOL mean score was 61.45 ± 17.54. Disregarding "sexual function" (too few responders) and "dialysis satisfaction scales" (no longer applicable), the best scale was "cognitive function", followed by "renal symptoms", "social support", and "effects of kidney disease". Perhaps unsurprisingly at this early post-operative stage, participants still reported a high degree of limitations in "Work", "Sleep" and "Burden" of renal disease. Descriptive statistics are reported in **Table 8.**

Table 8 KDQOL-SF ™ scores at six weeks from transplant

SIX WEEKS KDQOL-SF™					
	Scale	Mean	Median	Stan. Dev.	N
RENAL SCALES	Symptom/problem list	72.76	75.00	18.98	31
	Effects of kidney disease	68.74	62.50	24.29	30
	Burden of kidney disease	57.33	50.00	34.19	29
	Work status	17.74	0.00	27.53	31
	Cognitive function	74.19	80.00	22.23	31
	Quality of social interaction	64.52	66.67	21.66	31
	Sexual function	80.36	75.00	12.20	7
	Sleep	59.50	57.50	25.40	30
	Social support	71.11	75.00	23.13	30
	Dialysis staff encouragement	78.57	87.50	29.62	21
GENERIC SCALES	Patient satisfaction	84.21	83.33	16.17	19
	Physical functioning	51.45	50.00	30.99	31
	Role limitations—physical	12.50	0.00	21.53	30
	Pain	49.35	45.00	29.22	31
	General health	44.68	45.00	24.73	31
	Emotional well-being	62.71	64.00	26.58	31
	Role limitations—emotional	54.02	66.67	45.79	29
	Social function	53.23	50.00	31.95	31
	Energy/fatigue	41.34	40.00	22.88	31
SUMMARY SCALES	**Overall health rating**	**57.10**	**60.00**	**21.79**	**31**
	KDQOL	**61.45**	**63.53**	**17.54**	**31**
	PCS	**33.56**	**34.19**	**10.12**	**29**
	MCS	**45.06**	**47.99**	**13.09**	**29**

Diabetes QOL

Mean DQOL value was almost 70.00 (**Table 9**) with “Impact” being the scale with the highest rating, statistically better than “Worry” and similar to “Satisfaction”.

Table 9 DQOL: scores at six weeks from transplant

6 WEEKS DQOL				
Scale	Mean	Median	Stan. Dev.	n
Satisfaction	71.34	75	19.31	30
Impact	76.08	83.75	17.95	31
Worry	58.12	70.9	33.56	33
TOTAL DQOL	**68.05**	**65.72**	**16.27**	**33**
(GENERIC HEALTH ITEM	33.33	25	31.71	30)

<u>Generic Health Related Quality of Life</u>

SF-36

Mean PCS and MCS were 33.56 ±10.12 and 45.06 ± 13.08 respectively.

Emotional health scales still ranked above all the others generic items. “Pain” was by far the lowest scoring scale, likely in relation with recent surgery.

The distribution of the various scales mirrored pre-operative findings, with a noteworthy separation between mental and physical wellbeing.

However, I found a statistically significant albeit moderate correlation between MCS and PCS (Pearson correlation at 6 weeks: 0.376, $p < 0.001$), absent before transplantation, as to suggest a possible narrowing of the existing gap.

EQ-5D-5L health states frequencies and distribution:

At six weeks the proportion of individuals in group 1 (no problem/mild problem) for each domain – “Mobility”, “Self-Care”, “Activity”, “Pain”, “Anxiety”- was 70%, 94%, 50%, 63%, 70% respectively. Almost everybody had little if any limitation in self-care and over 2/3 of responders reported no or mild anxiety/depression. About 40% of participants complained of moderate to extreme pain, while limitations to daily activity were equally distributed across levels.

When looking at Irish normative data, the proportion of severity level 1-2 for each domain was still statistically lower, albeit this difference was smaller as compared to pre-transplant findings (**Table 10**).

Table 10 EQ-5D-5L: Frequency of participants reporting severity level 1-2 at six weeks from transplantation and Irish population norm

LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 35-44*	96.4%	100%	96.8%	90.1%	91.9%
6/52	70%	94%	50%	63%	70%
Difference	26.4	6	46.8	27.1	21.9
P	<0.0001	0.0003	<0.0001	<0.0001	0.0002

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

DQOL Generic Health Item, KDQOL Overall Health Item and EQ-VAS

Mean DQOL Generic Item was 33.33 ± 31.714, statistically lower than results obtained on the EQ-VAS (Mean (SD) = 66.79 ± 21.93, $p < 0.001$). KDQOL Single Health rating was 57.10 ± 21.79, essentially corresponding raw score between 5 and 6 on the 10 points Likert scale.

EQ-5D-5L index.

Mean EQ-5D-5L index was .605 ±.293, statistically lower than the 0.9 value reported in the literature as the mean EQ-index norm for similar age group.

Longitudinal Changes

At six weeks from surgery, participants were just recovering from major surgery. Unsurprisingly, most of the instruments didn't capture significant changes in HRQOL.

However, Diabetes QOL, VAS scores and most of the SF-36 physical health scales ameliorated significantly and dramatically.

Renal QOL

The increase in global KDQOL mean scores from baseline (56.40 ± 12.54) to six weeks from transplantation (61.45± 17.54) was not statistically significant (**Table 22**). However, the sub-group of "full-responders" experienced a statistically significant and very large increment throughout the entire study (partial $\eta^2 = .536$) as shown in **Appendix A3.18**. Pairwise progression of KDQOL at six weeks from

surgery was also statistically significant (**table 11**). Whether this discrepancy was a real result or related to decreased return rates during the core months of the pandemic it is difficult to establish. Regardless, a few components of renal-related QOL increased quickly for the whole study sample. The largest benefit seemed to be the improvement of "Burden", one of the lowest scales to start with (Burden: p < .001, Cohen's d = -4.166, very large effect size). A smaller, yet relevant, change was registered for the "Symptom/Problems" scale (Symptoms/Problem list: p .026, Cohen's d -.428, small/medium effect size). Details of longitudinal changes in KDQOL are summarised in **Tables 11** and in **Appendix A3.18**.

Table 11 KDQOL: pairwise progression at six weeks from transplant.

	KDQOL: CHANGES AT SIX WEEKS	
	KDQOL	
Timepoint	Baseline	6 Weeks
Mean	57.20	61.63
SD	14.01	17.81
t-test	Number = 24 t (23) = -3.160 Cohen's d = -.645 Sig = .004	

Diabetes QOL

DQOL improved from the very first time-point of data collection, with a large effect size or both global score (p <. 001 Cohen's d = -1.17) and individual scales. This was true for the whole study sample as well as for the sub-group of "full responders", as shown in **Tables 12** and **Appendix A3.19.**

Table 12. DQOL: pairwise progression at 6 weeks from transplant

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DQOL CHANGES AT SIX WEEKS		
Scale	Baseline	6 Weeks
Satisfaction Number = 27	Mean (SD) = 49.03 ± 17.48 Median = 45.00	Mean (SD) = 71.35 ± 19.31 t (26) = -6.357 p < .001 Cohen's d = -1.2 (large)
Impact Number = 29	Mean (SD) = 53.15 ± 18.31 Median = 52.50	Median = 83.75 Z = - 3.828 p < .001 r = 2.0 (large)
Worry Number = 29	Mean (SD) = 49.64 ± 24.49 Median = 45.45	Median = 70.9 Z = - 2.030 p = .042 r = .81 (large)
DQOL global NUMBER = 31	Mean (SD) = 52.49 ± 16.82	Mean (SD) = 67.82 ± 16.76 t (30) = -5.754 p < .001 Cohen's d = -1.033 (large)

Generic HRQOL

In the first few weeks post transplantation, both PCS and MCS showed some degree of amelioration, albeit not statistically significant. However, participants were already able to detect a remarkable improvement in "Overall health" and "General health perception" (General health perception: p = .007 Cohen's d = 2.1, very large effect size). And indeed, similar outcomes were captured by mean EQ-VAS, DQOL Generic Health Item (VAS: p = Cohen's d=. DQOL Generic Health Single Item: p < .001, Cohen's d = 1.9) and KDQOL Overall Health Item. The Difference in mean scores was statistically significant, with a very large effect size (KDQOL Overall health rating: p <.001, Cohen's d = 2.218).

The driving force behind this phenomenon was likely the striking improvement in physical functioning and energy levels (p = .001, Cohen's d = 1.8; Energy: p.003, Cohen's d = 1.3), quite surprising just a few weeks after major surgery. This was confirmed by the decrement in role limitations due to physical problems (Role Physical: p = .018, Cohen's d = 1.2).

None of the scales measuring emotional related quality of life improved statistically from baseline, however it is important to underline how MCS was statistically better than PCS at baseline (p < .001).

- Six Months from Transplantation

<u>Disease Specific Quality of Life</u>

Renal QOL

At six months from surgery, KDQOL was 69.71 ± 21.31. Remarkably, all the most paradigmatic domains of renal quality of life – Effects, Symptoms and Burden of kidney disease- were no longer amongst the worse rating scales. On the contrary, Effects ranked the highest, followed by cognitive function and Symptoms, while sleep and work remained the lowest. Details of KDQOL outcomes at six months can be found in **Table 13.**

Table 13. KDQOL-SF: ™ scores at six months from transplant

6 MONTHS KDQOL-SF™					
	Scale	Mean	Median	Stan. Dev.	n
RENAL SCALES	Symptom/problem list	75.09	78.41	20.25	22
	Effects of kidney disease	79.82	90.63	24.72	23
	Burden of kidney disease	73.10	87.50	32.99	23
	Work status	37.50	0.00	47.20	24
	Cognitive function	78.48	86.67	25.94	22
	Quality of social interaction	66.06	66.67	25.77	22
	Sexual function	96.88	100.00	6.25	4
	Sleep	59.58	53.75	20.91	24
	Social support	78.47	83.33	27.13	24
	Dialysis staff encouragement	86.46	100.00	28.43	12
GENERIC SCALES	Patient satisfaction	82.14	100.00	29.57	14
	Physical functioning	56.55	62.50	35.49	24
	Role–imitations--physical	45.45	37.50	41.29	22
	Pain	54.78	55.00	36.97	23
	General health	48.33	47.50	28.46	24
	Emotional well-being	65.91	68.00	26.17	23
	Role–imitations--emotional	63.77	100.00	42.54	23
	Social function	58.33	56.25	36.24	24
	Energy/fatigue	46.59	40.00	31.20	23
SUMMARY SCALES	**Overall health rating**	**56.67**	**60.00**	**26.32**	**24**
	KDQOL (Kidney Quality of Life Composite)	**69.71**	**68.48**	**21.31**	**25**
	PCS (Physical Health Composite)	**38.75**	**37.84**	**12.20**	**21**
	MCS (Mental Health Composite)	**44.99**	**50.07**	**13.72**	**21**

Diabetes QOL

DQOL summary scale score at six months from surgery was 72.47± 18.23, with Impact just slightly better than Satisfaction but statistically higher than Worry (p = 0.031), consistently with what already noted at six weeks from transplantation **(Table 14)**

Table 14. DQOL: scores at six months from transplant

6 MONTHS DQOL				
Scale	Mean	Median	Stan. Dev.	n
Satisfaction	70.1421	71.66	19.21284	28
Impact	79.0748	86.25	15.33777	27
Worry	63.7629	72.72	32.67793	28
TOTAL DQOL	72.468	75.22	18.23578	30
Generic Health Item	44.23	37.5	34.862	26

Generic Health Related Quality of Life

SF-36

PCS and MCS mean scores were 38.75 ± 12.20 and 44.99 ± 13.72, respectively. Ranking of individual scales mirrored the two previous timepoint of data collection, with mental well-being and physical health at the opposite side of the spectrum.

However, as previously noted at six weeks, there was a strong correlation between the two, as to confirm a substantive reduction of the initial discrepancy (Pearson's correlation at six months: 0.656 p< 0.001).

EQ-5D-5L health states frequencies and distribution:

At six months from surgery the proportion of individuals with no/little problems with mobility and daily activities was 67%. Participants with moderate to severe pain were still approximately 40% of the sample. Self-care ability was normal/near to normal in almost 90% of individuals and 75% of the sample had no or little mental health issues. Overall, findings were still statistically lower than age matched Irish population norm for all the domains as shown in **Table 15.**

Table 15. EQ-5D-5L Frequency of participants reporting severity level 1-2 problems at six months from transplantation and Irish aged-matched population norm.

EQ-5D-5L LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 35-44*	96.4%	100%	96.8%	90.1%	91.9%
6/12	67%	87%	67%	62%	75%
Difference	29.4	13%	29.8%	28.1	16.9
P	<0.0001	<0.0001	<0.0001	<0.0001	0.0045

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

DQOL Generic Health Item, KDQOL Overall Health Item and EQ-VAS

The mean DQOL general health item was 44.23 ± 34.86, while VAS score was 67.08 ± 23.5. EQ-VAS scores at this time-point were still statistically higher than both PCS and MCS. The mean KDQOL overall health rating 69.71 ± 21.31, that is 7/10 on the Likert Scale.

EQ-5D index

EQ-5D index mean score at six months was .635 ± .344.

Longitudinal Changes

At six months from surgery all the scales except MCS were statistically better than baseline. The correlation between PCS and MCS remained strong, suggesting a smaller gap between the two (Pearson's $r = .656$ $p < .001$). The increase in EQ-index scores, however, did not reach the threshold for statistical significance.

Renal QOL

KDQOL at six months reached statistical significance with medium effect size (**Table 16**). Looking at the individual components, changes in Burden, Effect and Symptoms of Kidney disease were statistically significant and even more meaningful, with very large effect size (Cohen's $d > .09$). Moreover, participants reported statistically higher levels of Satisfaction with the support received from family and friends ($z = -2.537$ $p = .011$ Cohen's $d = 1.211$).

TABLE 16. KDQOL: pairwise progression at six-months from transplant

	KDQOL CHANGES AT SIX MONTHS	
	KDQOL	
Timepoint	Baseline	6 Weeks
Mean	59.27	70.21
SD	± 14.21	± 21.62
t-test	NUMBER = 24 t (23) = -3.160 Cohen's d = -.645 p = .004	

DQOL

At six months DQOL and the individual scales continued to improve and were statistically better than baseline and six weeks outcomes, with moderate-large effect sizes (**Table 17**).

Table 17 DQOL: pairwise progression at six months from transplant

DQOL CHANGES AT SIX MONTHS		
Scale	Baseline	6 Months
Satisfaction Number = 25	Mean (SD) = 49.03 ± 17.48 Median = 45.00	Mean = 71.82 t (26) = -5.725 p < .001 Cohen's d = -1.1 (large)
Impact Number = 25	Mean (SD) = 53.15 ± 18.31 Median = 52.50	Median = 86.25 Z = - 3.943 p < .001 r = 2.6 (large)
Worry NUMBER = 25	Mean (SD) = 49.64 ± 24.49 Median = 45.45	Median = 65.29 Z = - 3.014 P = .003 R = 1.5 (Large)

GLOBAL DQOL N= 29	Mean (SD) = 50.23± 16.41	Mean (SD) =71.51 ± 18.08 T (23) = -6.278 P <. 001 Cohen's D = -1.166

HRQOL

As expected, moving away from surgery, the benefits derived from physical well-being continued to increase. Changes in Energy, General Health, Health ratings, Role limitations due to physical problems and Physical Functioning remained statistically significative with very large effect sizes.

In contrast, there was no breakthrough in scales related to mental wellbeing. (**Appendix A3.24-A3.25**).

All the single health rating items were statistically better than before transplantation. with large effect sizes, while changes in EQ-index were still not significant, despite a consistent upwards trajectory (**Appendix, A3.29**)

- One Year from Transplantation

Disease Specific Quality of Life

Renal QOL

Mean KDQOL one year after the surgery was 71.31 ± 17.77. A closer analysis of individual scales, though, showed much higher results in most domains ranging from 68.52 ± 20.45 (Quality of social interactions) to 81.67 ± 22.67 (Cognitive Function), with sleep and work weighting negatively on composite scores (Mean ± SD = 62.14 ± 26.29 and 52.94 ± 47.58, respectively).

Sexual Function scores computed on 12 responders (namely 21% of the population at one year), were quite high, albeit this was also true before surgery, in a similar proportion of individuals. (**Table 18**)

Table 18. KDQOL-SF: ™ scores at one year from transplant.

	Scale	Mean	Median	Stan. Dev.	n
RENAL SCALES	Symptom/problem list	79.44	80.68	16.72	36
	Effects of kidney disease	79.64	90.63	25.08	35
	Burden of kidney disease	71.01	75.00	26.61	36
	Work status	52.94	50.00	47.58	34
	Cognitive function	81.67	86.67	22.67	36
	Quality of social interaction	68.52	66.67	20.45	36
	Sexual function	80.21	93.75	25.82	12
	Sleep	62.14	67.50	26.29	37
	Social support	78.57	83.33	29.03	35
	Dialysis staff encouragement	86.96	100.00	26.24	23
GENERIC SCALES	Patient satisfaction	88.19	100.00	19.95	24
	Physical functioning	55.41	65.00	33.63	37
	Role–imitations--physical	55.56	50.00	41.88	36
	Pain	66.67	72.50	31.95	36
	General health	49.29	45.00	24.34	37
	Emotional well-being	72.22	80.00	23.03	36
	Role–imitations--emotional	71.30	100.00	41.52	36
	Social function	67.91	87.50	33.92	37
	Energy/fatigue	52.45	54.17	29.51	36
SUMMARY SCALES	**KDQOL-Overall health rating**	**68.89**	**70.00**	**19.39**	**36**
	KDQOL (Kidney Quality of Life Composite)	**71.32**	**71.85**	**17.78**	**37**
	PCS (Physical Health Composite)	**41.90**	**43.72**	**11.42**	**32**
	MCS (Mental Health Composite)	**47.60**	**53.12**	**13.78**	**32**

Diabetes QOL

Mean DQOL score at one year from surgery was 68.81 ± 17.78. Of all the scales, worry scale was the lowest and statistically worse than both Impact (p .0002) and Satisfaction (p = .008). (**Table 19**)

Table 19. DQOL: scores at one year from transplant

DQOL at 1 Year				
Scale	Mean	Median	Stan. Dev.	n
Satisfaction	69.70	71.66	21.98	41
Impact	76.00	81.25	17.07	40
Worry	53.26	52.72	31.95	41
TOTAL DQOL	68.81	70.6	17.78	41
Generic Health Item	39.19	25	28.59	37

Generic Health Related Quality of Life

SF-36

PCS and MCS mean scores were 41.9 ± 11.42 and 47.60 ± 13.76, respectively. The initial dichotomy between physical and mental health well-being was still very much true: none of the physical QOL scales were amongst the highest scoring variables. Moreover, there was no longer a meaningful correlation between PCS and MCS (p = 0.071).

EQ-5D-5L

EQ-5D-5L Health States Frequencies and Distribution

The proportions of participants with little if any problems for each– Dimension - Mobility, Self-Care-Activity-Pain-Anxiety/Depression- were 67%-92%-67%-66%-78%, respectively. Most individuals had maintained an elevated degree of independence in self-care and high levels of mental health, with approximately 70% of the study population having no or little problems in mobility and daily activities. However, over one third of the sample had still moderate to extreme issues with pain.

DQOL Generic Health Item, KDQOL Overall Health Item and EQ-VAS

VAS mean score and DQOL Generic Health Item were 71.85 ± 21.59 and 39.19 ± 28.59 respectively. Mean score for KDQOL Overall Health-rating Item was 68.89 ± 19.39.

EQ-5D-5L index

Mean EQ-5D index one year after surgery was 0.645 ± .364, hence still below 0.9, the value repeatedly reported as norm for this age range in other populations. (Alberta PROMs & EQ-5D Research & Support Unit (APERSU), 2018; Jensen MB et al, 2021; Garcia-Gordillo MA et al, 2016). Further details on these manuscripts can be found in Appendix **A3.17**.

Longitudinal Changes

Renal QOL

At one year from transplantation KDQOL and 70% of the individual scales were statistically better than baseline and the magnitude of changes was large (Cohen's d ranging from .74 for "Sleep" to 3.2 for "Burden"). However, there was no growth from the previous timepoint of data collection and three scales did not reach the threshold for significant improvement: "quality of social interactions", "sexual function", and "dialysis staff encouragement". Perhaps, though, the relevant one is "quality of social interactions", which, incidentally, ranked relatively high at baseline (Mean (SD) = 64.25 ± 20.75), but failed to improve much afterwards. Overall, the biggest changes in KDQOL occur early and no further statistically significant change occurred after six months, as confirmed by linear mixed modelling. A summary of global KDQOL changes throughout the study period is provided in **Table 22, while** mixed modelling outcomes are reported in Appendix **A 3.20**

Table 20 KDQOL: summary of post-operative changes

Baseline	6 Weeks
Mean (SD) =57.20 ± 14.01	Mean (SD) =61.63 ± 17.81
Number = 30 t (29) = -1.758 p = .089 Cohen's d = -.321	

Baseline		6 Months
Mean (SD) =59.27 ± 14.21		Mean (SD) =70.21 ± 21.62
	Number = 24 t (23) = -3.160 p = .004 Cohen's d = -.645	

Baseline			1 Year
Mean (SD) =58.63 ± 14.01			Mean (SD) =72.39 ± 16.77
	Number = 36 t (35) = -5.158 p < .001 Cohen's d = .860		

Diabetes QOL

At the end of the study period, I observed an inversion of DQOL towards lower values, which resulted statistically significant when compared to data collected at six months (t (28) = 2.471 p = .020 Cohen's d = .459) (**Table 21**). The mixed model analysis provided similar findings, albeit one-year results were still statistically better than baseline, in keeping with mixed modelling outcomes (Appendix **A 3.21**).

Table 21 DQOL: summary of post-operative changes

Baseline	6 Weeks
Mean (SD) = 52.49 ± 16.82	Mean (SD) = 67.82 ± 16.76
Number = 31 t (30) = -5.754 p < .001 Cohen's d = -1.033	

Baseline		6 Months
Mean (SD) = 50.23 ± 16.41		Mean (SD) = 67.82 ± 16.76
	Number = 29 t (23) = -6.278 p <. 001 Cohen's d = -1.166	

Baseline		1 Year
Mean (SD) = 49.46 ± 18.14		MEAN (SD) = 66.98 ± 16.60
	Number = 39 t (38) = -6.924 p < .001 Cohen's d = 1.509	

Individual scales were investigated to better define this phenomenon. Overall, all the scales were still statistically better than baseline. While both "Satisfaction" and "Impact" showcased just a marginal reduction in mean values from the previous time point (p = .709 and p = .764 respectively) the "Worry" scale plummeted notably (Worry, 6 months: mean (SD) = 63.76 ± 32.68; Worry, 1 year mean (SD) = 53.26 ± 31.95 z = -2.133, p = .033, Number = 27 Cohen's d = .90) as shown in **Table 23** Hence, the fall in Global DQOL at one year was essentially driven by increasingly higher levels of concerns, rather than worsening of diabetes related symptoms or satisfaction with treatment. Whether this was ascribable to Covid-19 stress it is difficult to establish, although data seems to suggest otherwise: when return rates were stratified in relation to the "first wave," no statistically significant difference in

DQOL “Worry” or MCS outcomes was identified, leaving the matter open for interpretation.

Despite this inflection, global DQOL was still statistically better than pre-transplantation, with a difference in mean values of approximately 11 points. In the context of the DCCT trial, developers of the instrument considered a 5-point difference as a significant HRQOL event. Hence, in our study, changes in DQOL after compared to before PT were statistically significant and clinically meaningful DQOL changes throughout the study period are reported in **Appendix A 3.19**, while **Appendix 3.21** summarises findings of the linear mixed-effect models.

Table 22. DQOL scales: Pairwise Progression at 1 year

DQOL SCALES: CHANGES AT ONE YEAR			
Scale	Baseline	1 Year	Significance
Satisfaction N= 41	Median = 45.00 Mean (SD) = 49.03 ± 17.48	Median = 71.66	Z = - 4.587 r = 2.1 (large) p < .001
Impact N= 38	Median = 52.50 Mean (SD) = 53.15 ± 18.31	Median = 81.25	Z = - 5.018 r = 2.8 (large) p < .001
Worry N= 36	Median = 45.45 Mean (SD) = 49.64 ± 24.49	Median = 52.72	Z = - 2.900 r = 1.1 (large) p = .004

Overall, despite the earlier change in diabetes related HRQOL, both disease specific PROMs had a similar trajectory during the study period, as depicted in Figure 5.

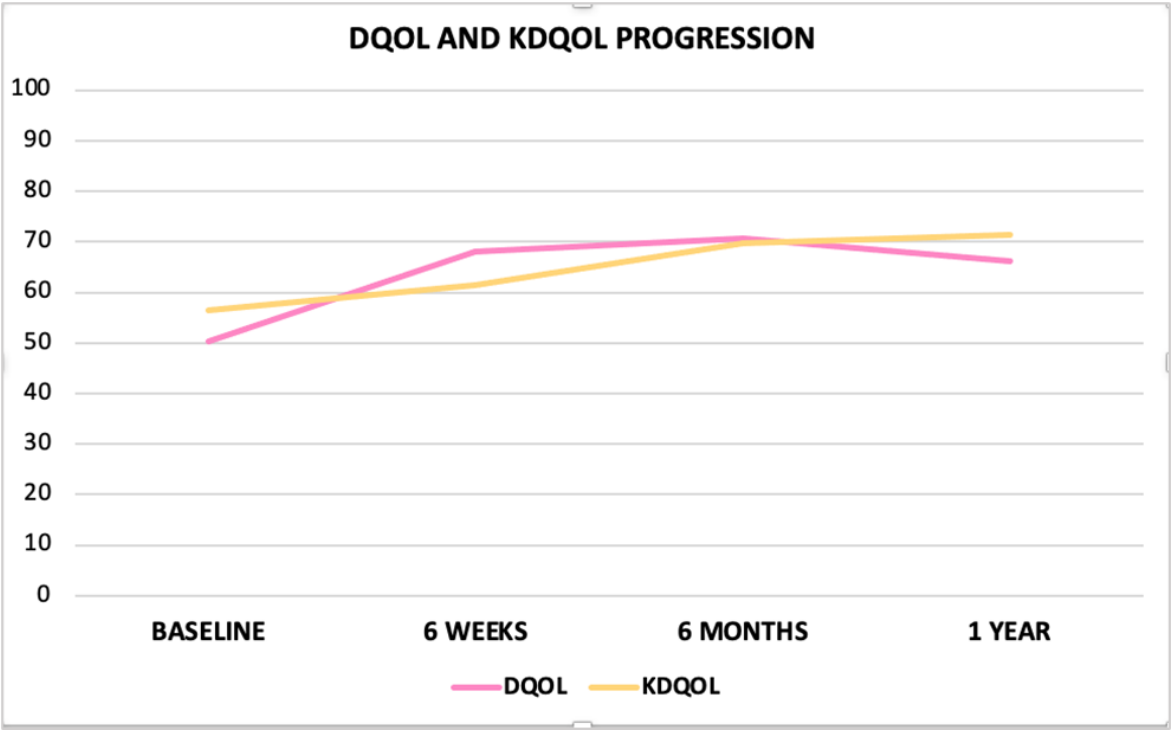


Figure 5 Comparison between DQOL and KDQOL trajectories

Generic HRQOL

At one year from transplantation PCS scores were still better than baseline, with the biggest growth occurring within the first six months from surgery and then reaching a plateau, as shown in both in fixed and linear mixed modelling analysis (Appendix **3.22-3.23**). Results from linear mixed modelling analysis A few scales never reached statistically significant improvements, more specifically “Role limitations due to emotional problems” and “Satisfaction.” The latter, though, was the highest-ranking scale at all timepoints; these results could, therefore, be due to ceiling effect.

Pairwise comparison of MCS outcomes to pre-transplant levels, showed no meaningful change in MCS at any timepoint, despite most SF-36 scales being statistically improved. Equally inconsequential were the changes in MCS within the

cohort of “full-responders.” However, by modelling variability in the data, it was possible to demonstrate a statistically significant estimate of fixed effect at one year from surgery, as shown in **Appendix 3.26**.

EQ-VAS, DQOL Generic Health Item and with KDQOL Overall Health Item scores increased from baseline, with a large size effect. Interestingly, there was a discrepancy between EQ-VAS and DQOL Generic Health Item scores at all timepoints; however, the absolute increment from baseline to one year for the two instruments was quite similar: 29 and approximately 27 points, respectively.

The distribution of severity of Health States at one year, dichotomised in two levels - “mild” and “severe impairment”- didn’t change significantly by the end of the study (Appendix A3.18). However, according to the Pareto classification of Health Change (Devlin, Parkin et al. 2010) 45% of participants had a better Health State, against 15% of those whose Health State had deteriorated.

The progressive increase in EQ-indexes resulted in a statistically significant growth from baseline, with a medium effect size (Cohen’s d = .669), confirming the potentially transformative effect of pancreas transplantation on HRQOL. The progression of EQ-indexes throughout the study period is shown in Figure 6. Linear mixed method analysis confirmed a statistically significant estimated fixed effect at the last time-point of data collection, hence at one year from surgery (**Appendix 3.30**)

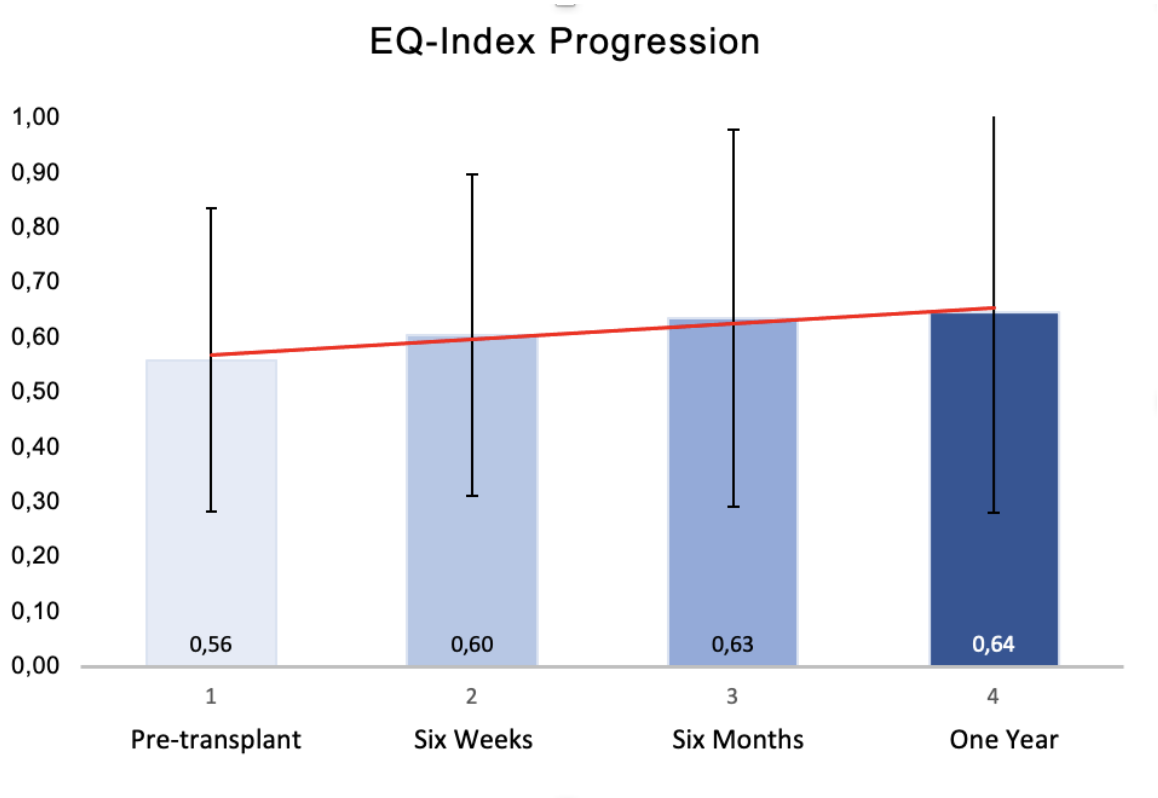


Figure 6. Progression of EQ-index from baseline to one year**.**

The longitudinal trajectory of generic HRQOL outcomes throughout the study period is summarised in **Figure 7,** while **Figure 8** shows a comparison between EQ-VAS, PCS and MCS changes.

Overall, by the end of the study period all disease specific measures and most generic HRQOL outcomes resulted in a statistically significant increase, with the largest effect sizes in generic HRQOL (**Figure 9** and **Figure 10**, respectively).

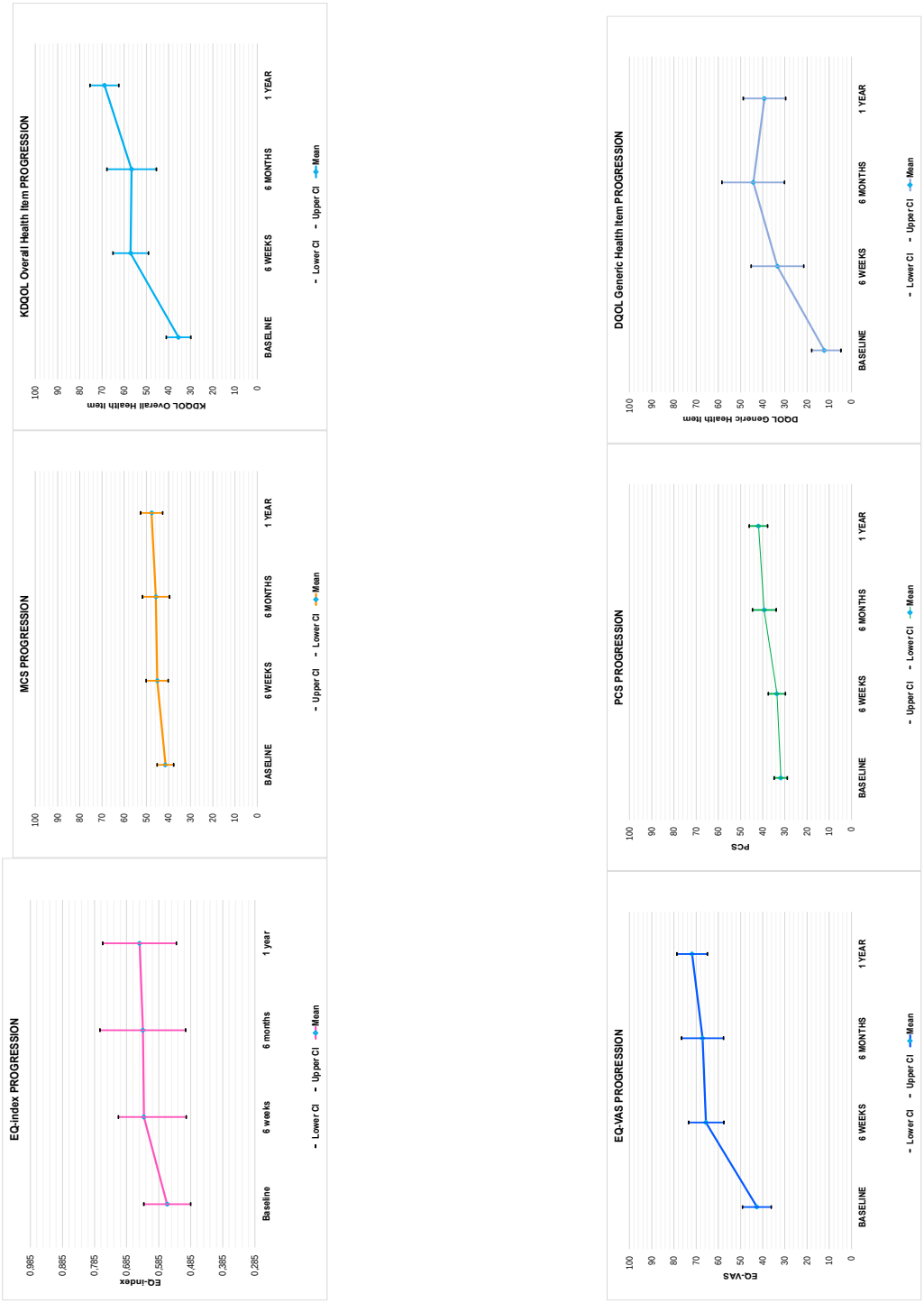


Figure 7 Generic HRQOL progression

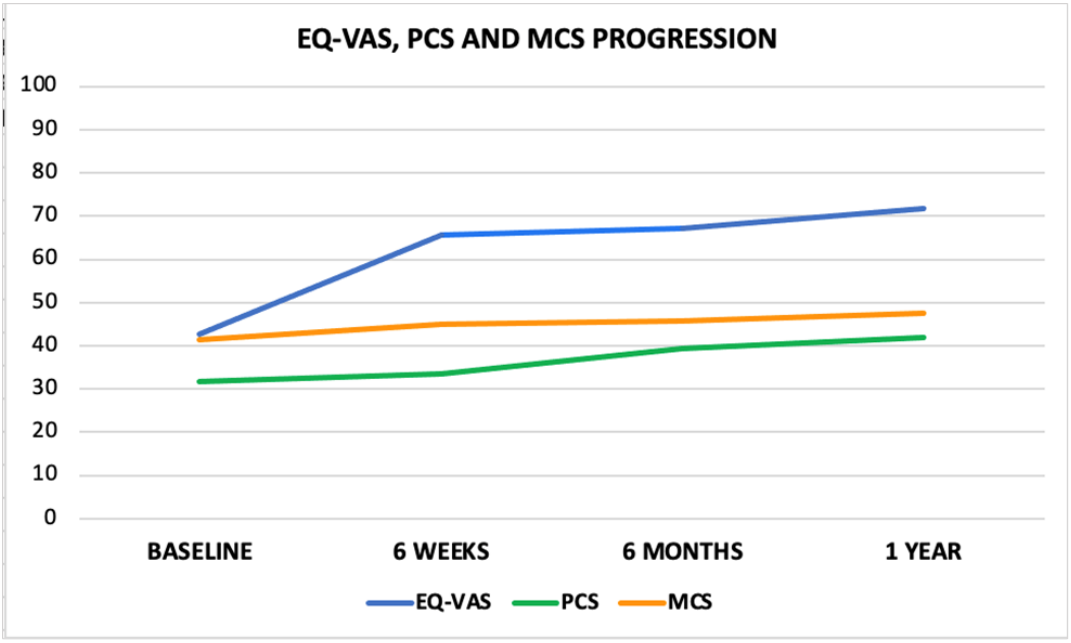


Figure 8 Comparison between EQ-VAS, PCS and MCS trajectories

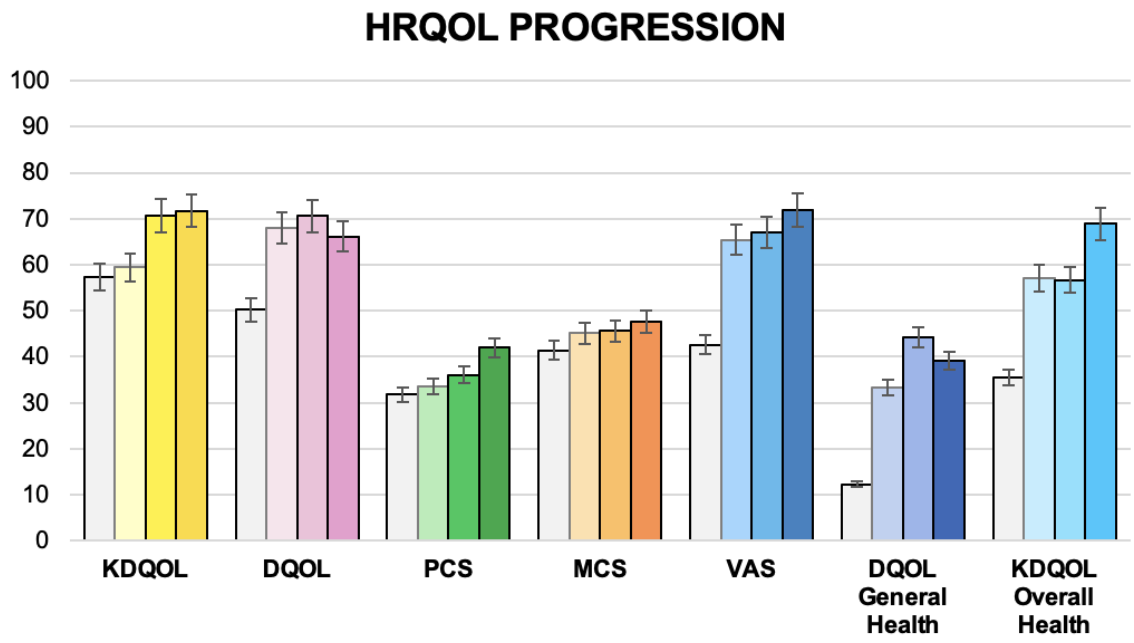


Figure 9 Progression of HRQOL from baseline to one year, stratified by PROM.

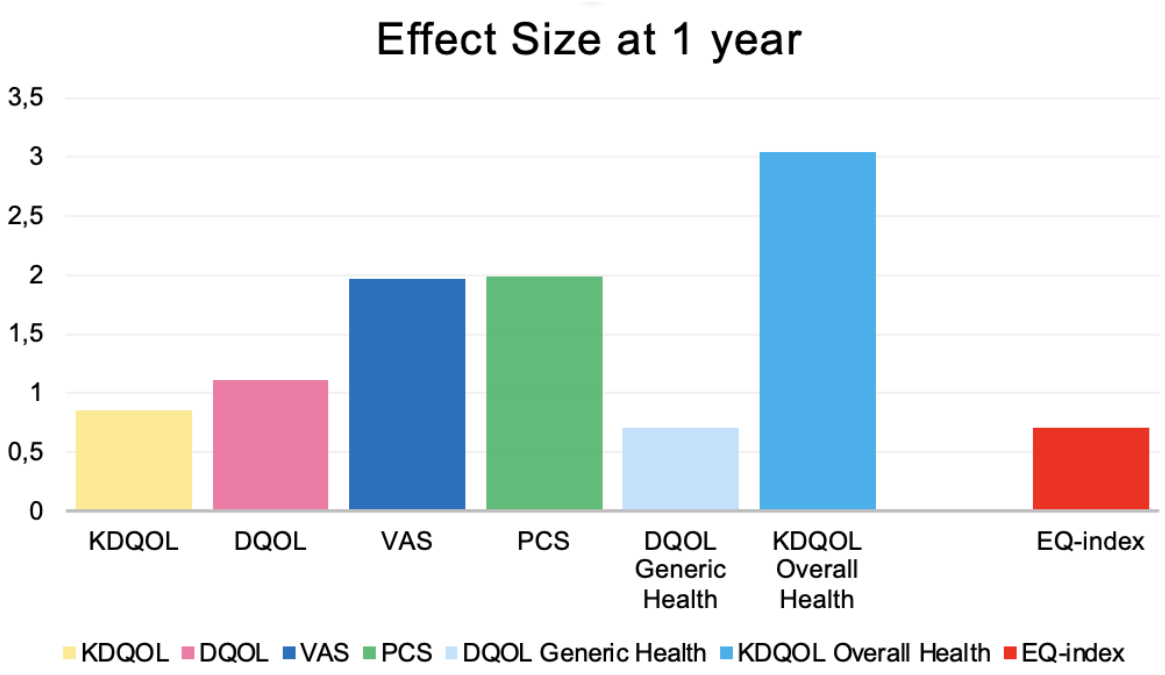


Figure 10 Effect size of changes at one year from transplant, stratified by PROM

- HRQOL and Population Norms

SF-36

Comparison between PCS and MCS with UK normative values, depicted a bleak scenario for physical health related QOL: despite the statistically significant increment in PCS, one-year mean values fell within the lowest 25% of the UK population (Jenkinson, 1998), as shown in **Appendix A3.32**

In contrast, MCS scores reached normative values. The discrepancy between these two aspects of HRQOL was, once again, confirmed by our findings. However, despite this difference, by the end of the study both scales were closer to population norms that to their own starting point prior to transplantation, as shown in **Figure 11**

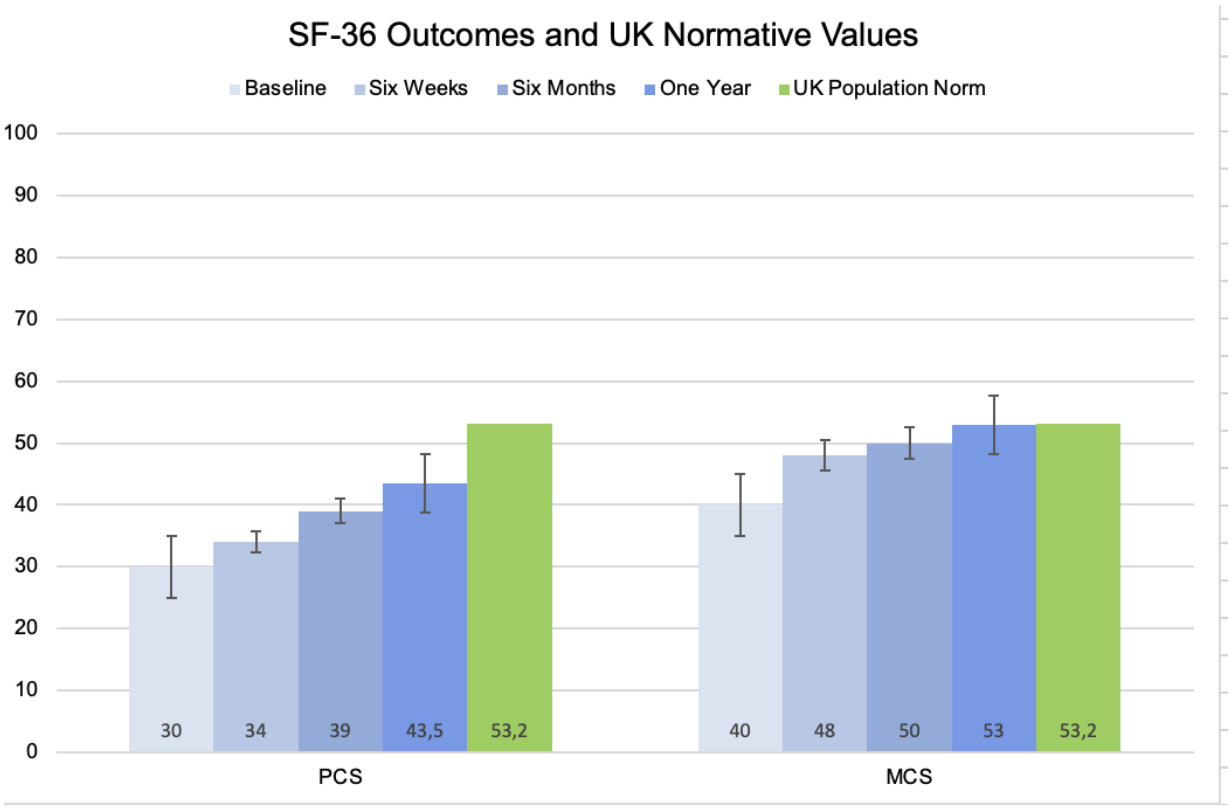
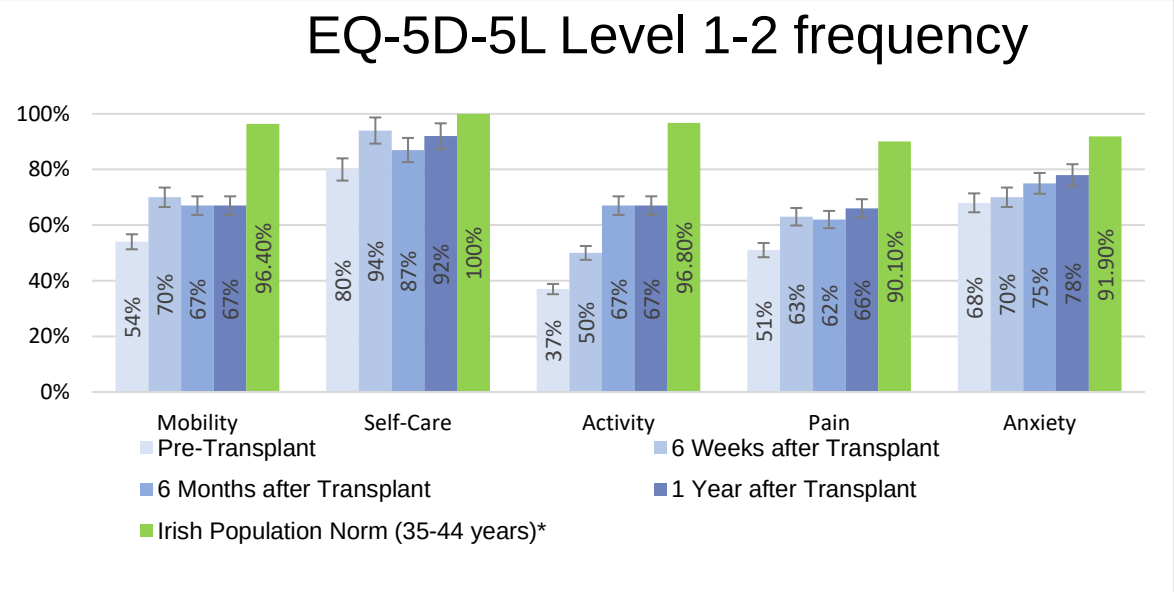


Figure 11 Comparison between PCS and MCS at all time points and UK normative values

EQ-5D-5L

The proportion of participants at level 1-2 in all 5 domains of EQ-5D-5L was statistically below age matched Irish normative values at all timepoints (**Figure 12**). However, while baseline EQ-5D-5L findings were below normative scores for each age range, the situation had clearly improved at one year. At the end of the study period, in fact, the proportion of participants with little/no "Pain" was within population norms for age 45-54, hence about one decade older. For the "Self-Care" domain, participants reached population norms of individuals aged 55-64, while for "Mobility" their scores were in keeping with the age group 65-75. The percentage of participants with little if any impairment in "Activity" was the same as individuals older than 75. The only domain that never reached population norms for any age group was "Anxiety/Depression", despite it being one of the highest scoring domains both before and after transplantation. Details of this relationship can be visualised in **Table 23.**



Data extrapolated from *Hobbins A et al. HRB Open Res 2018*

Figure 12 EQ-5D-5L: Progression of level 1-2 across domains and aged matched Irish population norms

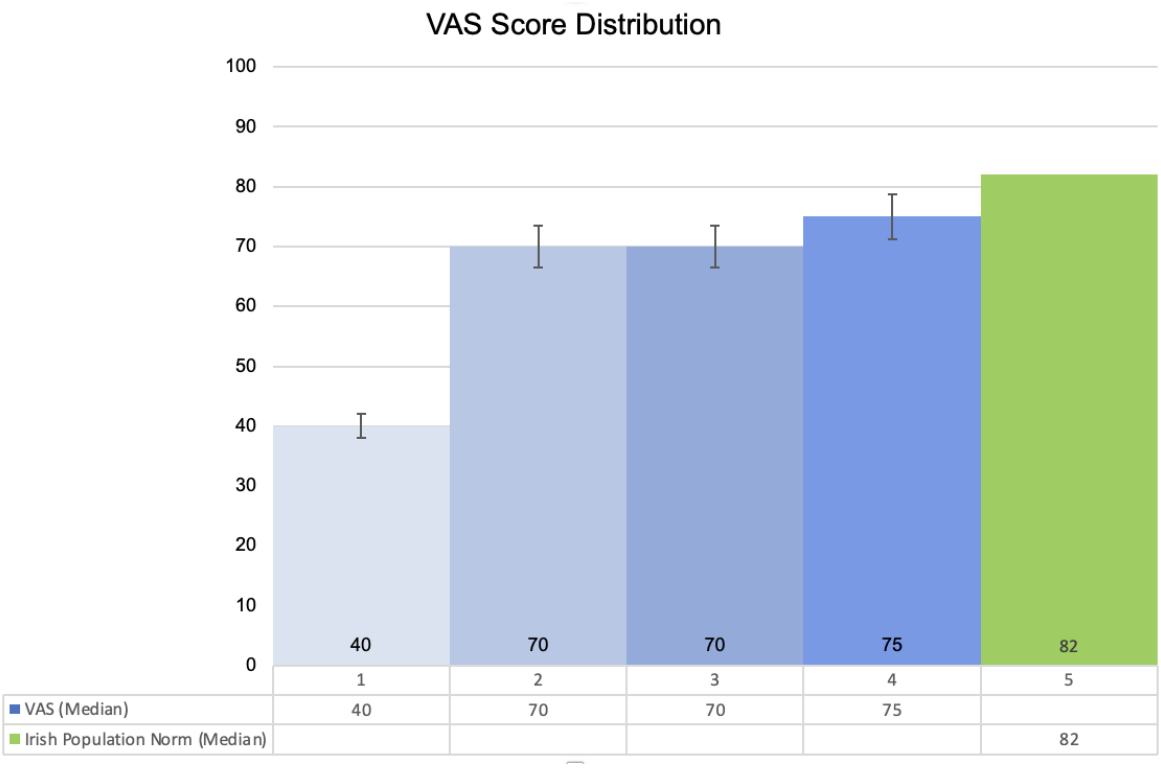
Table 23. EQ-5D-5L: distribution of level 1-2 across domains at one-year and comparison with Irish population norms, stratified by age.

EQ-5D-5L DOMAINS	STUDY POPULATION	IRISH NORMATIVE DATA*				
	1-YEAR POST-TRANSPLANT (Mean age 44 years)	35-44	45-54	55-64	65-74	75+
Mobility	67%	96.4% P < .0001	93%	88.4	80.1 P = .072	74.4
Self-Care	92%	100% P < .0001	98.2	97.8 P = .074	96.1	97.7
Activity	67%	96.8% P < .0001	93.4	91.2	85.2	74.5 P = .37
Pain	66%	90.1% P < .0001	79.1 P = .066	78.1	72.4	72.2
Anxiety/Depression	78%	91.9% P= .0007	89.5 P= .0007	94 P= .0012	93.6 P= .0027	92.2 P= .02

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

EQ-VAS

EQ-VAS was associated with the largest size effect of change from baseline, nevertheless improvements did not leave transplanted patients at the level of population norms. Yet, as shown in **Figure 13,** final EQ-VAS score was closer to population norms than to pre-transplant scores.



* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

Figure 13. EQ-VAS mean scores at all time-points and Irish normative values.

- Summary

In conclusion, by the end of the study most HRQOL measures had improved from baseline as shown in Figure 9 and in Appendix A3.22. By one year, disease specific QOL scales, EQ-VAS score and the KDQOL Overall Health Item reached the highest scores, as depicted in **Figures 5-7-8-9.**

The magnitude of this gain was different across scales.

The largest effect sizes were recorded for KDQOL General Health item, PCS, and EQ-VAS (PCS: Cohen's d from baseline = 1.99, VAS: Cohen's d = 1.97). DQOL gain ranked third in magnitude, with a very large effect size (DQOL: Cohen's d = 1.109) (**Figure 10).**

3.3.5 Predictors of HRQOL

Despite the small population size of the study, I sought to define which pre-operative variables were likely to have an impact on quality of life, if any.

Methods

Demographics, clinical, social, and transplant-related variables were considered potential predictors of HRQOL changes after pancreas transplantation. As a preliminary step, the relationship between these factors (independent variables) and each of the eight HRQOL final scales (dependent variables: “KDQOL”, “PCS”, “MCS”, “DQOL”, “DQOL General Health item”, “KDQOL Overall Health Item”, “EQ-VAS”, “EQ-index”) was investigated at all time-points of data collection.

Continuous variables were checked against HRQOL scales by means of correlations, while binary data were compared using independent t-test and Mann-Whitney U test.

Regression assumptions were checked, and data was transformed accordingly whenever feasible. Whilst nothing could be done for variables of interest with low frequencies, continuous non normally distributed potential predictors of HRQOL were pre-emptively dichotomised around median values.

Linear Regression

Linear regression was instrumental in confirming the consequential relationship between independent and dependent variable.

Potential predictors were regressed onto the 8 HRQOL PROMs, separately.

Whenever a HRQOL scale correlated exclusively with a single potential predictor, linear regression provided the necessary information regarding the weight of that variable in influencing outcomes.

If two or more factors seemed to concur in influencing an outcome, multiple regression was necessary to define the exact contribution of each.

Multiple Regression

Statistically significant variables in univariate linear regression were grouped within SPSS for multiple regression. By doing so, some factors gained further weight, some lost significance. For each HRQOL outcome, a model of best fit was sought by progressively removing non-contributing items and re-running the model.

Violation of regression assumptions such as normality, linearity, multicollinearity, and homogeneity of variances was checked for each possible combination of predictor factors. The best model was then selected by balancing conceptual justifications, F statistics, Significance and R^2 (amount of variance of the dependent variable accounted for by the synergistic effect of the predictors).

- Pre-operative Predictors of baseline HRQOL

Disease Specific Quality of Life

Renal-related QOL

At baseline, positive predictors of KDQOL were “pre-transplant transfusions” and “being employed”, while “History of Common Psychiatric Disorders “, “Gastrointestinal symptoms” and “Claudication” had a negative impact on outcomes. Overall, these factors were predictive of approximately 56% of variance. (Appendix **A3.33**)

Diabetes-related QOL

Gi symptoms” and “Previous blood transfusions” were also responsible for about 29% of variance in DQOL (Appendix **A3.34**).

Generic Health Related Quality of Life

PCS

“Peripheral Neuropathy” and "History of Cardiac Revascularisation” were the only two factors predicting PCS at baseline and contributed to 28% of the variation in the final score (Appendix **A3.35**)

MCS

“Smoking or having smoked” and “History of Common Psychiatric Disorders” ultimately accounted for 36% of variance in MCS (Appendix **A3.36**).

DQOL Generic Health Item

Multiple factors were associated to DQOL Generic Health Item, contributing to approximately 33% in variance, as shown in Appendix **A 3.27**

EQ-VAS

"Smoking of having smoked" was also associated with poorer general health perception as scored on EQ-VAS. Together with "Blindness" it predicted 19% of pre-operative EQ-VAS variance (Appendix **A3.38**)

EQ-Index

The EQ-index scores were influenced by "History of Common Psychiatric Disorders" and "GI symptoms", responsible for 24% of variance (Appendix **A3.39**)

KDQOL Overall Health Item.

No predictor factor was identified for this scale at baseline.

A synopsis of factors associated with baseline HRQOL is provided in Appendix **3.40**

- Six Weeks from Transplant: pre-operative predictors of HRQOL

<u>Disease Specific Quality of Life</u>

KDQOL

"History of common psychiatric disorders" and "Work status" continued to be powerful predictors of KDQOL at six weeks from surgery, along with "Blindness"

and “History of Psychotropic medications”. Their combination was responsible for approximately 47% of variance (Appendix **A3.41**)

DQOL

The combination of “Age”, “Time spent on the transplant waiting list”, “BMI” and “Daily insulin requirements at transplantation,” accounted for 46% of variance in Diabetes related QOL (Appendix **A3.42**)

Generic Health Related Quality of Life

PCS

PCS outcomes at six weeks were predicted by the model inclusive of “Gender”, “Psychotropic medications at transplantation” and “Gi symptoms.” Approximately 42% of the variance was explained by these variables (Appendix **A3.43**)

MCS

Whilst PCS was influenced by many variables, the only element that correlated with MCS was “Blindness”, which explained 15% of outcome variability (Appendix **A3.44**)

DQOL General Health Item

No valid predictor factor at six weeks was identified.

EQ-VAS

Positive predictor of VAS was “preserved urinary output”, while “being registered blind” and “gastrointestinal symptoms before transplantation” had a negative

impact. Overall, regression of these variables onto EQ-VAS scores at six weeks produced a model which explaining over 50% of variance (Appendix **A3.45**)

EQ-Index

Multiple factors were predictive of early EQ-index outcomes. Just like before surgery, “Gastrointestinal symptoms,” continued to correlate with EQ-index scores, along with “gender”, “haemoglobin and glucose tolerance test” at discharge and “duration of hospital admission”. This combination of variable was overall responsible for approximately 70% of variance (Appendix **A3.46**).

KDQOL Overall Health Item

“Age,” “Work status at transplantation”, “history of common psychiatric disorder” an “gastrointestinal symptom” concurred in determining 42% of KDQOL overall health item outcomes (Appendix **A3.47**).

A synopsis of predictors of HRQOL at six weeks from Transplantation is provided in **Appendix A3.47**

- Six Months from Transplantation: Predictors of HRQOL

<u>Disease Specific Quality of Life</u>

KDQOL

“Work Status”, “Psychotropic medications” and “Blindness” continued to predict KDQOL scores. At six months from surgery, “pre-transplant Gastrointestinal

symptoms" were again part of the model, which explained 78% in KDQOL variability (Appendix **A3.48**)

Diabetes-related QOL

DQOL at six months was negatively impacted by pre-transplant "Retinopathy", "GI symptoms" and "level of HLA sensitisation." The synergistic effect of these had the potential to influence 47% of variance (Appendix A3.**49**)

Generic Health Related Quality of Life

PCS

"Female gender", "common psychiatric disorders" and "Gastrointestinal symptoms" were negative predictor factors physical HRQOL at six months, while "full time work" prior to surgery was predictive of higher results. The combination of these variables explained almost the totality of variance (R^2 = 94%), as shown in Appendix **A3.50**.

MCS

"Work Status at transplantation", "common psychiatric disorders" "psychotropic medications", "Gastrointestinal symptoms" and "Blindness" all concurred in determining approximately 84% of MCS values (Appendix **A.51**)

DQOL Single Generic Health Item

The only factor influencing DQOL General Health ratings was "Retinopathy", responsible alone for 22% of variance. Despite the relatively low predicting value of

this variable, its importance resides in the high frequency with the study population, affecting early 92% of participants (Appendix **A3.52**).

EQ-VAS

VAS improvements throughout the study period were significant and large. Approximately 63% in variance at six months could be predicted by “gender”, “common psychiatric disorders”, “psychotropic medications”, “GI symptoms” and “being registered blind” (Appendix **A3.53**).

EQ-index

“Gastro-intestinal symptoms” continued to predict EQ-index levels, together with “preserved urinary output” and “haemoglobin level at discharge” . Overall, this model explained 53% of variance (Appendix **A3.54**).

KDQOL overall health item.

“Gastro-intestinal Symptoms”, “Psychotropic Medications” and “Blindness” were associated with lower of general health as compared to one year before. The predictive value of these variables was approximately 65% (Appendix **A3.55**).

A synopsis of predictors of HRQOL at six months from Transplantation is provided in **Appendix A3.56**

- One year from Transplantation: predictors of HRQOL

Disease Specific Quality of Life

Renal-related QOL

"Work Status" before transplantation, "common psychiatric disorders" and "Blindness" were the three predictors of KDQOL scores at one year, with an impact on variance of 33% (**Table 24**).

Table 24. Predictors of KDQOL at one year

PREDICTORS OF KDQOL AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-11.96	Inverse		.040
Blindness	-18.16	Inverse		.037
Work Status	8.70	Direct		.116
Constant	93.35			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.576	.332	5.461	3,33	.004

DQOL

Diabetes-related QOL outcomes seemed to be strictly related to the sphere of nutrition, with GI symptoms and low BMI as negative predictors. The model of best fit also included preserved sexual function at transplantation and time spent on the wating list. The combination of all these variables accounted for nearly 37% of variance (**Table 25**).

Table 25. Predictors of DQOL at 1 year

PREDICTORS OF DQOL AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Sexual Function	7.76	Direct		.188
GI symptoms	-_7.11	Inverse		.150
BMI	1.31	Direct		.049
Waiting List Time	.019	Direct		.048
Constant	24.66			.225
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.606	.368	5.235	4,36	.002

Generic Health Related Quality of Life

PCS

Of all the factors predicting PCS outcomes at different post-operative timepoints, "gender" was the most consistent. At one year from transplantation, together with "preserved urinary output at transplantation" and "number of chronic diabetic complications" could predict 56% of variance in physical HRQOL. (**Table 26**).

Table 26. Predictors of PCS at 1 Year

PREDICTORS OF PCS AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Gender	12.42	Direct		< .001
Preserved urinary output	10.48	Direct		.040
Number of chronic complications, binary: (<2, 3+)	-12.46	Inverse		.002
Constant	25.68			.045
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.747	.558	11.779	3,28	< .001

MCS

"Being registered blind" and "common psychiatric disorders" were the most recurrent predictors of MCS. At one year, combined with "retinopathy" they accounted for 55% of possible variations in outcomes (**Table 27)**

Table 27. Predictors of MCS at 1 Year

PREDICTORS OF MCS AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-12.85	Inverse		.002
Retinopathy	-9.60	Inverse		.077
Being registered Blind	-23.39	Inverse		< .001
Constant	108.17			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.742	.550	11.403	3,28	< .001

DQOL Single Generic Health Item

"Retinopathy" and "psychotropic medications at transplantation "were predictors of lower DQOL general health ratings at one year, influencing approximately 26% of variance at p = .002 (**Table 28**)

Table 28 Predictors of DQOL Generic Health item at 1 year

PREDICTORS OF DQOL Generic Health Item at 1 year				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Psychotropic Medications at transplantation	-21.55	Inverse		.020
Retinopathy	-31.77	Inverse		.015
Constant	127.48			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.512	.262	6.049	2,34	= .006

EQ-VAS

Approximately 17% of VAS outcomes were predicted by a combination of “common psychiatric disorders” and “age at transplantation”, with p = .031. (**Table 29**)

Table 29. Predictors of EQ-VAS at 1 Year

PREDICTORS OF EQ-VAS AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Age at transplantation	.528	Direct		.160
History of common psychiatric disorders	-14.01	Inverse		.063
Constant	67.10			.003
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.413	.171	3.813	2,37	= .031

EQ-index

“Psychotropic Medications” at transplantation was the only pre-transplant predictor of EQ-index scores. Together with “glucose tolerance test” scores at discharge and “creatinine levels at six weeks”, they were overall responsible for 32% of variance, with a p value of .022 (**Table 30)**.

Table 30 Predictors of EQ-index at 1 Year

PREDICTORS OF EQ-index AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Being on Psychotropic Medications	-2.48	Inverse		.071
Normal Glucose tolerance test at discharge	.166	Direct		.194
Serum creatinine at six weeks	.003	Direct		.176
Constant	.455			.198
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.561	.315	3.827	3,25	= .022

KDQOL overall health item.

"GI symptoms", "low BMI", "higher number of diabetes chronic complications" and "hypoglycaemia unawareness" were the factors associated with lower perception of general health as compared to one year earlier. The combination of all these pre-operative variables accounted for 40% in variance (**Table 31**)

Table 31 Predictors of KDQOL Overall Health Item at 1 Year

PREDICTORS OF KDQOL Overall Health Item AT 1 YEAR				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
GI Symptoms	-12.46	Inverse		.048
BMI	1.13	Direct		.155
Hypoglycaemia Unawareness	-15.76	Inverse		.009
Number of Chronic Complications	-4.65	Inverse		.514
Constant	87.24			.004
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.635	.404	5.250	4,31	= .002

A synopsis of pre-transplant predictors of HRQOL at one year from transplantation is provided in Appendix **A3.57**, while Appendix **A3.57** gives an overview of pre-transplant predictors of HRQOL predictors at all timepoints, stratified by instrument.

Summary

Of over 30 pre-transplant variables assessed, 20 potential predictors of HRQOL were identified. Some of these factors were almost ubiquitous across scales and time-points of data collection, while others were mostly/only associated with a specific domain or stage of the transplant journey.

The most frequent predictor encountered was “Gastro-intestinal symptoms”. All the scales analysed were influenced by this complication, albeit at different time-points.

The second most recurrent predictor of pre- and post-pancreas transplantation HRQOL was “Common Psychiatric Disorders” or being on “Psychotropic

Medications" prior to surgery. In other words, pre-transplant mental health seemed to influence most scales and not just those strictly related to emotional well-being. Interestingly neither was related to DQOL, while it featured heavily amongst predictors of KDQOL.

Equally "being registered blind" and "Work status" were amongst the recurrent predictors of renal related global scores but not of DQOL. The latter seemed to be more closely associated with variables related to nutrition and diet – such as GI symptoms, BMI, and insulin requirements. Another important predictor of diabetes QOL was the amount of time spent waiting for transplantation and, possibly for similar reasons, the degree of "HLA sensitisation". Surprisingly, Hypoglycaemia unawareness was never linked to diabetes related QOL, however it was a predictor of change in general health perception at one year. Equally unexpected, while "blindness" effected MCS scales consistently throughout the study, it was never a predictor of PCS.

In keeping with most literature, age and gender were predictors of HRQOL, although essentially limited to specific scales. Female gender was a negative predictor of PCS at all time-points post transplantation, while older age had a positive effect on early diabetes related QOL and VAS at one year from surgery. In general, VAS scores were predicted at different stages by a combination of all the above-mentioned variables: age, gender, mental health wellbeing, blindness, GI symptoms and preserved urinary output ahead of surgery.

Having a higher number of diabetes chronic complications didn't seem to effect pre-operative or early post-operative HRQOL, however it resulted predictor of physical wellbeing and overall perceived general health change at one year from surgery.

EQ-indexes at one year seemed mostly effected by post-operative factors, such as early pancreatic and renal function (glucose tolerance test results at discharge and serum creatine at six weeks, respectively).

Conversely, some of the factors associated with baseline HRQOL ceased to be relevant after surgery, such as “cigarette smoke”, at first associated to pre-operative MCS, VAS and DQOL generic health single item. Equally, “history of blood transfusion” affecting disease specific QOL at baseline, became meaningless after surgery, since 75% of participants required blood transfusions during the procedure. Peripheral neuropathy and claudication, amongst the factors effecting pre-transplant PCS and KDQOL respectively, were equally absent from the list of post-operative relevant HRQOL predictors. The unlikelihood of significant reduction in these symptoms in such a short period of time, might suggests that perhaps the magnitude of overall HRQOL improvements lessened their impact on HRQOL. This could also explain why the proportion of scales affected by GI symptom reached a peak of 75% at six months from surgery and then fell to 25% at the end of the study period.

3.4 CONCLUSIONS

Baseline data collection was seamless on almost the totality of the study sample, and this allowed a detailed description of participants’ characteristics.

Most patients needed a combined pancreas/kidney transplant. Of these, 77% were established on dialysis at transplantation. On average, duration of renal replacement therapy was approximately 500 days, slightly longer than the time

spent of the transplant waiting list. The wait for surgery was a little over 15 months, slightly longer than the national UK, as reported by NHS Blood and Transplant (NHS Blood and Transplant, 2020), despite low HLA sensitization rates.

The average pancreas transplant recipient, equally likely to be female or male, was more often Caucasian, approximately 40 years old, relatively slim, with a mean duration of diabetes of nearly 30 years. In terms of progression of disease, participants reflected the characteristics of the average pancreas/kidney transplant recipients, who are burdened by a disease advanced enough to have brought forward renal failure and possibly several chronic complications, but not to the point of jeopardising the chance to withstand major surgery.

Hence, the quantification of HRQOL served a dual purpose: it was instrumental in clarifying whether pancreas transplantation improves HRQOL, but it was also necessary to understand how deeply HRQOL is affected by diabetes in this selected cohort of patients with “intermediate” severity of disease.

And indeed, PROMs collected provided an exhaustive depiction of HRQOL on the pancreas transplant waiting list and revealed levels of quality of life which were overall quite poor. At this stage of disease progression, all aspects of living with the diabetes seemed equally burdensome. Results in renal related QOL were slightly less homogeneous but still quite low, with burden of renal failure and employment rates representing the worst scales. Support received by dialysis staff was the highest scoring scale, underlying the relevance of a holistic approach to renal failure to QOL outcomes. Generic HRQOL outcomes suggest a predominant role of poor physical health in determining low HRQOL, while the higher in social/emotional wellbeing possibly highlight some degree of adaptation to a chronic condition.

After transplantation, PROMs questionnaire return rates were jeopardised by lockdown, in an apparently random fashion. However, I did identify some differences between “never responders”, participants who did return at least one set of questionnaires and “full completers”. Ultimately, none of the participants with graft pancreatectomy belonged to the group of “full-completers”. Hence, the post-operative HRQOL described in this study pertains mostly to individuals with functioning organs.

Despite the reduced return rates, it was still possible to detect significant post-operative HRQOL changes at all points of data collection.

First and foremost, participants’ QOL was almost immediately improved by no longer having diabetes or requiring dialysis. In fact, the change in DQOL was already significant at six weeks from surgery and, although global renal QOL was not overall improved, some of the individual scales were. More specifically, early renal benefits seemed to be associated with freedom from dialysis rather than improvement of renal symptoms.

Astonishingly, just a few weeks after major surgery, “physical functioning”, “role limitation due to physical problems” and “energy” levels were all statistically higher.

Mental health improvement was not as obvious, albeit levels were higher than PCS to start with. And in fact, PCS and MCS at this stage, showed a moderate correlation, absent before transplantation.

These early changes were already enough for participants to perceive their general health as improved, as documented by statistically significant outcomes in VAS and

DQOL generic health item ratings. However, no tangible improvement in EQ-indexes was identified.

At six months, all the summary scales were statistically improved from baseline, except for MCS scores. The correlation between PCS and MCS was even stronger, suggesting perhaps of a reduction in the initial gap between physical and emotional well-being. EQ-indexes growth was still non-significant.

At one year from surgery, transplantation benefits were well established and so was HRQOL gain. However, KDQOL and PCS scores seemed to reach a plateau, while there was a statistically significant inflection in DQOL from the previous time-point, essentially driven by the “Worry” Scale. On the contrary, participant’s perception of general health continued to improve throughout the study, as captured by EQ-VAS, DQOL Generic Health Item and EQ-Health States distribution. Consequently, mean EQ-index at one year was statistically better than pre-transplant values.

Ultimately, at one year from surgery, male gender, older age, preserved ability to work, preserved sexual function and urinary output at transplantation as well as an overall lower number of chronic complications were predictors of higher HRQOL.

In contrast GI symptoms, history of psychiatric disorders and need for psychotropic medications, sever ophthalmic complications/blindness, lower BMI, hypoglycaemia unawareness, HLA sensitisation and longer time on the transplant waiting list, were predictors of worse outcomes. Interestingly, psychological well-being seemed to

influence outcomes of many domains object of the study besides mental health scales. Details on the direction of the associations between these factors and PROMs outcomes at one year can be found in **Tables 26-27-2829-30-31-32-33.** Sample size was insufficient to stratify differences in HRQOL gains based on type of transplant received. Equally, results for variables with a very low or very high frequency could not be interpreted, because of lack of statistical meaning.

A further cross-sectional study- described in the following chapter- was set up on the historic cohort of Oxford Transplant Centre pancreas transplant recipients to investigate HRQOL and potential predictors in the longer term.

4 CHAPTER 4: CROSS-SECTIONAL OBSERVATIONAL STUDY ON LONG TERM QUALITY OF LIFE IN PANCREAS AND PANCREAS- KIDNEY TRANSPLANT RECIPIENTS.

4.1 INTRODUCTION

The analysis of pancreas transplant outcomes collected worldwide (Gruessner and Gruessner 2016) has highlighted how the turning point for graft survival is the first year after surgery: reaching this mark with a functioning transplant is a significant predictor of long-term success of the procedure (Gruessner and Gruessner 2016.)

The first cause of graft loss in this time period is “death with a functioning graft,” followed by “immunological loss”. Whatever the outcome, by the end of the first year most recipients reach their new “status quo” (Gruessner AC, 2016).

If it is true that euglycemia is associated with reduced risk of diabetic long term complications (The Diabetes Control and Complications Trial Research Group, 1996) and that successful pancreas transplantation can lead to improvement of pre-existing complications (Fioretto, Steffes et al. 1998, Coppelli, Giannarelli et al. 2005, Giannarelli, Coppelli et al. 2006), it is reasonable to infer that pancreas transplantation likely contributes to a stable clinical condition.

However, health is not exclusively determined by absence of disease as underlined in the WHO definition: “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (Organization 1946).

Hence, HRQOL is inevitably a composite concept, where individuality plays a major role.

Moreover, some of the stressors which have shaped pancreas transplant recipients'–whole lives - such as fear of hypoglycaemic spells,–for example - may persist despite the success of their transplant. For these reasons, it seemed quite relevant to understand what HRQOL in pancreas transplant recipients looks like after the first year, which of the different forms of pancreas transplantation determines the highest levels of long term HRQOL and if there are any pre- and peri-operative predictors.

A deeper knowledge of these aspects could provide insight into the ideal timing of this intervention and enhance clinical management.

In consideration of the inherent risk of bias embedded in cross-sectional studies, a single centre project seemed the most reliable approach.

Over 1000 pancreas transplants have been performed at the Oxford Transplant Centre since 2002, with a stable waiting list of approximately 60-70 individuals. On this account, it seemed possible to accrue an adequate sample size without incurring blatant selection biases.

4.1.1 Objectives and Outcome Measures

The primary objective of the study was to assess long-term HRQOL after pancreas transplantation. The secondary aim was to establish if there were differences in

various types of pancreas transplant recipient, possibly stratified by transplant function. In particular, it seemed interesting to compare long-term outcomes of patients who had sought transplantation as treatment of diabetes and renal failure against those who received the intervention to resolve life-threatening hypoglycaemia unawareness. Finally, the research aimed to identify which pre- and post-operative factors correlated with best/worst HRQOL, if any. Hence, the outcome measures were pre- and post-transplantation clinical data and PROMs, as shown in **Appendix A4.1.**

4.2 METHODS

4.2.1 Summary of Study Design

This was a single centre, retrospective study of patients who had undergone pancreas transplantation at the Oxford Transplant between February 2003 and August 2021.Any adult who underwent pancreas transplantation at Oxford Transplant Centre was eligible for this study, except for patients not fluent in English or who were terminally ill. Potential participants fell in two separate cohorts: individuals who had hypoglycaemia unawareness only (PTA recipients) and those who had developed renal failure or both (SPK, PAK and PASPK recipients). Patients active on the Oxford Pancreas Transplant waiting list were invited to participate as control group. Further invitations were sent to new patients who became “active” during the study period. Participants and controls were asked to complete the study’s surveys at a single time point and to allow the research team to correlate their clinical data to HRQOL scores.

The consenting process started either by telephone or via email, based on individual preferences. It was then finalised either by post or via Redcap, a secure online platform provided by the University of Oxford, Medical Science Division.

Similarly, participants had the opportunity to complete the paper or electronic version of the study questionnaires.

Participants who verbally agreed to return the study PROMs but did not do so within one month, were contacted again (up to two times) and the study documents re-sent if necessary.

Once the data was collected, it was analysed for two separate projects: a longitudinal and a cross-sectional study.

Demographics, clinical and HRQOL data was collected from all study participants and control group. Descriptive statistics were stratified by transplant type and compared to identify clinical predictors of long term HRQOL. Some recipients had completed the Short Form 36 – one of the study questionnaires- as part of their pre-transplant assessment. Upon recruitment, the research team sought permission to retrace and eventually include this material in the DPhil project. Hence, pre- and post-transplant data was used in the longitudinal study to gain insight on the trajectory of HRQOL in the longer term.

4.2.2 PROMs Selection

The pool of potential study participants was a mix of pancreas and pancreas/kidney– recipients - with or without functioning grafts - and individuals waiting for the intervention. In the absence of a specific pancreas transplant PROM, it seemed quite difficult to find suitable disease specific instruments. For this reason, and in a bid to reach acceptable return rates, it was decided to use relatively short and reliable generic HRQOL instruments: SF-36 and EQ-5D-5L (Appendixes **A4.4** and **A3.6**, respectively). However, there seemed to be one disease specific domain worth investigating, potentially present across all study cohorts: fear of hypoglycaemia. This condition is not just the prerogative of individuals with untreatable hypoglycaemia unawareness, but it may be present even in case of mild hypoglycaemia (Martyn-Nemeth, Schwarz Farabi et al. 2016). As a consequence, the Hypoglycaemia Fear Survey II – Worry (Appendix **A4.50**), a specific PROM developed and extensively used to measure hypoglycaemia fear, was included in the protocol (**Table 32**).

Table 32. Study PROMs

STUDY PROMS	
SF-36®	Short Form 36 Survey Instrument
EQ-5D-5L® EQ-VAS	EuroQol Five Dimensions Questionare Visual Analogue Scale
HFS-II W	Hypoglycaemia Fear Survey -II Worry Scale

- SF-36®

The Short-Form 36® (Appendix 4.51) was developed by RAND as part of The Medical Outcome Study (MOS) in 1992 and it has been used across clinical conditions ever since. It includes 36 items and covers 8 health domains: bodily pain, general health perception, mental health, physical functioning, role limitations due to emotional problems and role limitations due to physical health, social functioning, and vitality. (**Appendix 4.2**). A health profile can be calculated from the scoring of the 8 domains. The scoring system transforms data collected on a Likert scale into a 0-100 scale, where 0 is the worst possible and 100 the best possible outcome. It is identical to the generic questionnaire embedded within the KDQOL-SF™ described in Chapter 3, subsection 3.3.2 and allows for the calculation of mental and physical component summary scores. According to Parizi and colleagues, it is the most frequently used PROM in transplantation (Shahabeddin Parizi, Krabbe et al. 2019) and it shows adequate psychometric properties in patients with diabetes, renal failure and transplant recipients (Gibbons and Fitzpatrick 2009, Gibbons and Fitzpatrick 2010).

- EQ-5D-5L®

As described in Chapter 3, EQ-5D-5L allows the computation of a health status out of 3125 possible combinations and an associated health index or utility value to be assigned to that state. EQ-indexes were calculated as in the previous study, according to the latest NICE's recommendations, by mapping the data gathered with EQ-5D-5L onto the EQ-5D-3L value set (Hernández, Wailoo et al. 2012, Hernandez, Pudney et al. 2020). The Visual Analogue Scale (EQ-VAS) allows the

individual to rate the perceived health status from a minimum of zero (worst imaginable health) to 100 (best imaginable health) and it therefore embeds a degree of subjective interpretation of HRQOL. Like the SF-36, this instrument has been deemed suitable for individuals with diabetes and renal failure (Gibbons and Fitzpatrick 2009, Gibbons and Fitzpatrick 2010).

- Hypoglycaemia Fear Survey- II Worry (HFS-II W).

One potential common denominator to many participants was fear of – hypoglycaemia - whether residual or recurrent. As highlighted in the previous chapter, by the end of the first year after transplant, the initial downward trajectory of diabetes related QOL was essentially related to increased "Worry". Hence, it seemed worthwhile to include the "Worry" scale of the Hypoglycaemia Fear Survey-II in our long-term study. This instrument derives from the Hypoglycaemia Fear Survey, developed to quantify behavioural and psychological responses to problematic hypoglycaemia in patients with type 1 diabetes (Cox, Irvine et al. 1987). It has good psychometric properties (Gonder-Frederick, Schmidt et al. 2011) and it has been deemed appropriate for pancreas and islet transplant recipients (Speight, Reaney et al. 2010). HSF-II is made of two separate subscales: Behaviour (HFS-II –) – 15 items - and Worry (HFS-II W) – 18 items (**Appendix A4.3**). Questions revolve around frequency of behaviours and concerns related to hypoglycaemic crisis. Responders are invited to rate each question on a 5 points Likert scale ranging from "0" (never) to "4" (almost always). Each subscale can be administered separately and allows for an independent summary score. A global HFS value can be calculated by the sum of the two summary scores.

According to the developers, HFS-II shows good correlation with other PROMs focused on psychological and generic wellbeing. In particular, HFS-II W showed a statistically significant inverse correlation with SF-12 MCS (Gonder-Frederick LA et al, 2011).

4.2.3 Clinical Data

Data on pre-transplant characteristics and post-operative course was collected from transplant pre-assessment forms, participant's paper case notes, electronic patient record (EPR) and Oxford Transplant Centre Pancreas Transplant Database.

Transplant outcomes at discharge, one year, five years and at recruitment were investigated in terms of graft function, glucose tolerance test/glycated haemoglobin, creatinine, and haemoglobin levels.

The relationship between clinical data and HRQOL was investigated as long-term outcomes, pre-operative predictors and in relation to population norms.

4.2.4 Statistical Analysis

The degree of correlation between binary/continuous or continuous/continuous variables, was investigated with Pearson's and Spearman's Correlation for normally and non-normally distributed data, respectively. Frequencies of categorical variables were compared with χ^2 (with Yates continuity correction for 2 by 2 tables) or Fisher's test, when the value of more than 25% of cells was "5" or less.

Continuous QoL outcomes, including the EQ-5D-5L utility index, were analysed with generalized linear models (t-tests, Mann-Whitney test, Wilcoxon Singed Rank Test, multivariate regression). The level of statistical significance adopted throughout the

study was p = 0.05. Values of p reported refer to two-tailed significance. Overall, the statistical approach was similar to the one adopted from the previous study and data was analysed with the same software (Microsoft SPSS).

4.2.5 Impact of Covid-19 on chosen methods

The initial plan was to set up this study in the spring of 2020 for the duration of one year. However, requests to set up new non-Covid 19 related studies were halted until April 2021. Further delays in obtaining permissions for this study were caused by the backlog accrued from the pandemic. The research commenced in August 2021 and finished in April 2022, significantly reducing the time available to reach out to potential participants and maximise recruitment. In a bid to appeal to as many individuals as possible, I included a digital data collection option for consenting and completion of the study PROMs.

4.3 OUTCOMES

4.3.1 Recruitment And Return Rates

The initial plan was to set up this research at the start of 2020 and collect data for one year. However, this was disrupted by the Covid-19 pandemic: the study began at the end of August 2021, significantly shortening the time available for recruitment and data collection. The first patient was enrolled on 19/11/21. The study finished on 30-04-2022. Potential participants who verbally agreed to take part received consent forms and study PROMs simultaneously, either by post or via a personal link to the online platform Redcap. Thereby, recruitment and return rates would theoretically overlap. A total of 124 recipients initially accepted to participate, however 26 (21%) never returned either consent form or study PROMs. Approximately 80% had received the study documents by post, while 20% chose the link to the online platform (**Appendix A4.5**), however the electronic modality was only available for the last third of the recruitment period.

In conclusion, although return rates were technically 100%, it is fair to say that conceptually the actual figure is approximately 80%, which can be considered an acceptable target. There was no statistically significant difference in return rates in relation to response modality. In contrast, the number of patients on the waiting list recruited was too low to represent a statistically meaningful control group: only 8 people were actually enrolled in this cohort. The study is therefore a cross-sectional analysis between the two main categories of pancreas transplant recipients: those with end stage renal failure (recipients of SPK, PAK and PaSPK) and those with

hypoglycaemia unawareness (PTA recipients), for a total of 98 final study participants.

4.3.2 Clinical Data

Of the 98 recruited recipients, 85% were individuals who had developed renal failure as a consequence of diabetes. The great majority received a Simultaneous Pancreas/Kidney transplant (75%). A small contingent of patients conceptually belonging to this cohort (8.2%), had a functioning kidney transplant - either as a result of Kidney Transplantation Alone or as outcome of a previous SPK where the pancreas had failed. That being the case, they received a Pancreas after Kidney or Pancras after SPK.

The remaining 15% of the study population were individuals who received a Pancreas Transplant Alone for life threatening hypoglycaemia unawareness (**Figure 14).**

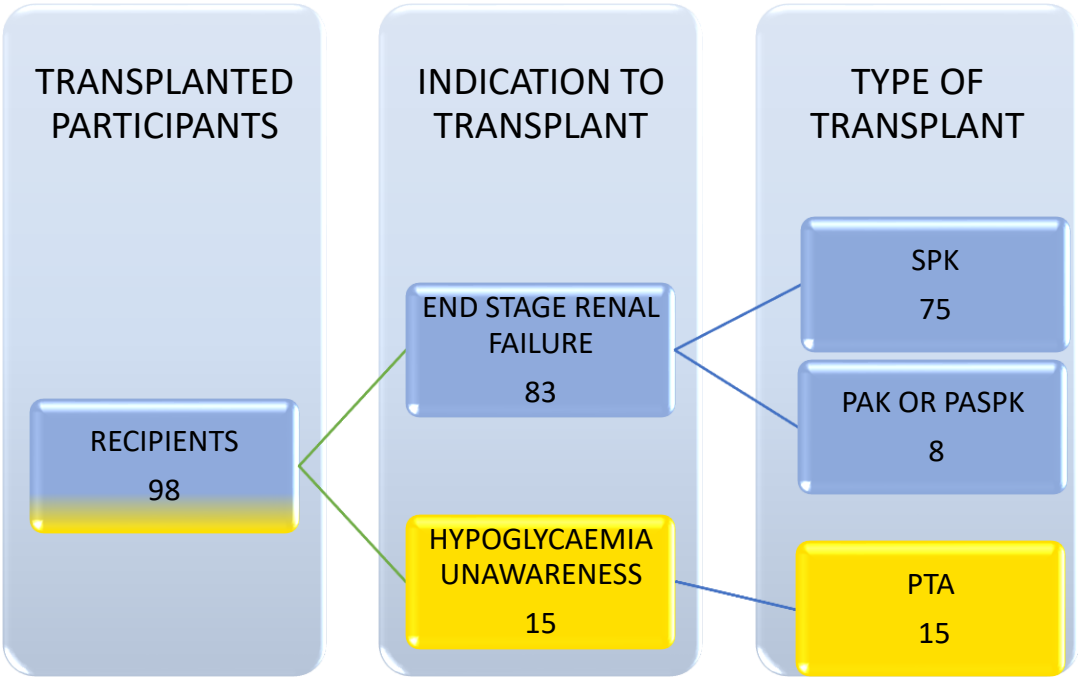


Figure 14. Diagram of study participants, stratified by type of transplant received.

Upon recruitment, 97% of study participants had reached 1 year since transplantation, 92% had reached two years follow up and 75.5% had reached the five-year mark. The meantime from transplantation was 8.6 years, with no significant difference between SPK/PAK/PaSPK and PTA recipients as shown in **Table 5** (see below**).** Unlike our previous study, it was possible to compare results of these two conceptually different categories of recipients and ascertain the degree of variability in their clinical features as well as their HRQOL outcomes. Hence descriptive statistics were stratified by type of pancreas transplant recipient, to identify baseline differences across groups, before and after transplantation.

Results were also checked against time from transplantation, by splitting the sample in two groups at the median percentile: participants up to 8 years from surgery and participants who had been transplanted for over 9 years.

- Pre-operative data

Despite the relatively long time from transplantation, it was possible to retrieve most pre-transplant clinical variables of interest from pre-transplant assessment forms and the Oxford University Hospitals digital patient encounter platform. However, data that was sporadically recorded at the time, for example “history of common psychiatric disorders” or “use of psychotropic medications at transplantation”, couldn’t be acquired retrospectively in a reliable way. The progression of renal failure in the life of patients with type 1 diabetes represents a clinical turning point and it correlates with increased mortality risk (Groop, Thomas et al. 2009). For this reason, it would be sensible to speculate how SPK/PAK/PASPK and PTA recipients

might display numerous clinical differences. However, our study only highlighted a handful of dissimilarities such as age at transplantation, gender, history of cigarette smoking, hypertension and, unsurprisingly, frequency of hypoglycaemia unawareness. All the other pre-operative variables considered, including number of complications of diabetes, glycated haemoglobin levels, duration of diabetes to mention a few important ones, were not statistically different. One possible interpretation is that the stringent clinical criteria observed in selecting pancreas-kidney recipients might result in a smaller clinical gap between these two separate cohorts, despite the presence of renal failure. PTA recipients were more frequently females, never smokers and younger than patients requiring both pancreas and kidney transplant, while the latter were twice as frequently hypertensive and affected by hypoglycaemia unawareness in just one third of the cases.

The study group was made up predominantly of Caucasian individuals (93%) of working age (Mean 46.36 ± 8.66 years), relatively slim (BMI = 25.8 ± 4), at their first transplant (85%). The average recipient had been diagnosed with diabetes during adolescence, had a daily insulin requirement of approximately 46 units/day, mean HbA1c levels of 68.39 mmol/mol ± 19.3 (= 8.3%), and 3 or more complications of the disease. Besides renal failure, retinopathy was the most frequent chronic complication, affecting approximately 94% of participants, followed by neuropathy (66%), hypoglycaemia unawareness (42%) and gastrointestinal symptoms (36%). Cardiocirculatory complications such as history of ischemic heart disease, stroke or claudication were present in less than 10% of cases. The sample was relatively unsensitised for transplantation (Mean CRF= 19.4 ±30.1) and the mean time spent wating for a transplant was approximately 1.3 years.

There was no statistically significant difference across groups when looking at the proportion of individuals who had completed their pre-transplant assessment SF-36 (table), although the total number was low (29 participants, 30% of the study sample).

Furter details on pre-operative descriptive statistics can be found in Appendices **A4.3-A4.4**.

- Transplant Data

With regards to transplant-related data, the only significant dissimilarities across groups were exocrine component drainage and ITU admission, however both were established ahead of surgery. In fact, at our centre, pancreas grafts are routinely anastomosed to a loop of small bowel in case of SPK but most commonly to the recipient's bladder if the organ is transplanted alone (this being a change of technique over earlier practice). Also, after SPK patients go invariably to ITU for monitoring, while that is not the case for PTA recipients. All recruited SPK and one half of PAK/PASPK patients were enteric drained, while over 75% of PTAs were anastomosed onto the bladder. The latter, in particular, might have implications on HRQOL: different types of drainage are associated with different complications. Although some investigators found no differences between recipients with enteric or bladder drained pancreas (Lo, Stratta et al. 2001), in our study a high proportion of patients ended up requiring enteric conversion (67% in 8.5 years of follow-up).

Most grafts were from donation after brainstem death (DBD, 83%). Mean donor's age was 39.04 years (± 13.76) with no statistically significant gender differences. Mean pancreatic cold ischaemic time was 11 ± 2 hours (CIT), and anastomotic time

approximately 60 minutes. Usually the pancreas, which is thought to be more vulnerable to ischaemia-reperfusion injury, gets implanted first. Thus, kidney's cold ischaemic time was inevitably longer. (**Appendix A4.7**).

- Post-transplant Data

Insulin independence was immediate in 90% of cases and 74% of SPK recipients had primary kidney function. The number of patients who certainly received blood transfusion was four times higher than those who didn't (44 vs 11), with no differences across groups. However, this data was only available for about one half of the sample, making this result unreliable. There were no statistically significant differences in terms of medical complications, which occurred in 41% of cases.

Approximately 66% of recipients required some form of radiological investigation (MR in the early years, CT angiogram in more recent eras): 35% of these did not highlight any substantial problem. The most frequent radiologically diagnosed abnormality was the presence of intra-abdominal collections/haematomas (52% of CTs, 36% of recipients). Pancreatic venous thrombosis was present in 46% of CTs (32% of recipients), albeit partial and clinically silent for the great majority of patients (83%) but were all treated with therapeutic anticoagulation. Five patients developed complete thrombosis requiring graft pancreatectomy (5.1%). Indirect signs of pancreatitis, such as peripancreatic fat stranding, heterogenous enhancement of the gland, oedema, were present in approximately 24% of scans (17% of recipients). **(**Appendix A4.7). No renal graft was explanted, although some CT evidence of kidney perfusion defects was found in 8 out of 73 (11%) of SPK recipients. Equally less common were bowel anastomosis complications, with a percentage of duodenal leak of approximately 6% of the total sample.

Overall, surgical –complications - either clinically evident or identified radiologically - occurred in about a half of recipients. Conservative management resulted in resolution in 42% of situations. In other words, 6 out of 10 patients who developed surgical complications returned to the operating theatre. There was a statistically significant difference in re-laparotomy rates across groups, with PTA recipients being two and a half times more likely to return to theatre (47% vs 18%), despite a similar numerical incidence of complications. Despite this, the mean hospital stay was essentially the same in the two cohorts (SPK = 17.2 ± 9.2 days, PTA 17.9 ± 10.6 days. At discharge 93% of recipients were insulin independent and the totality were free from dialysis. Glucose tolerance testing was performed on 70% of patients, with average 2 hours glucose levels of 7.43 ±2.39 mmol/l. SPK/PAK/PaSPK had statistically higher mean creatine – as expected - and lower haemoglobin levels. Details on peri-operative outcomes can be found in **Appendix A4.9**

Approximately 94% of patients who had reached the one-year mark (89 out of 95), were insulin independent, and 99% of SPK/PAK/PASPK recipients was still dialysis free (79 out of 80). mean glycated haemoglobin (HbA1c) and creatinine levels were 35 ± 8 mmol/mol (5.4 ± 2.9 %) and 119 ± 36 umol/l respectively. There no longer was a statistically significant difference in renal function between SPK and PTA recipients. The discrepancy in haemoglobin levels persisted, however SPK recipients were no longer anaemic, whereas PTA recipients had mean haemoglobin values of 108 ± 15 g/L.

A total of 90 out of 98 participants reached the 2-years follow-up. Of these, 90% were still insulin independent, whilst 97% of SPK/PAK/PASPK recipients were dialysis free. mean HbA1c and creatinine levels were essentially unchanged.

At five years pancreatic graft survival was 85% of patients who had reached this timepoint (63 out of 74), while 57 out of 60 SPK/PAK/PASPK recipients were still off dialysis (95%). Hence, metabolic control and renal function were quite stable (**Appendix A4.10**) At the time of data collection – at a mean of 8.6 ± 4.5 years after surgery- 92% of participants had preserved pancreatic function: 9 SPK/PAK/PASPK and 4 PTA recipients were on dialysis. “Actuarial” HbA1c, creatinine and Hb levels refer to approximately 30% of participants. In this smaller cohort I didn’t find any statistically significant difference in transplant in graft survival rates between PTA and SPK recipients, which, however, continued to show higher haemoglobin levels.

Thus, just like in the prospective longitudinal study, HRQOL results pertain essentially to individuals with successful transplantation.

- Summary

The study population was essentially made of two cohorts: patients who had received a pancreas and a kidney transplant (85%) and patients who had received a pancreas transplant alone (15%). A few clinical differences across cohorts were identified, with more SPK recipients being male, older, and hypertensive. As expected, there was a statistically significant difference in hypoglycaemia unawareness frequency across groups. Long term outcomes across cohorts were similar: pancreas graft survival at the time of data collection- approximately 8 to 9 years from transplantation- was above 90% and over 80% of both groups had preserved renal function.

4.3.3 Patient Reported Outcomes

A small proportion of the cross-sectional study participants had completed SF-36 questionnaires before transplantation, as part of their pre-transplant assessment. Hence it was possible to investigate long term longitudinal changes in HRQOL after pancreas transplantation in this sub-group of patients. Both this small "longitudinal study" and the actual "cross-sectional study" object of this chapter are reported below.

- Longitudinal Study

A total of 29 individuals (30%) had completed pre-operative SF-36. Of these, 22 received a Simultaneous Pancreas Kidney, while 7 received a Pancreas Transplant Alone. There were no statistically significant differences in baseline clinical features between this sub-group and the totality of study participants.

<u>Pre-transplant</u>

Pre-transplant SF-36 were compared to post-transplantation outcomes.

Results were first analysed as a whole and then stratified by indication to transplantation/type of transplant received, to identify differences in baseline and long term HRQOL across groups: no statistically significant difference before transplantation emerged, as shown in **Appendix A4.11**. Hence, I report results from the totality of the sample.

The highest scores were achieved in “role-emotional” and “social function” (Mean 74.7 ± 42.4 and 71.9 ± 24.5 respectively), with “role-physical”, “emotional wellbeing” and “pain” following closely (see table x). “Physical functioning” occupied an intermediate position (59.8± 28.6), while “energy” and “general health” scored the lowest (34.8 ± 24.3 and 32.4 ± 20). The resulting summary scores were quite low, with mean PCS and MCS scores of 36.8 ±10.8 and 47.1 ±10.18, respectively. There was no correlation between the two summary scores before surgery, as to suggest a significant gap between physical and mental wellbeing (Pearson Correlation = .100, p = .635).

Post-transplant

The second time point of data collection occurred at approximately 9 ± 5 years from transplantation, with no differences across groups. In the longer term, the highest scoring scales were relative to mental health domains: emotional wellbeing and role emotional were 73.9 ± 15.7 and 67.8 ± 38.3. Physical and social function scores were almost identical, with mean values around 60 (**Appendix 4.12**) there seemed to be a lesser gap between PCS and MCS, yet there was still no correlation between the two (Pearson Correlation = .107 p =. 596).

Longitudinal Changes

Although there were no meaningful differences across groups in individual and summary scales both before and after transplantation, I identified a few statistically significant longitudinal changes (**Appendix 4.14**). Looking at the group as a whole, a few domains seemed either stable or trending upwards, such as “emotional well-being”, “physical functioning”, “general health” and “energy/fatigue” (Appendix

A4.12). Other clearly showed a downwards trajectory, such as “role emotional”, “social functioning” “role physical” and “pain”, which was the only statistically significant change identified, albeit with a very large effect (Cohen’s d = .933) as shown in **Figure 15**

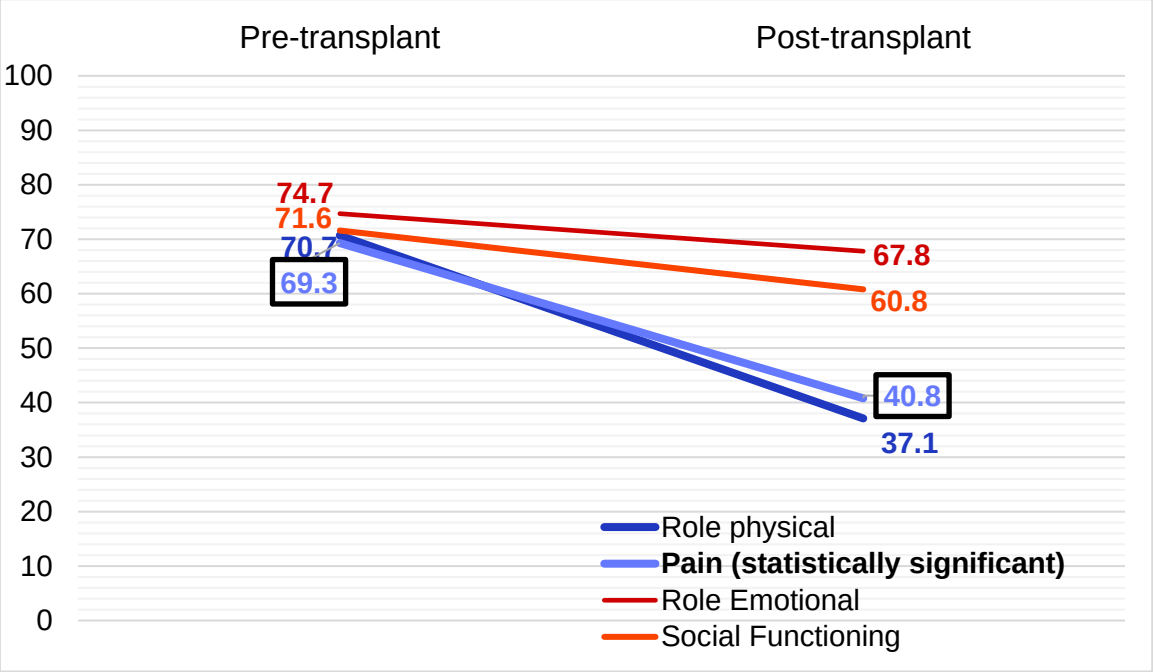


Figure 15. Longitudinal SF-36 results: domains with a downward trajectory

The increase in pain perception was no longer statistically meaningful when looking at the two transplant cohorts separately, although it seemed that PTA recipients tended to experience more “pain.” Other differences between SPK and PTA recipients were the change in “general health” and “energy/fatigue” levels: in the first of these, both groups reported values higher than baseline, but the growth was meaningful for SPK only, with a medium-large effect size. In contrast, while SPK recipients reported statistically higher “energy,” in the case of PTA it had plummeted from 42 ± 31.5 to 24 ± 24. Although this drop was not significant it was quite noticeable. Similarly, the fall in “role physical” looked dramatic but failed to reach

the threshold for significance. The analysis of PCS and MCS mean scores didn't highlight any meaningful change neither for the whole group **(Figure 16)** or for the separate cohorts (**Appendix A4.15-A4.16**).

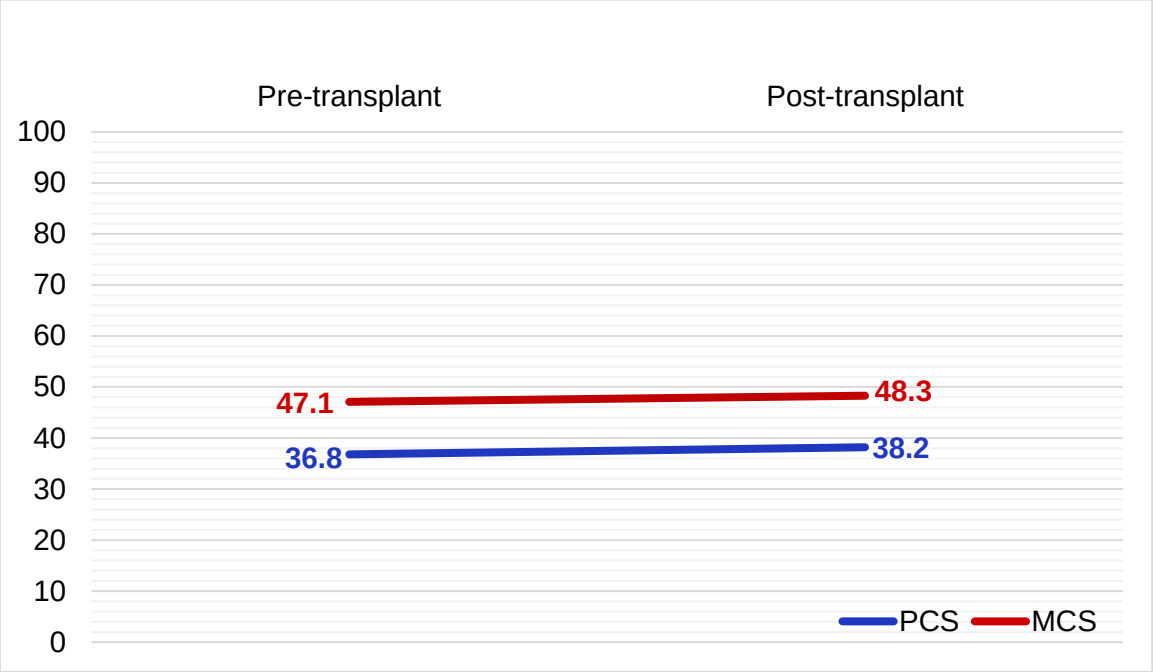


Figure 16. SF-36 results: PCS and MCS trajectory

Population Norms

As previously illustrated, longitudinal changes in PCS and MCS were not statistically significant and there was no correlation between the two components at any timepoint of data collection, for any group. In keeping with these findings, results obtained by comparing SF-36 outcomes (median scores) to UK population norms showed discrepancies between physical and mental well-being. Participants' PCS scores were low for all transplant categories and fell within UK population's lowest quartile at both timepoints. On the contrary, MCS scores fell within the second quartile even prior to surgery, and afterwards as shown in **Figure 17**

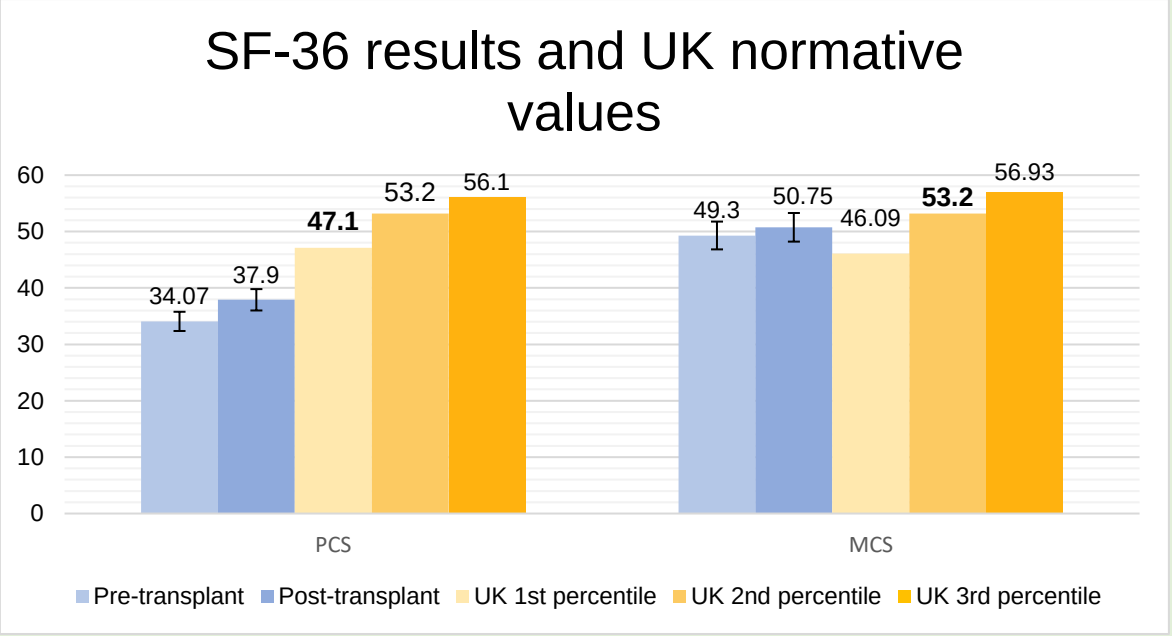


Figure 17. PCS and MCS trajectory and UK population norms (Jenkinson, 1998)

The only exception is represented by PTA recipients: for these patients' mental health fell slightly below the 25% percentile after surgery. A detailed breakdown of SF-36 scores for the whole sample, for SPK/PAK/PASPK and PTA relatively to UK normative data can be found in **Appendixes A4.17-A4.18-A4.19** The size of the sample did not allow any meaningful stratification based on time from transplantation, hence the data reported refers to a mean follow-up of 8.61 ± 4.46 years.

- Cross-sectional study

Potential participants were asked to complete a set of PROMs and were given the opportunity to choose their preferred modality of completion (paper, digital and by phone with the aid of a member of the research team).

Over 80% chose the paper method, while the rest opted for the online platform.

When stratified by response modality, there was no statistically significant difference between actual participants and individuals who didn't finalise the consenting/completion of study procedures ($\chi^2 = 0.002$, p = 0.89). In other words, completion modality had no impact on return rates.

SF-36

All the categories of pancreas transplant recipients had similar SF-36 scores, except for the "energy/fatigue" domain, as shown in table: PTA recipients had significantly lower levels than SPK/PAK/PASPK, with a medium effect size (p = .019, Cohen's d = .494). Again, the highest scores were mental health scales (**Appendix A4.20**). There was a correlation between role limitations due to physical health and those due to emotional health, essentially driven by SPK recipients (Spearman's rho = .448 p < .001). No such association was found in PTA recipients, underlying how the gap between physical and mental well-being might be wider in this group. In keeping with this hypothesis, the correlation between PCS and MCS scores resulted meaningful for SPK recipients only (Spearman's rho = .321 p = .005), essentially

due to PTA recipient's low PCS scores (SPK Mean (SD) = 40.5 ± 12.1; PTA Mean (SD) = 34.4 ± 13.2).

EQ-5D-5L Health States

The proportion of participants with no limitation in any domain (Health State 1-1-1-1-1) was approximately 16%, hence closer to English senior rather than adult population (20% and 40%, respectively) (Lifestyles Team, NHS Digital, 2019).

When EQ-5D-5L distribution for the entire study population was dichotomized in two severity levels (Level 1-2 = little/no problems; Level 3-5 = moderate to severe problems), the proportion of participants in the least impaired group was approximately 40%: the majority of individuals reported more severe conditions (Appendix A4.20). The most favourable results were in "self-care" domain: nearly 90% of participants declared none/mild limitations. This proportion was statistically higher than all the other domains, which, on the contrary, were quite homogeneous amongst themselves. In other words, "self-care" was highly preserved (90% Level 1-2) despite the statistically significant lower outcomes in "pain" (71% Level 1-2), "Activity" (66% Level 1-2), "mobility" (64% Level 1-2) and "depression/anxiety" (72% Level 1-2) (Appendix A4.21). Further details on severity levels distribution on the entire study samples are reported in **Appendix A4.23**

There was no statistically significant difference in severity level distribution across transplant categories, except for "pain", much worse in PTA recipients. (**Appendix A4.24**) Interestingly, this was also the only SF-36 domain that deteriorated significantly in the longitudinal study, albeit with no variation across transplant

groups. Severity level distribution was then stratified in relation to time from surgery: it was essentially the same, both when looking at the sample as a whole and when looking at the two separate transplant cohorts (**Appendix A4.25-A4.26-A4.27-A4.28**)

Population Norms

Health status distribution was compared to population norms. Pancreas transplant recipients reached aged matched Irish normative values only in the domain “pain” (**Appendix A4.29**) while their “mobility” and “usual activity” scores were similar to 20 yrs. older general population. “Self-care” and “anxiety/depression” never reach population norms of any age range (**Appendix A4.30**).

When looking at the two different transplant cohorts, the distribution of health status for SPK recipients reached population norms in “pain”, whilst PTA recipients did not. The opposite was true for “self-care”, while every other domain was essentially similar across groups and statistically inferior to population norms (Appendices **A4.31-A4.32**).

EQ-VAS

EQ-5D-5L allows respondents to directly rate their health status with the Visual Analogue Scale. Mean VAS values for the totality of the study population were 67.7 ± 21.2. There was no statistically significant difference across transplant cohorts both as a whole (**Appendix A4.33**) and stratified by time from surgery. In other words, participants reported similar health ratings regardless of the type of transplant received or its timing. In all cases, VAS scores did not reach Irish population norms for the same age group, as displayed in **Figure 17.**

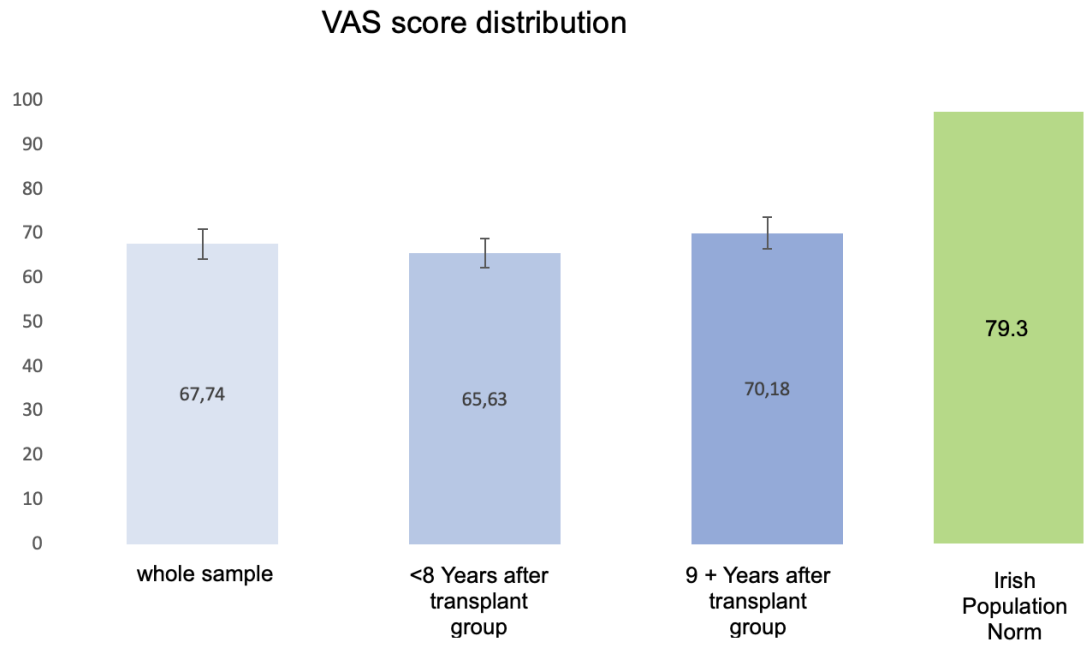


Figure 18. Comparison between EQ-VAS outcomes and Irish population norms, stratified by time from surgery.

EQ-Index

EQ-index mean score for the total population was 0.675 ± 0.258. Differences across groups were not statistically significant (**Appendix A4.34**). Because of the lack of current UK normative values, data from other countries was used to provide some context. Pancreas transplant recipient scores compared unfavourably with age matched general population from Canada, Germany, Denmark, and Spain, reported in Appendix A3.17 (Garcia-Gordillo, Adsuar et al. 2016, APERSU 2018, Grochtdreis, Dams et al. 2019, Jensen, Jensen et al. 2021).

HSF-II Worry

In their flagship article assessing psychometric properties of HSF-II, its developers analysed HSF-II data from a few studies and provided separate results for the two components of this survey, “Behaviour” an “Worry.” Aggregated data on 488 patients with type one diabetes, reported a mean score of 22.3 (± 14.4) in the “Worry” scale. However, results were significantly higher for patients who had experienced recurrent hypoglycaemia unawareness crisis within one year (mean (SD) = 34 ± 16.6). These Figures were used to get a contextualised understanding of our results (Gonder-Frederick, Schmidt et al. 2011). The mean HSF-II Worry summary score for this study was 12.1± 14.7, approximately one half and one third of the above figures reported by Gonders and colleagues Interestingly, there was no difference in HSF-II W results between SPK/PAK/PASPK and PTA recipients (**Appendix A4.35**). This lack of difference might be related to longstanding euglycemia in both cohorts, but it could simply be a consequence of the small sample sizes.

Overall, participants reported quite low hypoglycaemia-induced worry: the proportion of patients never or rarely experiencing concerns in each of the 18 questions ranged from 98.9% to 85.7%, as depicted in **Appendix A4.36**.

Fear of nocturnal–hypoglycaemia - possibly the biggest threat of them all (Evans M et al, 2013) - was a frequent concern in approximately 15% of participants. A list of HFS-II worries ranked by frequency of concern can be found in **Appendix A4.37**.

Most interestingly, PTA and SPK recipients had similar HSF-II Worry. In other words, the type of transplant received did not determine any meaningful difference in HFS-II Worry global score, which compared favourably with reference levels provided by the developers of the instrument (Gonder-Frederick, Schmidt et al. 2011). In my view, this finding is particularly useful to shed some light on HRQOL after Pancreas Transplant alone. Despite not having data on hypoglycaemia fear levels before transplantation, I know from the literature that they are higher in patients with recurrent hypoglycaemic crisis (Wild, von Maltzahn et al. 2007). Potential PTA recipients fall into this category by definition: they get transplanted because of recurrent life-threatening hypoglycaemic crisis, in the absence of prodromic symptoms. Hence, Pancreas Transplant Alone, by restoring euglycemia, likely treats life changing fear associated with hypoglycaemia unawareness.

- Summary

The small longitudinal arm of this study showed no changes in the trajectory of SF-36 outcomes, except for “pain,” which was statistically worse after transplantation. However, this difference was no longer evident when stratified on type of transplant

received. Moreover, recipients of pancreas and kidney showed an improvement in energy level and general health perception, while PTA recipient did not.

Cross-sectional analysis of the whole study sample showed how PTA recipients had higher levels of pain than SPK+PAK+PASPK recipients, who scored within Irish matched normative data in EQ-5D-5L “pain” domain. However, PTA recipients showed normal “self-care” levels, unlike the rest of study participants. Almost every other generic HRQOL domain, as captured by EQ-5D-5L or SF-36, was below population norm except MCS scores, with no differences across cohorts or time from surgery.

4.3.4 Predictors of HRQOL

Pre- and post-transplant clinical variables were regressed against HRQOL scales (SF-36 PCS and MCS; EQ-5D-5L VAS and EQ-index; HFS-II W summary score) to find potential long-term predictors. It was not possible to stratify this analysis by type of transplant received or time from surgery, as the small number of individuals within each cohort would contradict regression requirements. Hence, the data presented below pertains to the totality of the study population.

For all the variables that showed a statistically significant relationship with one or more of HRQOL scale, regression assumptions were checked; linear and multiple regressions were performed to identify a model of best fit to predict each HRQOL outcome of interest.

Very few pre-operative variables concurred to build the final predictive models, albeit many of them correlated with HRQOL scales when analysed individually. The most recurrent predictors of long-term HRQOL seemed to be associated with long term renal function, rather than pancreas transplant itself, with the exception of HFS-II scores. It can be concluded that, although it was possible to identify predictors of long term HRQOL after pancreas transplantation, a few –ore variables - included for reference in Appendices A.38 to A.42 – would likely have been statistically meaningful if sample sizes had been larger.

PCS

SF-36 Physical Component Summary was statistically associated to “ethnicity”, “working status at transplantation”, “type of dialysis before surgery”, being “registered blind” and “creatinine at 5 years follow-up.” However, some of these variables lost significance within multiple regression analysis. Hence only “Work Status” and “5 years creatinine” were included in the model of best fit and they accounted for approximately 24% of variance in PCS outcomes (**Appendix A4.38**)

MCS

“Type of dialysis” before transplant also correlated with SF-36 Mental Component Summary in conjunction with “Haemoglobin levels at discharge”. However, when regressed together, the model lost statistical significance. Of the two variables, only “type of dialysis” ultimately predicted approximately 11% of long-term MCS (**Appendix A4.39**)

EQ-VAS

Many variables seemed to influence EQ-VAS outcomes, but the final model only included “claudication” and “pancreatic exocrine drainage” which accounted for 11% of variance in EQ-VAS. (**Appendix A4.40**)

EQ-index

“Work status at transplantation” and “serum creatinine at 5 years” were the only two predictors included in the model best fit for EQ-index outcomes, out of a mix of pre- and post-operative statistically relevant variables. Regression highlighted how 23% of EQ-index scores were influenced by these two factors. (**Appendix A4.41**)

HSF-II W

The presence and number of pre-transplant diabetic complications such as retinopathy, history of cardiac and/or cerebral ischemic disease, hypoglycaemia unawareness, all individually correlated with HSF-II W summary score. Equally, the type of pancreas endocrine drainage seemed to play a role in long term HSF-II W scores. However, the model lost significance when all these factors were pooled together. Ultimately, only hypoglycaemia unawareness and previous cardiovascular or cerebrovascular disease resulted in a valid equation and accounted for 17% of variance. (**Appendix A4.42**)

4.4 CONCLUSIONS

The initial plan to compare an historic cohort of pancreas transplant recipients with patients currently on the pancreas transplant waiting list was abandoned: just a handful of potential controls returned the questionnaires. This was as surprising as

difficult to interpret. One possible explanation could be that patients waiting for transplantation, might overall feel less involved in transplant related matters, including research. Or, more likely, the invitation letter might not have highlighted clearly enough the importance of having a robust control group. Whatever the reason, as good practice prevents the research team from contacting potential participants directly, I am not able to provide a definite explanation to the matter. Ultimately no not transplanted patient was included in the study.

Clinical data was recorded prospectively before and after transplantation, hence, despite the retrospective nature of this study, it was possible to accrue quite a large amount of information, essential for the aims of this study. Equally, long term transplant function outcomes were available for an adequate proportion of people.

Unfortunately, that was not the case for evidence on the progression of diabetic chronic complications. This shortcoming didn't allow us to quantify and analyse the trajectory of potentially invalidating symptoms and conditions.

There was no statistically significant difference in the proportion of males and females enrolled, while there was a pronounced discrepancy in ethnicity groups distribution, with individuals from with BAME background being statistically less represented when compared to England and Wales 2021 Census data for the entire population (chi square = 5.49, p = 0.019) (GOV.UK 2021). At transplantation, the average participant was approximately 57 years old and BMI within the healthy range, had developed type 1 diabetes as an adolescent and had been living with the disease a little over 32 years. About one half of the sample was working a paying job or as a homeworker.

With regards to diabetes severity, nearly 85% of the sample had more than two chronic complications. Renal failure, retinopathy and neuropathy were the most frequent, followed by hypoglycaemia unawareness and gastrointestinal symptoms.

Large artery atherosclerosis, in the form of previous cardiac or cerebral disease, claudication and amputations, was overall infrequent. This is likely due to uncompromising selection criteria at listing for transplant, in the bid to filter out potential candidates unlikely to withstand complex surgery.

And indeed, approximately 63% of recipients experienced a difficult post-operative course, due to a combination of medical and surgical complications, developed by 40 and 50% of recipients, respectively. The overall frequency of post-operative relaparotomies amounted to approximately 22% of the entire sample.

Transplant pancreatectomy was necessary in 5% of cases, no renal graft was explanted, and the great majority of patients were discharged home free from insulin (93%) and dialysis (100%), after about 2.5 weeks. At one, two- and five-years follow-up, graft survival figures were essentially unchanged. Insulin independence at recruitment- at a mean of 8.5 years from surgery, was still 93%, making it fundamentally a study on long term HRQOL outcomes after successful pancreas transplantation. The proportion of patients with a failed pancreas was too small to allow results stratification based on graft function.

Nevertheless, the total population size allowed for some degree of cross-sectional analysis between patients who had developed renal failure and those who approached pancreas transplantation to resolve life threatening hypoglycaemia unawareness.

Very few pre-transplant differences were identified between SPK/PAK/PASPK and PTA recipients, albeit some potentially related to HRQOL outcomes, such as gender, age at transplantation and history of hypoglycaemia unawareness, to mention those most likely consequential. PTA recipients were almost all females and slightly younger, respectively a negative and positive predictor of HRQOL in the general population, as illustrated by population normative values for SF-36 (Jenkinson 1998) and EQ-5D (Hobbins et al. 2018). All PTA recipients suffered from hypoglycaemia unawareness -–by definition - while about 70% of SPK/PAK/PASPK had no such problem.

Duration of ITU admission was different in the two cohorts, but this was the direct consequence of clinical protocols and it its therefore not considered relevant. The other post-operative discrepancy between SPK/PAK/PASPK and PTA recipients was the type of enteric drainage, similarly, decided a priori. However, in consideration of the different type of post-operative problems enteric and bladder drained pancreases can determine, this was considered a notable finding. And indeed, the proportion of patients who required enteric conversion of their bladder drained pancreas was approximately 67%.

In keeping with this, I found that the type of enteric drainage correlated both with EQ-VAS an HFS-II Worry scales, but not with other scales HRQOL domains. But, most importantly, it did not correlate with the type of transplant received or long-term graft survival.

In other words, the type of pancreatic exocrine drainage was and independent predictor of hypoglycaemia fear and general health perception, with the best scores associated with enteric drainage.

A few of these pre-and post-transplant differences across cohorts could potentially determine marked variability in post-transplant PROMs responses.

However, long term HRQOL outcomes were quite homogenous, with very few statistically relevant discrepancies between SPK/PAK/PASPK and PTA recipients, even when time from transplantation was evaluated, which seemed an important aspect to consider.

In the small longitudinal arm of this study, performed on 30% of the total sample, just one of the SF-36 scales- “pain”- changed statistically in the long term, and for the worse. However, when looking at the two different cohorts of recipients separately, the downwards trajectory of “pain” was no longer statistically significant in either group. The opposite phenomenon occurred for “general health” and “energy”: both scales improved significantly in SPK/PAK/PASPK recipients, but not in PTA ones nor in the population as a whole.

PCS and MCS results were quite similar across transplant cohorts before and after transplantation, regardless from the duration of follow up, and there was no meaningful longitudinal change in either. Moreover, I found no correlation among the two summary scales, possibly in relation to a dichotomy between physical and mental health. This lack of striking differences could be ascribed to the small sample size.

Nonetheless, figures from the wider cross-sectional study provided a similar scenario: type of transplant had no impact on any SF-36 scale except for “energy”, significantly worse in PTA recipients.

Again, PCS and MCS scores were not statistically different across transplant cohorts, however for SPK/PAK/PASPK there was a correlation between the two components, which was absent in PTA recipients, perhaps denoting a deeper divide between physical and emotional wellbeing in this latter group.

Data collected with EQ-5D-5L was consistent with SF-36 findings. No difference was identified between SPK/PAK/PASPK and PTA recipients in overall severity level distribution, regardless of time from transplantation. However, when looking at each domain individually, PTA recipients had statistically more burdensome levels of “pain”. Consistently with this finding, SPK recipients reached Irish aged matched normative values for “pain”, while PTA did not. The exact contrary occurred for “self-care” domain, where it was PTA recipients who reached population norms.

No other major generic HRQOL differences were found with EQ-VAS and by computing EQ-indexes, both below normative values and quite consistently so across groups.

Hypoglycaemia fear compared positively with the average scores found in patients with type 1 diabetes, as provided by the developers of the tool (Gonder-Frederick et al. 2011). There was no difference in frequency of hypoglycaemia “worries” across transplant cohorts, despite an irrefutable difference in prevalence of hypoglycaemia unawareness prior to transplant. Unsurprisingly, hypoglycaemia unawareness before surgery was one of the predictors of long term HFS-II outcomes.

In summary, at approximately 8.5 years from surgery, almost all the generic HRQOL domains were below population norms. The type of transplant received didn’t seem to have a major impact on findings, with the exception of a few variables suggesting

a bigger divide between physical and mental wellbeing in PTA recipients. Equally, time from transplantation had no weight in determining HRQOL results.

Finally, questionnaires administration modality had no impact on return rates. This finding seems particularly important, considering that approximately 14% of the study population was registered blind and almost 95% suffered from diabetic retinopathy at the time of surgery. In other words, visual impairment doesn't seem to be a barrier to electronic data collection, which is of paramount relevance in in an increasingly digitalised society.

4.5 EARLY AND LONG-TERM HRQOL OUTCOMES

The longitudinal study described in chapter 3 finished at one year from transplantation, while the mean time from surgery in the cross-sectional study was 8.6 ± 4.5 years. It would be tempting to somehow compare the two projects and understand similarities and differences in HRQOL scales.

From a broader perspective, whether patients' HRQOL continues to improve with time, deteriorates or reaches a plateau is indeed the crux of the matter. Aware of the inevitable methodological impasse in doing a reliable metanalysis, the data reported below should be regarded as the attempt to identify gross differences and general trends, rather than a finely tuned comparison.

The proportion of PTA recipients in each of the two studies was statistically different: 2 out of 62 and 15 out of 98 respectively (Fisher's exact test = .017). In consideration of this discrepancy and of the small numbers, it seemed reasonable to limit the analysis to SPK/PAK/PASPK recipients from both projects: 60 and 83 participants, respectively.

4.5.1 Clinical Data

Demographics and clinical variables were compared to understand the degree of baseline differences between the two groups. (**Appendix A4.43**). In a few instances, the proportion of data available in the two studies was statistically different (HLA sensitisation, post-operative scans, duration of Intensive Care admission, serum creatinine at discharge and blood tests results at one year).

Hence, although all these figures are reported **Appendix A4.44** for completeness (grey rows), they shouldn't be regarded as reliable. Ultimately, "Age at Transplantation" and "Duration of diabetes" were the only pre-transplant differences across studies, with participants from the cross-sectional cohort being older and with a longer history of diabetes. After transplantation the two groups differed in "duration of hospital admission"- longer in the historic cohort of recipients- and "Haemoglobin–at discharge" - lower in participants to the first study- possibly both expression of a progressively increased confidence in management.

4.5.2 Patient Reported Outcomes

With the methodological caveats highlighted above I juxtaposed results from the two studies. I report findings from the main HRQOL scales explored.

- Before transplantation

Preoperative SF-36 outcomes data were available for 44 participants from the prospective study and 20 participants from the cross-sectional one.

Despite the few differences in baseline clinical features, PCS and MCS outcomes were similar across groups (**Appendix A4.45**)

- After Transplantation

Post-operative outcomes at one and 8.6 years from surgery, were overall quite similar across all PROMs (**Figures 19** and **20**), and below population norms, except for MCS median scores, which were normal by the end of the prospective study and at longer follow-up. In summary HRQOL results are quite stable in time. Further details on comparative outcome can be found in the Appendix, **A4.45-A4.46-A4.47-A4.48**

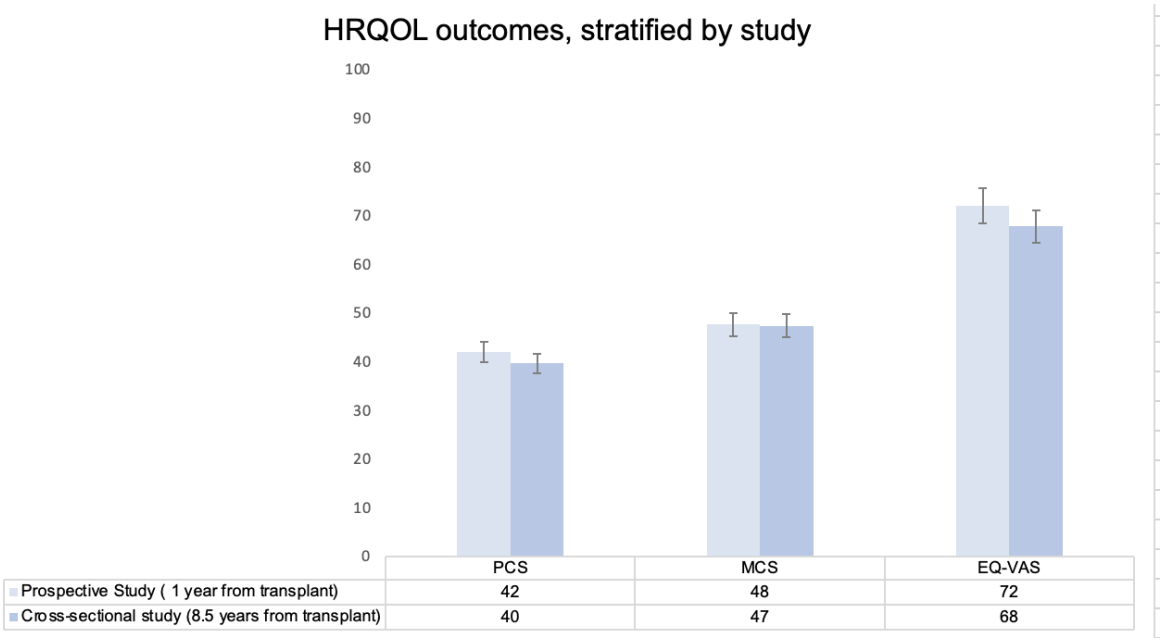


Figure 19. Post-transplant PCS, MCS, EQ-5D-5L outcomes, stratified by study.

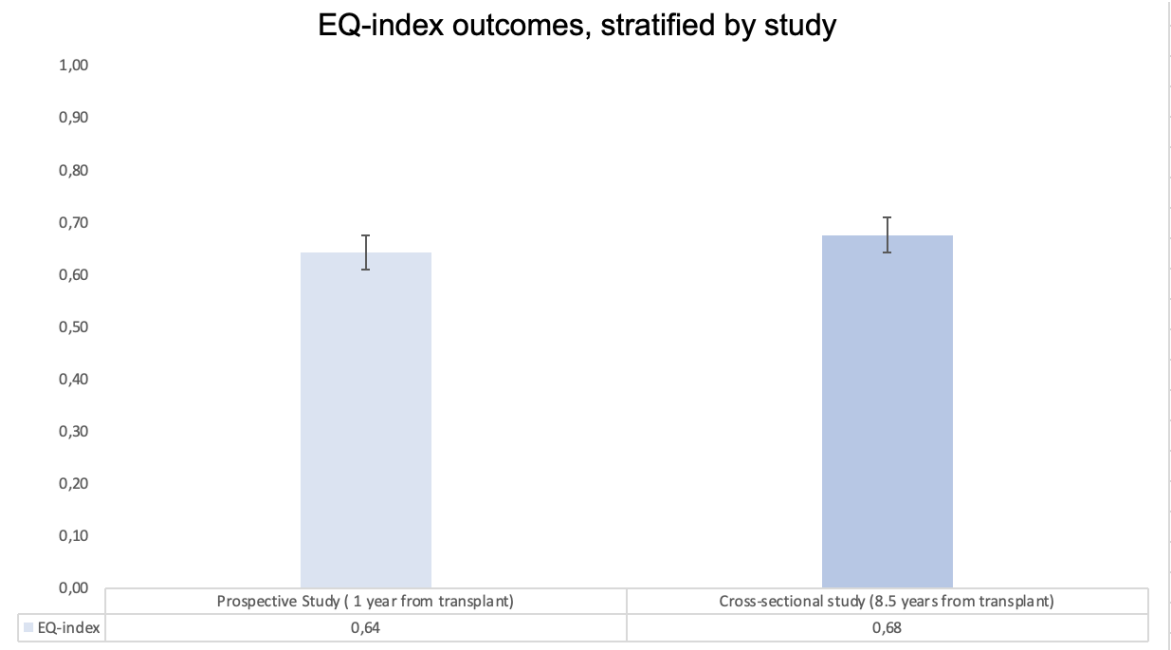


Figure 20. Post-transplant EQ-index outcomes, stratified by study.

4.5.3 Predictors of HRQOL

Juxtaposition of predictor factors for the two studies, suggests that, while in the first year from surgery HRQOL outcomes are essentially influenced by pre-operative variable-diabetic complications, that is not the case a few years from surgery. (**Appendix A4.49**). The data accrued allows to speculate that renal function might have a substantial impact on generic HRQOL and health indexes in the longer term.

“History of psychiatric disorders” or “Psychotropic medications at transplantation” figured heavily amongst predictors of one-year HRQOL. Unfortunately, no such information was available for the cross-sectional study.

These results were juxtaposed to outcomes from the cross-sectional study, to gain a broader prospective on how to interpret long term findings. This analysis was limited to SPK/PAK/PASPK, essentially because of too few PTA recipients in the first study (2 participants).

4.5.4 Conclusions

As imagined, recipients' clinical features from both studies were very much the same, except for "age at transplantation", "duration of diabetes", "duration of hospital admission" and "haemoglobin levels at discharge": in the historical cohort recipients were older, had diabetes for a significantly longer amount of time and they were discharge home later, with higher haemoglobin levels. No other statistically significant differences emerged.

The studies had two PROMs in common: SF-36 (embedded in the KDQOL) and EQ-5D-5L, making it possible to observe the relationship between one- and 8.5-year outcomes. Pre-transplant PCS and MCS from both projects were compared and no difference was identified: results were quite low and well below population norms in both cases. Similarly, post-transplant PCS and MCS were essentially the same. None of the instruments captured any striking differences across studies.

In both studies predictive models of HRQOL outcomes were developed. It seemed that many predictors of one-year outcomes such as "gender" or "preserved urinary output at transplantation", did not have an impact on HRQOL in the longer term. There was no overpowering evidence of shared predictors or trends. One interesting aspect identified was that all the predictors of one-year HRQOL were essentially pre-transplant factors, while at a longer follow-up a few operative/post-operative features gained relevance, such as, for example, "type of pancreatic

exocrine drainage” and “creatinine levels at 5 years from transplant”. These findings suggest how the most prominent changes in HRQOL occur during the first year from surgery and support the importance of this period in the overall long-term well-being of recipients. In other words, although it was not possible to use this data for an exact statistical longitudinal analysis, it seems that the early improvements in HRQOL might be long lasting, at least in patients with preserved graft function. Moreover, many years from transplantation, all types of pancreas transplant recipients have little, if any, hypoglycaemia fear.

However, regardless of the success of the operation and regardless of improvements, many generic HRQOL scales, with the exception of SF-36 MCS, do not reach population normative values.

5 CHAPTER 5: DISCUSSION

5.1 INTRODUCTION

The purpose of this DPhil was to investigate HRQOL after pancreas transplantation in patients with type 1 diabetes with or without end stage renal failure.

This final chapter presents a summary of the research, in relation to the initial objectives. It also aims to provide a possible interpretation of the information accrued and, in acknowledging originality and limitations of our work, it offers an overview of possible further research avenues on the topics of HRQOL, Patient Reported Outcome Measures and Pancreas Transplantation.

- Relevance of the research question.

Pancreas transplant recipients are individuals of working age who mostly developed type 1 diabetes during adolescence. The natural trajectory of their disease is the progression towards highly debilitating complications, with decreased life expectancy (Livingstone SJ, 2015) and poor HRQOL (Whittemore R, 2012).

The metabolic mayhem triggered by lack of insulin, leads to structural alterations of the arterial bed and vasa nervorum. Although any behavioural pattern increasing atherosclerotic risk (smoking, sedentary life, obesity to mention a few) can potentially worsen the evolution of diabetic complications, it is only sustained euglycemia which can potentially stop their progression (The Diabetes Control and Complications Trial Research Group, 1996).

Type 1 diabetes can “per se” impact negatively on HRQOL (Whittemore R, 2012), but the real turning point is represented by the onset of its chronic repercussions (Jacobson A, 2013). Hence pancreas transplantation has the potential to improve HRQOL in the short-term by treating diabetes, but also – indirectly- prevent it from deteriorating, by altering the course of systemic manifestations. A longstanding concern in the context of pancreas transplantation is that because this is an intervention that has always been provided in patients with well-established chronic complications, they may never really experience any benefit at all.

The primary reason that patients are treated at such an advanced stage of their disease is that pancreas transplantation in all its modalities is an unequivocally high-risk operation. This is then performed on a relatively high-risk group of patients, who would logically benefit from less invasive treatments. Hence, it is common agreement that surgical risks must be weighed against clinical and HRQOL gain (Sutherland DE. et al, 2009). In view of the aforementioned considerations, studies on HRQOL after pancreas transplantation seem as relevant as ever, in the bid to offer appropriate counselling and a tailored therapeutic approach for each prospective candidate, but perhaps also to provide further insight on the ideal timing for the intervention.

- Structure of the thesis

As a preliminary step, I conducted a systematic review of the literature to collate and interpret the current knowledge on the topic, while identifying the most suitable Patient Reported Outcome Measures for this population.

The second part of the research was a prospective longitudinal study designed to define the trajectory of generic and disease specific HRQOL before and up to one year after surgery and to identify possible predictors of better/worse outcomes.

Finally, a cross-sectional study on an historic cohort of pancreas transplant recipients was designed to gain further insight on medium/long term HRQOL outcomes across different cohorts of pancreas transplant recipients.

5.2 CURRENT KNOWLEDGE ON HRQOL AFTER PANCREAS TRANSPLANTATION: THE SYSTEMATIC REVIEW

Simultaneous Pancreas Kidney Transplant represents two thirds of the totality of pancreas transplants (Gruessner AC, et al., 2016); inevitably most of the existing literature on “HRQOL after pancreas transplantation” is actually about “HRQOL after pancreas AND kidney transplantation”. Henceforth, unless otherwise specified, the data reported below refers to SPK transplant recipients.

5.2.1 Evidence accrued.

The systematic review conducted for this DPhil included a total of 102 studies, published throughout 3 decades of activity. This is -per se- a remarkable finding: the possibility of quality-of-life improvements was considered a likely asset of the procedure from the very start. At first, patients would undergo SPK transplant, with little knowledge on long-term benefits and a vivid perception of the dangers related to surgery. This could in part explain why research on HRQOL in pancreas transplantation began relatively early in the history of this procedure, in order to

document additional benefits that could help justify the surgical risks. And indeed, the frequency of quality-of-life studies declined as pancreas transplantation became an established therapeutic strategy in its own right. Perhaps the ground-breaking information provided by the DCCT trial on the impact of euglycemia on the progression of diabetic complications (Diabetes Control and Complications Trial Research Group, 1993) contributed to a shift of focus towards objective clinical findings only. However, the recent concerns about falling levels of pancreas transplantation in the States (R.J. Stratta, A.C. et al, 2016) might have reignited interest in HRQOL studies. In other words, there is probably a newly perceived need to justify the larger procedure.

Despite the relatively large number of studies identified, it was not possible to draw unequivocal conclusions on the state of HRQOL after pancreas transplantation. The significant variability in study design, outcome measures chosen, populations analysed, shortfalls in methodology in conjunction and the small sample size of many manuscripts represented a relevant barrier to a reliable metanalysis. Ultimately, despite confounders, some results seem to recur.

- Longitudinal changes in HRQOL after Pancreas Transplantation

The strongest evidence on the positive impact of Pancreas Transplantation on HRQOL, comes from cohort studies -longitudinal observational studies prospectively investigating changes related to an intervention or condition-which stack below randomised control trials in the “evidence-based medicine pyramid”. However, they only constitute less than 25% of the literature included in this review.

Most of these manuscripts concur in documenting an upward trajectory in HRQOL, albeit with many differences in the most frequently improved domains. This variability in outcomes essentially reflects the variability in PROMs selected; in our opinion, though, it also underlines the breadth of possible HRQOL benefits of successful SPK transplantation. However, even authors who used the same instruments occasionally reported divergent results (Gross CR et al., 2000; Smith GC et al. , 2010). These discrepancies might be due to the fact that, although 75% of these studies were conducted with or by quantitative research specialists, they were still plagued by potentially relevant confounders: small population size (median size: 22 participants), sample attrition, short follow up.

- Cross-Sectional Studies on HRQOL after pancreas transplantation

The great majority of manuscripts included in this review were cross-sectional studies: observational research depicting HRQOL after pancreas transplantation at a single point in time, without any pre-transplant HRQOL information. Many investigators reported positive effects of SPK transplantation on HRQOL so much so as to reach population normative values for SF-36 (Drognitz O, et al., 2004; Jurgensen JS et al, 2008; Kenmochi T et al. , 2010 ; Tai Q et al., 2010; Smith GC et al. , 2010; Sugitani A et al. , 2011; Anderson KT et al. , 2011). Other manuscripts documented the opposite: despite improvements, SPK recipients continued to score significantly below normative values (Matas AJ et al , 1998; Isla-Pera P, et al, 2009; Bolesta K et al., 2016). When compared to patients on the pancreas transplant waiting list, successful SPK recipients reported higher HRQOL (Isla Pera, Moncho

Vasallo et al. 2009, Bolesta, Kuhn et al. 2016, Gibbons, Cinnirella et al. 2020, Posegger, Linhares et al. 2020). Nevertheless, both cohorts had significantly worse psychological profiles than patients with type 1 diabetes and no renal impairment., indirectly confirming the role of diabetic complications on patient's wellbeing.

Comparative data between SPK and KTA transplantation supported superior HRQOL after SPK, especially when assessed with disease or symptom specific instruments. (Voruganti LNP and Sells RA, 1989; Nathan DM et al., 1991; Esmatjes E et al, 1994; Hathaway DK et al. , 1995; Kožnarová R et al., 2001; Sureshkumar KK et al., 2002; Salonia A et al, 2011; Nyumura I et al, 2016). Differences in generic HRQOL seemed more nuanced, with occasionally contradictory evidence. (Nakache R et al., 1994; Kiebert GM et al., 1994; Esmatjes E et al, 1994; Secchi A et al, 1998; Gross CR et al., 2000; Sureshkumar KK et al, 2005; Anderson KT et al. , 2011).

Interestingly, the gap between SPK and KTA outcomes seemed to increase with time, for both generic and disease specific domains, likely due to progressive deterioration of HRQOL after KTA, rather than further improvements in SPK recipients (Nakache R et al., 1994; Nakache R. et al, 1989; Gross CR et al., 2000; Sureshkumar KK et al, 2005).

In general, there was little evidence on the individual contribution of insulin independence and freedom from dialysis to HRQOL. In my opinion, any attempt to establish the importance of each by looking at "graft loss" should be regarded as misleading: it would be difficult to separate the repercussions of "return to insulin and or/dialysis" from the underlying causes, occasionally traumatic. To put it differently, HRQOL implications of losing a transplant go beyond the effects of

returning to insulin injections or dialysis. This underscores the importance of diabetes and renal specific PROMs, which, however, were hardly used, especially in combination. Initially, this might have been a direct consequence of actual paucity of available disease specific measures; in some other cases, though, investigators might have deliberately opted for a simpler assessment of generic HRQOL; finally, approximately 50% of the studies were conducted by clinicians only, with no expertise on HRQOL research: it is possible that this resulted in a less informed selection of study PROMs. A paradigmatic example on the importance of disease specific questionnaires is represented by the data accrued on Pancreas Transplant Alone recipients. In this cohort of patients, hypoglycaemia fear is, de facto, one of the most relevant reasons for impoverished quality of life (Wild D et al., 2007). However, it was measured in just one manuscript (Scalea, Pettinato et al. 2018). In all other studies, “rehabilitation rates”, “employment rates”, “health status” and “health related physical activity” were used as outcome measures (Sutherland, Gruessner et al. 2001, Vistoli, Croce et al. 2010, Triscornia, Nardi et al. 2017).

In other words, most studies addressing HRQOL after PTA did not investigate the main - if not the only - factor effecting HRQOL in this population.

It is reasonable to conclude, therefore, that there is little compelling evidence in the published literature investigating HRQOL benefits of after Pancreas Transplant Alone. As a further consequence, the published evidence is insufficient to establish which form of pancreas transplant is associated with highest HRQOL outcomes.

- Qualitative Studies

The systematic review of the literature also included a small percentage (5%) of qualitative studies: research aimed at eliciting non numerical data from patients, in the attempt to capture attitudes and recurrent themes potentially impactful on their quality of life. The most frequent recurrent post-transplant theme was the perception of living a “new life”. Other important issues were the perception of regained control on one’s existence and return a normal life without diabetes (Isla-Pera P, et al, 2012). However, the latter was a double-edged issue: not being able to relate to the concept of “normality” was a source of dismay for some (Jackson S et al. , 2013).

By breaking the bond between the disease and one’s identity, transplantation triggered a process of “reaffirmation of identity of self”(Langenbach, Stippel et al. 2004). However, some described disappointment in acknowledging that, despite no longer “being diabetic”, chronic complications would still impoverish their HRQOL.

Pre-transplant fear of the procedure was replaced with post-transplant fear of graft loss. Also, some individuals developed complex feelings towards “their” donor.

- PROMS utilised.

Most unexpectedly, no pancreas transplant specific validated instrument was ever developed. Instead, there was a striking variability in PROMs utilised: HRQOL after pancreas transplantation has been investigated with at least 70 validated tools, alone or in combination. In my view this is not simply fortuitous: it is clearly the reflection of the many repercussions of type 1 diabetes on HRQOL.

With such a wide range of potential areas to investigate, it is likely that PROMs were selected based on what researchers arbitrarily deemed more relevant on a case-by-case basis. The absence of a pancreas transplant specific PROM represents a

real challenge in HRQOL research after pancreas transplantation: it is simultaneously cause and expression of the extraordinary variability in HRQOL data, thus one of the main obstacles to comparative analysis.

5.2.2 Systematic review of –he literature - conclusions

This analysis of the existing literature has produced some valuable outcomes:

1. It has provided an up-to-date overview of all published literature on HRQOL after pancreas transplantation, from the beginning of this activity.
2. It has offered some evidence of improved HRQOL after pancreas transplantation, in particular after Simultaneous Pancreas Kidney Transplantation.
3. It has suggested that recipients' mental health can reach population norms after transplantation.
4. It has shown that, although rarely used, disease specific instruments are essential to fully characterise changes in HRQOL after pancreas transplantation.
5. It has demonstrated the difficulty of capturing all the intricacies of this population and the trajectory of HRQOL after transplantation using the existing PROMs.
6. It has provided indirect evidence on the main obstacles to developing a bespoke pancreas transplant PROM with adequate face-validity and feasibility.

5.2.3 POST-TRANSPLANT HRQOL CHANGES: THE PROSPECTIVE LONGITUDINAL OBSERVATIONAL STUDY.

The primary aim of the prospective longitudinal observational study was to assess the trajectory of HRQOL after transplantation, while minimising methodology shortfalls. For this reason, the study was designed under the supervision of experts from the University of Oxford Health Nuffield Department of Population Health

The choice of outcome measures was evidence based. All the PROMs selected were validated, presented good psychometric properties, and were deemed suitable for patients with diabetes and/or renal failure (Gibbons E et al, 2009; Gibbons E et al, 2010).

- Summary of findings

Almost 90% of participants underwent SPK transplantation during the study period and almost all responders at one year were individuals with preserved pancreas and kidney function. Hence, this is essentially a cohort study on the trajectory of HRQOL after successful SPK transplantation. Before transplantation patients had diabetes related HRQOL scores lower than those reported in the context of the DCCT trial, elicited with the same instrument used for this DPhil (DQOL). In other words, despite our study participants being healthy enough to withstand major surgery, their pre-operative HRQOL was already worse than patients with type 1 diabetes with little if any complications (Diabetes Control and Complications Trial Research Group, 1996). And indeed, chronic complications featured amongst the most frequent negative predictors of pre-transplant HRQOL.

Overall, diabetes and renal failure had a similar impact on pre-operative HRQOL. Notably, disease specific HRQOL was slightly better than generic well-being: patients seemed to deal better with the constrictions of diabetes and renal failure, rather than their repercussions on general health.

Another notable finding was the statistically significant gap between participants' physical and mental wellbeing, as captured by both SF-36 and EQ-5D-5L.

Such a discrepancy is possibly due to the natural history of diabetes itself: after a dramatic onset, eventually the reality of living with diabetes sinks in, leaving few other options besides adaptation. Moreover, the progression of complications occurs unrelentingly, yet slowly, leaving patients time to build some resilience.

Despite all these considerations, both physical and mental HRQOL scores before transplant were significantly below population normative values. In the aftermath of surgery, the first perceived benefits of transplantation involved diabetes HRQOL scales and "burden" of kidney disease: this might possibly be the consequence of "simply" no longer requiring insulin and dialysis, as well as being on the other side of a major operation. The ramifications of these changes, though, are underscored by the statistically significant increase in "general health": just a handful of weeks after transplantation, patients already perceived their health as better than before transplantation. Most improvements, though, became manifest with time, when patients started experiencing the longer-term benefits of euglycemia, resolution of uraemia and freedom of a life without dialysis and restrictions.

Physical HRQOL continued to ameliorate and so did general health perception, as suggested by the statistically significant increase of KDQOL-SF^{TM}, PCS scales and EQ-VAS.

Overall, the biggest changes in HRQOL seemed to occur within the first six month. Afterwards, renal, and physical related HRQOL reached a plateau, while diabetes related HRQOL curve showed a slight inflection, albeit not steep enough to become statistically significant when compared to baseline. The reason for this is likely multifactorial. In first instance, once the novelty of transplantation settles down, patients presumably develop some degree of adaptation to their new reality.

Moreover, the most dramatic clinical benefits of SPK occur early after surgery: the plateau in HRQOL might be actually mirroring the trajectory of clinical changes.

Outcomes at one year, show how successful SPK transplantation has indeed the potential to boost the life of this selected cohort of patients. Mental health improvements were possibly the smallest, but big enough for patients to gradually reach population norms. However, physical HRQOL was not restored to the level of population norms (Jenkinson 1998) and diabetes related HRQOL was still not as good as patients who never developed chronic complications of the disease (Jacobson, Braffett et al. 2013). Regardless, participants scored statistically higher EQ-indexes at one year from surgery, ultimately attaching a higher value to life with a functioning SPK, rather than a life with diabetes and renal failure.

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- Prospective longitudinal observational study. Conclusions

By the end of the study, most domains investigated were statistically better than before surgery. In summary, at one year from transplantation:

- Global DQOL score had increased from baseline by approximately 11 points, which is twice as much as 5-point difference indicated a “significant HRQOL event” by the developers of the instrument (Jacobson A, 2013):
- Renal and the SF-36 Physical Component Summary scale were statistically higher than baseline, although plateauing
- SF-36 Mental Component Summary scale had reached population normative levels.
- EQ-VAS was statistically higher than prior to surgery, with a large effect size.
- The application of Pareto criteria for Health Changes (Devlin N et al, 2010), showed that 45% of participants scored a better Health State than before transplantation, against 15% of individuals whose health state had deteriorated.
- EQ-index scores were statistically higher than before surgery: patients attached a higher value to life with a successful SPK than life with diabetes and renal failure.
- History of psychological disorders and chronic complications were still the most frequent predictors of HRQOL at one year.

5.2.4 LONG TERM HRQOL AFTER PANCREAS TRANSPLANTATION: THE CROSS-SECTIONAL OBSERVATIONAL STUDY.

- Summary of findings

The long-term trajectory of HRQOL after pancreas transplantation was essentially a flat line: there were no statistically significant changes in SF-36 summary scores from before to up to a mean of 9.5 years form surgery.

SPK recipients seemed to have a slightly better long term HRQOL, with higher energy levels, general health perception and MCS scores within population norms.

However, PCS values were below the 25% percentile both before and after transplantation, for all cohorts.

- Cross-sectional Observational Study

Despite the longstanding insulin independence and freedom from dialysis (when applicable) both physical and mental HRQOL scales were below population normative values, with concordance between SF-36 and EQ-5D-5L findings.

In general, long term HRQOL was quite similar across groups, however SPK reported higher energy levels and milder pain, if any. Equally, there were no statistically significant differences in fear of hypoglycaemia between PTA and SPK recipients, which compared favourably with reference levels provided by the developers of the instrument (Gonder-Frederick, Schmidt et al. 2011). In my view, this finding is particularly useful to shed some light on HROLF after Pancreas Transplant alone. Hypoglycemia fear, frequently associated with brittle diabetes (Wild, von Maltzahn et al. 2007), was low if not absent, in most PTA recipients. Time from transplantation had no effect on any of the outcome measures analysed.

- Early and Long-term HRQOL outcomes

Given the time constraints of the DPhil, it was not possible to document whether improvements in HRQOL achieved during the first year after SPK transplantation would be sustained in time. However, I sought to gain a broader understanding of long term HRQOL outcomes by juxtaposing the results from my two principal studies. Participants baseline clinical features were quite similar across studies, and so where SF-36 baseline scores available for 20 patients from the small longitudinal arm of the cross-sectional study. This is suggestive of minimal selection bias; hence it indirectly provides a degree of legitimacy to the data reported below.

Interestingly, there were no statistically significant differences between results at 1 and 8.5 years. Hence, it seems possible to cautiously assert that post-transplant improvements achieved during the first yea– from surgery – small or big - are sustained over time. Equally, the EQ-indexes, similar across studies, highlighted how the value patients attach to transplantation is not time dependent.

5.3 LIMITATIONS AND ACHIEVEMENTS OF THE RESEARCH.

As I were aiming to investigate HRQOL after Pancreas Transplantation, I identified a number of knowledge gaps that could be addressed in the context of a DPhil. Our work contributed to resolve some, while others were still pending at the end of the research and represent open avenues for further studies.

5.3.1 Limitations

In retrospect, there are a few matters I would have liked to address differently from the start but decided against; other limitations of the research emerged along the way.

- In the absence of a pancreas transplant PROM, I made an arbitrary selection of the aspects of HRQOL worth investigating. Perhaps, the biggest limitation in both studies is lack of transplant related HRQOL items. This matter was identified early during the development of the thesis. However, questionnaires portfolio for the first study was already burdensome, and it was felt that adding one extra questionnaire could have been counterproductive. The issue of comparing renal and diabetes related HRQOL seemed more compelling, hence the idea of exploring transplant related HRQOL was dropped. With regards to the second study, I opted for a set of short and quick instruments, in the bid to optimise the chance of a population size large enough to compare groups. Hence, transplant related HRQOL items were, yet again, spared. Therefore, I left a potentially important area of HRQOL unexplored. This reiterates the importance of a well-balanced, feasible pancreas transplant PROM, designed to include all relevant aspects of HRQOL.
- The addition of an adequate control group could have added further reliability to the data accrued, with a quasi-experimental design. In the longitudinal cohort study most participants were transplanted within the study period, eroding on the size of the potential control group. With regards to the cross-sectional study, “Participant’s Information Sheet” and other relevant

documents were redacted with pancreas transplant recipients in mind. In retrospect, I could have stressed more the importance of the control group, and possibly give more thought on how to effectively engage with patients on the waiting list. It could have been useful to underline how results from this research could potentially inform both post and pre-transplant management/counselling. Ultimately, this was likely a topic worth exploring with Patient and Public Involvement representatives before redacting the study documents and protocol.

- The instruments used in our research are not “weighted”. In other words, participant did not have the possibility to rate the importance of each question on their wellbeing. This could have added further insight on what really matters to patients and whether the HRQOL changes determined by pancreas transplantation occur in domains that they deem relevant.
- One of the biggest challenges during the prospective longitudinal study was maximising return rates by making it easier for patients to respond. Digital data collection represents, at least theoretically, a swifter strategy and one that might be more appealing to patients who use digital technology. Had I taken these aspects into serious consideration when setting up the study, I might have pursued this avenue. This approach was well received amongst participants of the cross-sectional study. With hindsight, it might have been helpful in terms of return rates during the pandemic. Another limitation of the cross-sectional study was the lack of data on pre-transplant psychiatric history. Both the systematic review and our cohort study had found this variable to be amongst the most important predictors of HRQOL in the short

term. Hence, I cannot comment on an aspect potentially relevant to long term HRQOL.

- The main shortfall of the cross-sectional study is a relatively high risk of selection bias. The sample size was small in relation to the number of surviving pancreas transplant recipients. Hence, this could be a selected group of enthusiastic responders willing to engage with research, as the high proportion of patients with preserved graft function seems to suggest. Hence, I am not able to claim that findings can be generalised. As valuable as the data accrued may be, it is important to underline that our study does not explicitly address repercussion of graft failure on HRQOL.

5.3.2 Contributions to the field

Taking the above-mentioned limitations into account, this DPhil contributed to acquire relevant information on HRQOL outcomes after pancreas transplantation. Moreover, it provided further insight on the challenges in investigating HRQOL in this population. Ultimately, this research:

- Provided an up-to-date, methodologically rigorous overview on three decades of studies on HRQOL after pancreas transplantation.
- Highlighted the existing knowledge gaps:
    - insufficient data on HRQOL after Pancreas Transplant Alone
    - limited knowledge on diabetes, renal and transplant related HRQOL
    - absence of robust information on post-operative evolution of chronic complications and their relationship with HRQOL
    - absence of a bespoke pancreas transplant questionnaire

- Provided a prospective analysis with controlled follow-up time points on the trajectory of HRQOL changes up to one year from successful SPK transplantation. Moreover, the data was collected at a single centre, which contributed to increase standardisation and decrease confounding factors. Considering the relative low volume of pancreas activity of many transplant centres, this seems like a significant achievement, despite the implicit compromise in generalisability.
- Presented information on longitudinal changes of generic HRQOL at a mean of 9 years after the intervention, one of the longest available prospective longitudinal follow-ups, albeit uncontrolled.
- Demonstrated the equivalent weight of insulin independence and freedom from dialysis on longitudinal changes in HRQOL after SPK. To our knowledge this is the only single centre prospective longitudinal cohort study based on both diabetes and renal specific PROMs and it is the largest in size.
- Shown how successful PTA transplantation is associated with low levels of hypoglycaemia fear in the medium-long term. Although this finding was expected, it had yet to be documented with an adequate validated instrument.
- Documented longitudinal changes in EQ-5D-5L outcomes analysed with validated methodology recommended by NICE, including the statistically significant improvement of health indexes from before to one year after pancreas transplantation, unprecedented in the available literature.
- Identified likely predictors of HRQOL outcomes both in the medium and long term.

- Demonstrated feasibility of studies based on relatively lengthy PROMs: despite the vast array of generic and disease specific instruments included in the cohort study portfolio, return rates at one year were satisfactory.
- Shown how digital data collection can be an option for pancreas transplant recipients, despite diabetic retinopathy.

5.4 DISCUSSION

Pancreas transplantation is often defined by patients as a “life changing” experience. This statement per se underlines the not-so-hidden potential of this operation to determine changes in HRQOL. Whether these changes are good or bad, transient, or long-lasting, generic, disease specific or both has been object of investigations dating as long as the procedure itself.

This DPhil study has shown that successful SPK transplantation can indeed improve HRQOL, and that most changes occur within the first 6 months from surgery. However, despite diabetes and renal failure being effectively treated, most HRQOL scales never return to levels found in the general population (Jenkinson, 1998; Hobbins, A et al , 2018), except for mental health scales. Moreover, there doesn’t seem to be any further gain in the long term, despite sustained euglycemia and freedom from dialysis. These findings could, and probably should, be interpreted keeping in mind that, I only have a partial “denominator” to check results against: I couldn’t find any quantifiable data on the evolution of chronic complications. These featured highly amongst predictors of one-year HRQOL, hence they could be in part responsible for the low HRQOL outcomes, despite the success of the procedure.

Ultimately, the questions that springs to mind are: is a stable HRQOL after pancreas transplantation really a bad finding? Are these levels of HRQOL “as good as it gets” because of persistence of diabetes related complications? Potentially yes, and this might be acceptable for our patients, as the statistically significant increase in EQ-index and normative levels of SF-36 MCS seem to confirm. However, we have little scientific evidence in support of this, essentially for the lack of a specific validated

Pancreas Transplant PROM, capable of capturing all the intricacies of this population, while maintaining adequate feasibility and acceptability. What if a PROM - amongst other things - could weigh the burden of chronic complications and detect changes before and after surgery? What would be the trade-off if it were the case that (e.g.) early transplantation were able to provide the prospect of a life without diabetes, renal failure, AND chronic complications of the disease? Far from advocating for early transplantation based on the outputs of this research, I feel that this is nonetheless an avenue that needs exploring with suitable instruments.

In conclusion, there is an urgent need of a validated pancreas transplant PROM, tailored around the needs of this population. This research provided evidence-based information on some of the characteristics this instrument should have: it should be able to investigate diabetes, renal and transplant HRQOL and provide a weighted assessment of symptoms related to chronic complications. Equally it should address hypoglycaemia fear, theoretically making possible to compare HRQOL outcomes between Pancreas Transplant Alone and Islet Transplant Recipients, the two alternative strategies for the treatment of hypoglycaemia unawareness. In my vision, the mere existence of such an instrument could further the general knowledge on this topic. Moreover, if administered in the context of routine annual reviews, it could help clarify the trajectory of relevant symptom and transplant specific domains in the long term, which is still a pending matter.

There is a clear appetite for such an instrument and its use could spread quickly outside the boundaries of our transplant centre, making it easier to perform reliable metanalysis of future studies.

From the knowledge accrued with this research, I feel that its logical continuation would be a qualitative study to elicit and filter which of the manifold aspects related to HRQOL in diabetes, transplantation and renal failure are actually meaningful to our patients. This should be the first step of a collaboration between clinicians, outcome researchers and psychometric experts in the development of a bespoke Pancreas Transplant HRQOL questionnaire. Such instrument could then be the core of a subsequent multi-centre cohort study aimed at evaluating long term HRQOL changes in pancreas transplant recipients, in relation to the evolution of chronic complications, which should be recorded prospectively. As a complement to the pancreas-specific PROM, a generic instrument should also be used to assess health indexes, to make cross-disease comparison and comparison with the general population.

Finally, as a clinician venturing into the field of quantitative research, I came across a few difficulties, which became part of the learning process of this DPhil. Amongst various methodological issues, appraising the quality of quality-of-life studies was no small task. The only guidance available is over 30 years old and possibly dated (Gill and Feinstein 1994). However, HRQOL studies in clinical practice no longer represent a niche: they are becoming part of the standard of care. Thus, future research could focus on filling this small, yet important, knowledge gap.

5.5 CONCLUSIONS.

The main objective of this study was to investigate HRQOL changes after pancreas transplantation. I have demonstrated that successful SPK transplantation can indeed improve HRQOL fairly soon after surgery, and that the benefits seem to be stable in time. However, patients never return to population normative values, with the exception of mental health domains. It is likely that chronic complications continue to affect many aspects of HRQOL. There is an urgent need for a bespoke pancreas transplant PROM to understand the reasons behind these somewhat limited results. Ultimately, we could identify areas of care amenable of improvements and perhaps promote a better life and life-quality four our patients.

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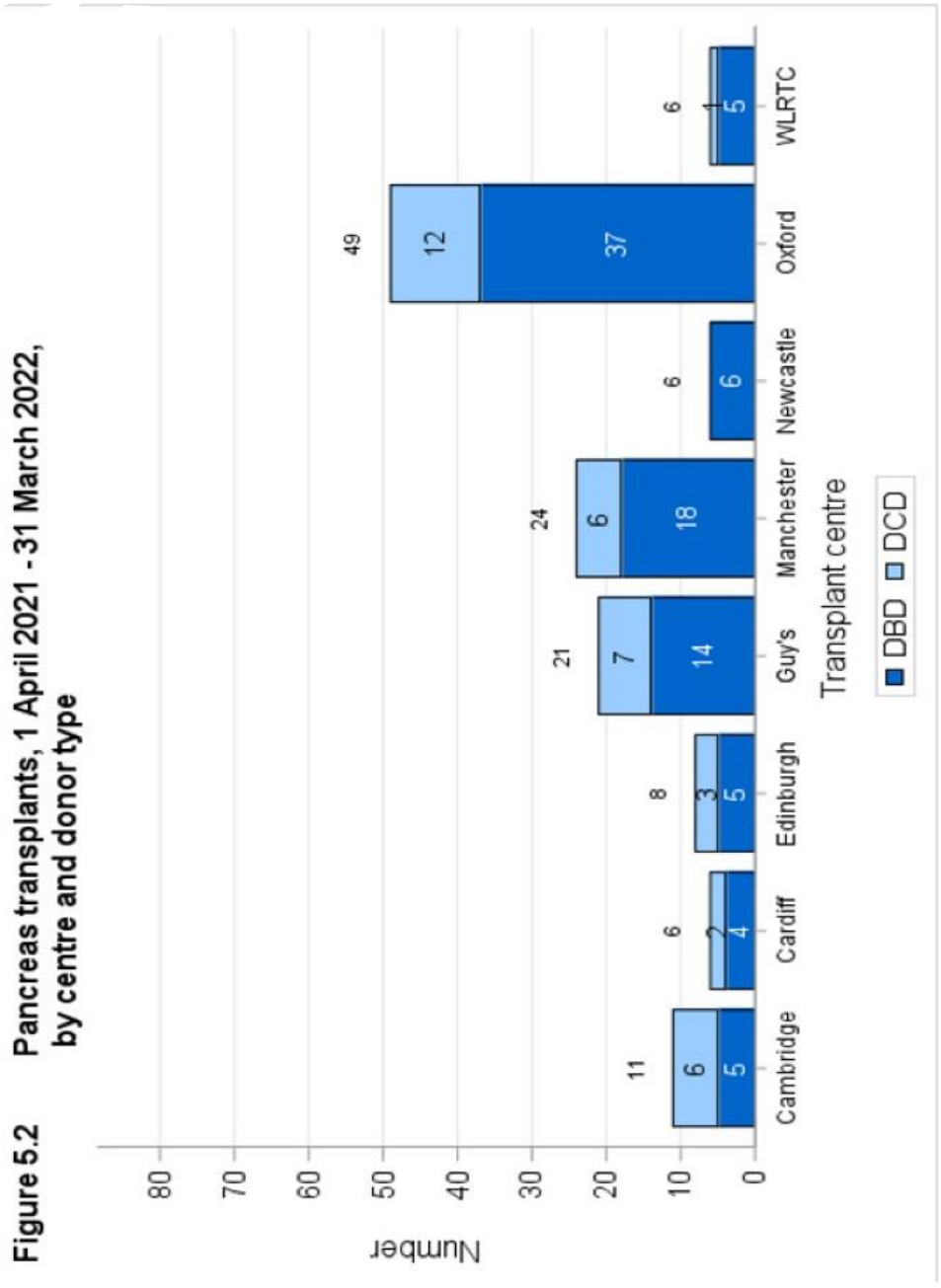
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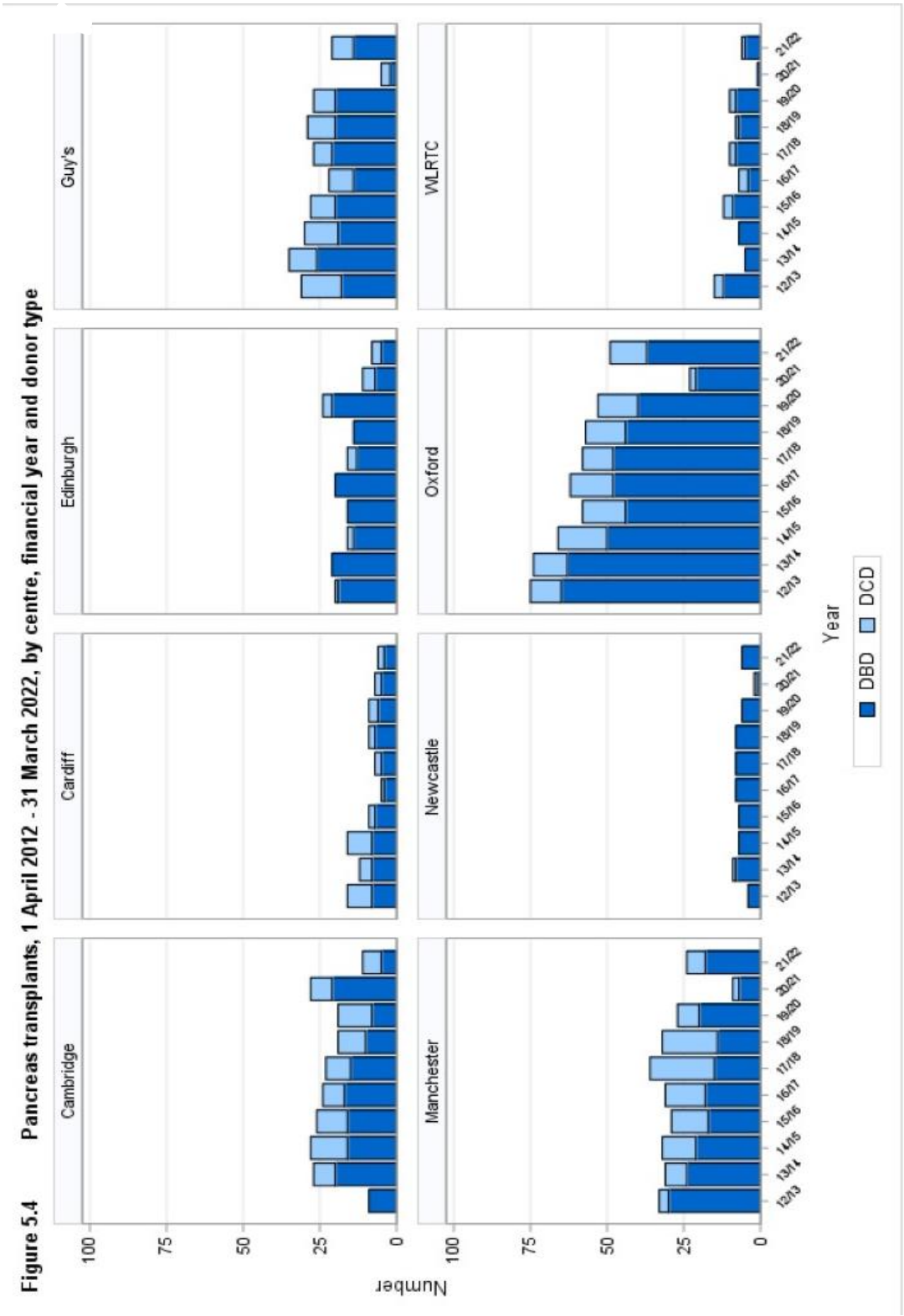
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APPENDIXES

APPENDIX 1: Supplementary material for Chapter 1

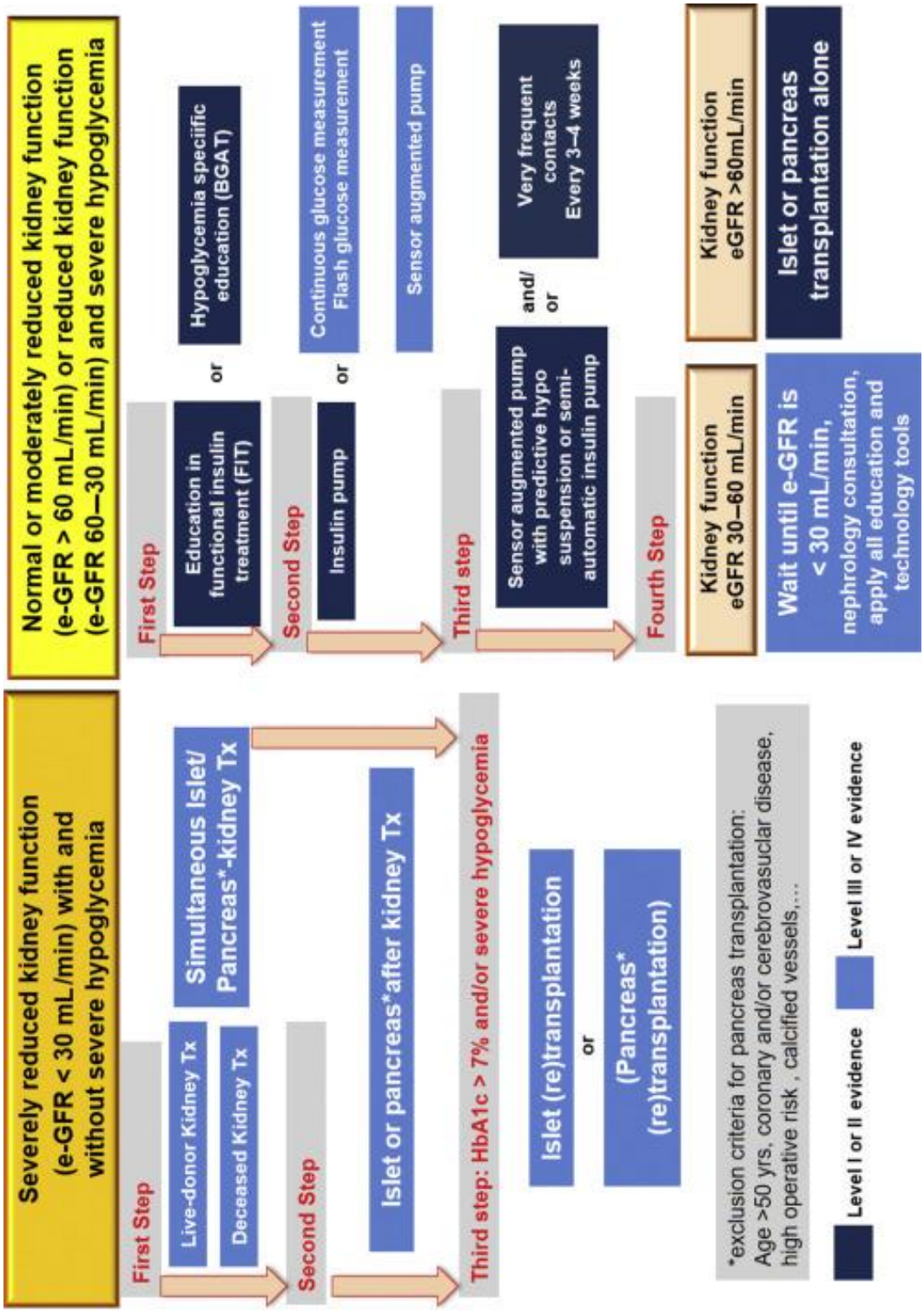


- **A1.1** Pancreas Transplant annual activity (2021-2022), stratified by donor type and centre (NHS Blood and Transplant 2022)



DBD: Donation after Brain Death, **DCD**: Donation after Circulatory Death **WLRTC:** West London Renal &Transplant Centre

- **A1.2** Ten years Pancreas Transplant activity (2012-2022), stratified by donor type and centre(NHS Blood and Transplant 2022)



- **A1.3** “Evidence-based treatment algorithm for patients with T1D and severe hypoglycaemia with and without reduced kidney function” (Leheman 2020)

- **A1.4** PROMs appraisal criteria (Mokkink, Terwee et al. 2010)

COSMIN definitions of domains, measurement properties, and aspects of measurement properties

Term			Definition
Domain	**Measurement property**	**Aspect of a measurement property**	
Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: e.g. using different sets of items from the same health related-patient reported outcomes (HR-PRO) (internal consistency); over time (test-retest); by different persons on the same occasion (inter-rater); or by the same persons (i.e. raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to 'true'† differences between patients
	Measurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though they are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses *(for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups)* based on the assumption that the HR-PRO instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypotheses testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument are an adequate reflection of the performance of the items of the original version of the HR-PRO instrument
	Criterion validity		The degree to which the scores of an HR-PRO instrument are an adequate reflection of a 'gold standard'
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability*			Interpretability is the degree to which one can assign qualitative meaning - that is, clinical or commonly understood connotations – to an instrument's quantitative scores or change in scores.

† *The word 'true' must be seen in the context of the CTT, which states that any observation is composed of two components – a true score and error associated with the observation. 'True' is the average score that would be obtained if the scale were given an infinite number of times. It refers only to the consistency of the score, and not to its accuracy (ref Streiner & Norman)*
* *Interpretability is not considered a measurement property, but an important characteristic of a measurement instrument*

APPENDIX 2: Supplementary material for Chapter 2

- **A 2.1** Search Terms

Pubmed MeSH* TERMS
PANCREAS TRANSPLANTATION
ISLET OF LANGERHANS TRANSPLANTATION
QUALITY OF LIFE
QUALITY-ADJUSTED LIFE YEARS

*MeSH: Medical Subject Headings

- **A 2.2** Search Strategy for Ovid MEDLINE(R)

SEARCH STRATEGY
1. exp PANCREAS TRANSPLANTATION/
2. (pancrea$ adj5 transplant$). ti,ab.
3. (pancrea$ adj5 graft$). ti,ab.
4. (pancrea$ Adj5 allograft$). ti,ab.
5. exp Islets of Langerhans Transplantation/
6. ((islet$ or "beta-cell" or "beta-cell") adj5 transplant$). ti,ab.
7. ((islet$ or "beta-cell" or "beta-cell") adj5 graft$). ti,ab.
8. ((islet$ or "beta-cell" or "beta-cell") Adj5 allograft$). ti,ab.
9. (SPK or "simultaneous pancreas kidney" or "simultaneous kidney pancreas" or PTA or PAK or "pancreas after kidney" or "pancreas transplant alone"). ti,ab.
10. or/1-9
11. exp QUALITY OF LIFE/
12. exp QUALITY-ADJUSTED LIFE YEARS/
13. exp Patient Reported Outcome Measures/
14. ("quality of life" or "quality-of-lifeor QOL" or HRQOL or HRQL). ti,ab.
15. ("patient reported outcome$" or "PrOMS" or "PROM"). ti,ab.
16. (QALY$ or "quality adjusted life years" or "quality-adjusted-life years"). ti,ab.
17. (EuroQol or EQ-5D or EQ-5D-5L or EQ-5D-3L or EQ-5D-Y). ti,ab.
18". (SF36 or "SF-36").ti,ab.
19. or/11-18
20. 10 and 19

- **A 2.3** Downs and Black Checklist

DOWNS AND BLACK CHECKLIST				
Reporting				
1	***Is the hypothesis/aim/objective of the study clearly described?***	yes 1	no 0	
2	***Are the main outcomes to be measured clearly described in the Introduction or Methods section?*** If the main outcomes are first mentioned in the Results section, the question should be answered no.	yes 1	no 0	
3	***Are the characteristics of the patients included in the study clearly described?*** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	yes 1	no 0	
4	***Are the interventions of interest clearly described?*** Treatments and placebo (where relevant) that are to be compared should be clearly described.	yes 1	no 0	
5	***Are the distributions of principal confounders in each group of subjects to be compared clearly described?*** A list of principal confounders is provided.	yes 1	no 0	partially 1
6	***Are the main findings of the study clearly described?*** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	yes 1	no 0	
7	***Does the study provide estimates of the random variability in the data for the main outcomes?*** In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should Be answered yes.	yes 1	no 0	
8	***Have all important adverse events that may be a consequence of the intervention been reported?*** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	yes 1	no 0	
9	***Have the characteristics of patients lost to follow-up been described?*** This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected inclusion. This should be answered “no” where a study does not report the number of patients lost to follow-up.	yes 1	no 0	
10	***Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?***	yes 1	no 0	

External validity *All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.*				
11	***Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*** The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	yes 1	no 0	Unable to determine 0
12	***Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*** The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	yes 1	no 0	Unable to determine 0
Internal validity - bias				
13	***Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*** For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	yes 1	no 0	Unable to determine 0
14	***Was an attempt made to blind study subjects to the intervention they have received?*** For studies where the patients would have no way of knowing which intervention they received, this should Be answered yes.	yes 1	no 0	Unable to determine 0
15	***Was an attempt made to blind those measuring the main outcomes of the intervention?***	yes 1	no 0	Unable to determine 0
16	***If any of the results of the study were based on "data dredging", was this made clear?*** Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.			
17	***In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*** Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	yes 1	no 0	Unable to determine 0

18	***Were the statistical tests used to assess the main outcomes appropriate?*** The statistical techniques used must be appropriate to the data. For example non- parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should Be answered yes.	yes 1	no 0	Unable to determine 0
19	***Was compliance with the intervention/s reliable?*** Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should Be answered yes.	yes 1	no 0	Unable to determine 0
Internal validity – confounding (selection bias)				
20	***Were the main outcome measures used accurate (valid and reliable)?*** For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be Answered as yes.	yes 1	no 0	Unable to determine 0
21	***Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*** For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case- control studies where there is no information concerning the source of patients included in the study.	yes 1	no 0	Unable to determine 0
22	***Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*** For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	yes 1	no 0	Unable to determine 0
23	***Were study subjects randomised to intervention groups?*** Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	yes 1	no 0	Unable to determine 0
24	***Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete And irrevocable?***	yes 1	no 0	Unable to determine 0
25	***Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*** This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non- randomised studies if the effect of the main confounders was not investigated or con- founding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	yes 1	no 0	Unable to determine 0

26	***Were losses of patients to follow-up taken into account?*** If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should Be answered yes.	yes 1	no 0	Unable to determine 0
Power				
27	***Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*** Sample sizes have been calculated to detect a difference of x% and y%.	yes 1	no 0	Unable to determine 0

- **A2.4** Prisma Flow Diagram (Page et al, 2021)

A2.5 Systematic Review: synopsis of included studies

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Adang, Engel et al. 1996 Netherlands (Maastricht) English	Full Article	Quantitative	1þ	4/8 (50.00)	22	SPK (both functioning): 17 SPK (failed pancreas): 5	0	Yes	5-12-18 months	Visual Analogue Scale (VAS), Rotterdam Symptoms Checklist (RSCL), Nottingham Health Profile 1&2 (NHP1-2), Affect Balance Scale (ABS) State Trait Anxiety Inventory (STAI-D1), Family Impact Questionnaire (FIQ)	**VAS:** Global Quality of Life. **RSCL:** Symptoms. **NHP-1:** Physical, Social, Sleep, Emotional. **NHP-2:** Relationships, Vocational. **ABS:** Wellbeing. **STAI-D1:** Anxiety. **FIQ:** Social Support

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Adang, Kootstra et al. 1998 Netherlands (Maastricht) English	Full Article	Quantitative	17	5/8 62.50)	18	SPK (both functioning): 18	0	Yes	5-12-18 months	Visual Analogue Scale (VAS), Rotterdam Symptoms Checklist (RSCL), Nottingham Health Profile 1&2 (NHP1-2), Affect Balance Scales (ABS)	**VAS:** Global Quality of Life. **RSCL:** Symptoms. **NHP-1:** Physical, Social, Sleep, Emotional. **NHP-2:** Relationships, Vocational. **ABS:** Wellbeing.
Alharbi, Aquil et al. 2017 Canada (Ontario) English	Conference Abstract	Quantitative	n/a	n/a	42	SPK (both functioning): 33 SPK (failed pancreas): 9	0	No	3 months, 1 year, 5 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Mental Health, Physical Functioning, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Anderson, Hart et al. 2011 USA (North Carolina) English	Conference Abstract	Quantitative	n/a	n/a n/a	40	SPK: 40	KTA: 48 KTx for all causes: 119 Population Normative Values	Yes	3-12-24 months	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Barama, 2009 Canada (Montreal) English	Conference Abstract	Quantitative	n/a	n/a n/a	100	SPK: 100	KTA: unspecified	No	10 years?, Unclear	Unspecified Instrument + Structured Interview	Unspecified

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Ben-Youssef, Baron et al. 2006 USA (California) English	Full Article	Quantitative	n/a	n/a n/a	3	SPK (both functioning): 2 PTA: 1	0	No	< 18 months	Single Item	Global QOL
Bentdal, Fauchald et al. 1991 Norway (Oslo) English	Full Article	Quantitative	11,00	1/8 (12.50)	27	SPK (both functioning): 11 SPK (failed pancreas): 16	0	No	Mean: 62 months Range: 40-84	Interview	Rehabilitation, Physical, Social

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Bozek-Pajak, Ziaja et al. 2016 Poland (Multicentre) English	Full Article	Quantitative	16,00	1/8 (12.50)	30	SPK (both functioning): 27	KTA + SPK (failed pancreas): 23 + 3	No	Mean: 45 +/- 22.5 months	Kidney Disease Quality of Life Short Form (KDQOL-SF)	**KDQOL-SF:** SF-36 Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning + Renal related domains: Symptoms/Problem, Work, Effects of Kidney Disease, Burden of Kidney Disease, Social Interactions, Sleep, Social Support, Dialysis Staff, Satisfaction
Brons, Calne et al. 1989 UK (Cambridge) English	Full Article	Quantitative	9	0/8 (.00)	13	SPK: 13	0	No	< 5 years, unspecified	Ad hoc questionnaire	Vocational, Social, Independence, Global Quality of Life

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Bolesta, Kuhn et al. 2016 Germany (Bochum) English	Conference Abstract	Quantitative	n/a	n/a	146	SPK (both functioning): 146	WL: 51	No	Unspecified	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Boyd, Martin et al. 2001 USA (Cinicinnati) English	Full Article	Quantitative	10	2/8 (25.00)	23	SPK: 23	KTx for all causes: 100	No	Unspecified	Short Form 12 (SF-12), Cincinnati Transplant Questionnaire (CTQ)	**SF12:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **CTQ:** Transplant Related HRQOL

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Bruce, Newell et al. 1996 USA (Illinois) English	Full Article	Quantitative	12,00	2/8 (25.00)	50	SPK (both functioning): 50	0	No	Mean: 4.3 years Range: 3-8	Symptoms Checklist- 90 (SCL-90), Sickness Impact Profile (SIP),	**SCL-90:** Psychosocial Adjustment, **SIP:** Health Status, Disability, Physical And Psycosocial
Cetingok, Hathaway et al. 2007 USA (Tennessee) English	Full Article	Quantitative	14	6/9 (67.00)	15	SPK: 15 Liver: 17 KTx all causes: 31	0	Yes	6 months	Affection Deficity Hyperactivity Disorder Simptoms Infrequency Scale (ASIS), Sickness Impact Profile (SIP), Spitzer Quality of Life Index (QLI)	**ASIS**: Psyco-Emotional Status, **SIP:** Health Status, Disability, Physical And Psycosocial, **QLI:** Health Perception, Self Care, Work, Social

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Dew, Switzer et al. 1997 USA (Maryland) English	Full Article	Review	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Drognitz, Benz et al. 2004 Germany (Tubinga) English	Full Article	Quantitative	13,00	2/8 (25.00)	43	SPK (both functioning): 33 SPK (re-transplants): 2 SPK (failed kidney): 3 SPK (failed pancreas): 1 SPK both failed: 1		No	Mean: 9.1 years Range 5.9-12.9	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Esmatjes, Ricart et al. 1994 Spain (Barcelona) English	Full Article	Quantitative	12,00	2/8 (25.00)	12	SPK: 12	KTA: 10 DM type-1 (RRT): 10	No	> 1 year	Karnowsky, Spizer Quality of Life Index (QLI), Index Of Integration To Normal Life (RNLI)	**KARNOWSKY:** performance status **QLI**: Health Perception, Self Care, Work, Social, **RNLI:** Activity, Daily Living, Perception Of Self, Rehabilitation, Physical Ablilities, Mobility, Social, Family, Personal Relationships
Friedrich, Niebel et al. 1999 Germany (Gladbeck) German	Full Article	Objective Measures	11,00	n/a n/a	16	SPK: 16	0	No	Unspecified	No PROMS	Work, Pregnancies as surrogate markers of QOL

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Gaber, Hathaway et al. 1994 USA (Tennessee) English	Full Article	Quantitative	10,00	2/8 (25.00)	21	SPK (both functioning): 12	KTA (functioning): 7	Yes	1 year	Sinckness Impact Profile (SIP)	**SIP:** Health Status, Disability, Physical And Psycosocial
Gibbons, Cinnirella et al. 2020 UK (Multicentre) English	Full Article	Quantitative and Qualitative	16,00	5/9 56.00)	95	SPK: 95	WL: 41	Yes	1 year	Mixed methods	**ADQOL:** Diabetes Qol, **RDQOL**: Renal Qol **W-BQ12:** Wellbeing, **EQ-5D-5L AND VAS:** Health Status And Utility Scores, **RTSQS**: Renal Treatment Satisfaction Status, **RTSQC:** Renal Treatment Satisfaction Change, **DTSQS**: Diabetes Treatment Satisfaction Satus, **DTSQC:** Diabetes Treatment Satisfaction Change

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Gross, Limwattananon et al. 1998 USA (Minnesota) English	Full Article	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Gross, Limwattananon et al. 2000 USA (Minnesota) English	Full Article	Quantitative	16	4/8 (50.00)	65	SPK (both functioning): 65	KTA (functioning): 87 DM type 1 (not transplanted): 41	Yes	1 year, 3 years	Short Form 36 (SF 36), Karnowsky, Center for Epidemiological Studies-Depression Scale (CES-D), Index Of Wellbeing (IWB), Life Satisfaction and Diabetes Satisfaction Item, Transplant Items, Employment Rates, Hospital Episode Statistics (HES)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **KARNOWSKY:** Performance Status, Health Satisfaction item, Life satisfaction item, **IWB**: Wellbeing. Satisfaction with diabetes, Transplant specific items, Employment rates, **HES**: Hospital Episode Statistics. Diabetes severity index

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Gross and Zehrer 1992 USA (Minnesota) English	Full Article	Quantitative	12	1/8 (12.50)	131	SPK (both functioning: 65 SPK (failed pancreas) + SPK (both failed): 66	0	No	Range: 1-11 years	Short Form 20 (SF 20)	**SF 20:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Gruessner 2017 USA (New York State) English	Conference Abstract	Objective Measures	n/a	n/a n/a	4476	SPK : 3670, PAK; 448 , PTA: 358	0	No	1 year	n/a	WorkStatus

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Hanlon, Cooper et al. 2019 USA (Washington State) English	Full Article	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Hart, Milde et al. 1997 USA (Iowa) English	Full Article	Quantitative		4/8 (50.00)	n/a	SPK, Liver, Ktx all causes : 300		No	Unclear	Unspecified	Sexual function and Satisfaction, Global QOL and Satisfaction

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Hathaway, Wicks et al. 2000 USA (Tennessee) English	Full Article	Quantitative	15	6/9 (56.00)	20	SPK: 20	KTx for all causes: 37	Yes	6 months	Sickness Impact Profile (SIP)	
Hathaway, Hartwig et al. 1994 USA (Tennessee) English	Full Article	Quantitative	10	2/8 (25.00)	15	SPK: 15	KTA: 15	Yes	6 months	Affection Deficity Hyperactivity Disorder Simptoms Infrequency Scale (ASIS), Sickness Impact Profile (SIP), Spitzer Quality of Life Index (QLI)	**ASIS**: Psyco-Emotional Status, **SIP:** Health Status, Disability, Physical And Psycosocial, **QLI**: Health Perception, Self Care, Work, Social

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Hathaway, Winsett et al. 1996 USA (Tennessee) English	Full Article	Quantitative	10,00	3/8 (37.50)	98	SPK+KTA: 98	0	No	1 year	Affection Deficity Hyperactivity Disorder Simptoms Infrequency Scale (ASIS), Sickness Impact Profile (SIP)	**ASIS:** Psyco-Emotional Status, **SIP**: Health Status, Disability, Physical And Psycosocial
Humar, Ramcharan et al. 2001 USA (Minnesota) English	Full Article	Quantitative	11	2/8 (25.00)	398	SPK: 193, PAK: 205	0	No	Unspecified	Short Form 36 (SF 36), Center for Epidemiological Studies-Depression Scale (CES-D),	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning , **CES-D** depression, Well-being

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Isla Pera, Moncho Vasallo et al. 2012 Spain (Barcelona) English	Full Article	Qualitative	n/a	n/a	20	SPK (both functioning): 20	0	No	Unclear	Qualitative	Qualitative
Isla Pera, Moncho Vasallo et al. 2009 Spain (Barcelona) English	Full Article	Quantitative	16	3/8 (37.50)	69	SPK (both functioning): 69	WL: 34, Population Normative Values	No	Unclear	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Jackson, Gleeson et al. 2013 UK (Bristol) English	Conference Abstract	Qualitative	n/a	n/a	15	SPK: 15	0	No	Range: 7 weeks - 3 years	Semi-structured interview	Psychological Wellbeing.
Johnson, Schellberg et al. 1990 USA (Minnesota) English	Full Article	Quantitative	10	2/8 (25.00)	17	SPK: 15, PTA: 2	0	Yes	3-6-9 months, 1 year	Karnowsky	**KARNOWSKY:** Performance Status, **Items** on: family, mental and emotional wellbeing, vocational/work, self-image, daily activities, diet, social and sexual fx

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Kansal, Johnson et al. 2013 UK (Newcastle) English	Conference Abstract	Quantitative	n/a	n/a	30	SPK (both functioning): 24 SPK (failed pancreas): 6	WL: 6	No	Unspecified	WHOQOL-BREF,, Roland Morris Disability Questionnaire, Hospital Anxiety and Depression Scale (HADS), Clinical Outcomes In Routine Evaluation (CORE-10), Generaised Anxiety Disorder Assessment (GAD-7)	**QOL BREF:** Physical Health, Psychological Health, Social Reltionships Environmental Health, **RMD:** Disability **HADS/GAD7:** Depression/Anxiety
Kenmochi, Asano et al. 2013 Japan (Chiba) English	Conference Abstract	Quantitative	n/a	n/a n/a	6	SPK (living donor): 6	0	No	Unspecified (5 years?)	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Joseph, Baines et al. 2003 UK (Bournemouth) English	Full Article	Review	n/a	n/a n/a	n/a		n/a	n/a	n/a	n/a	n/a
Jurgensen, Ulrich et al. 2008 Germany (Berlin) English	Full Article	Quantitative	12	2/8 (25.00)	101	Male SPK: 101	Population Normative Values	No	Unspecified	Short Form 36 (SF 36), Quality of Wellbeing (QWB), Internationa Index of Erectile Function (IIEF)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning , **QWB:** Wellbeing, **IIEF:** Sexual Function

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Kansal, Johnson et al. 2013 UK (Newcastle) English	Conference Abstract	Quantitative	n/a	n/a	30	SPK (both functioning): 24 SPK (failed pancreas): 6	WL: 6	No	Unspecified	WHOQOL-BREF,, Roland Morris Disability Questionnaire, Hospital Anxiety and Depression Scale (HADS), Clinical Outcomes In Routine Evaluation (CORE-10), Generaised Anxiety Disorder Assessment (GAD-7)	**QOL BREF:** Physical Health, Psychological Health, Social Reltionships Environmental Health, **RMD:** Disability **HADS/GAD7:** Depression/Anxiety
Kenmochi, Asano et al. 2013 Japan (Chiba) English	Conference Abstract	Quantitative	n/a	n/a n/a	6	SPK (living donor): 6	0	No	Unspecified (5 years?)	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Kinkhabwala, Wilkinson et al. 1996 USA (California) English	Full Article	Quantitative	6	1/8 (12.50)	12	SPK (both functioning): 12	0	No	Unspecified	Unspecified	Global QOL, Sense Of Wellbeing
Knight and Daly 2004 USA (Texas) English	Full Article	Objective Measures	13	3/8 (37.50)	33	SPK: 33	KTA: 15	Yes	>6 months	n/a	Employment Status, Clinical Outcomes as surrogate markers of QOL

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Kessler, Boudjema et al. 1996 France (Strasbourg) French	Full Article	Quantitative	11	3/8 (37.50)	13	SPK (both functioning): 13	Non-listed DM type 1: 6	No	Mean: 18.1 +/- 2.7 months	Diabetes Quality of Life (DQOL),	**DQOL**: Diabetes Related Satisfaction, Impact, Worry
Kiebert, van Oosterhout et al. 1994 Netherlands (Leiden) English	Full Article	Quantitative	5	2/8 (25.00)	28	SPK (both functioning): 17	KTA (functioning): 23 SPK (both organs failed): 11	No	Median: 31 months Range: 2-73 months	Ad hoc	Physical, Disease Specific items, Psychological and Social Wellbeing, Daily Activities, Level Of Functioning, Global QOL expectations, Burden Of Treatment

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Kinkhabwala, Wilkinson et al. 1996 USA (California) English	Full Article	Quantitative	6	1/8 (12.50)	12	SPK (both functioning): 12	0	No	Unspecified	Unspecified	Global QOL, Sense Of Wellbeing
Knight and Daly 2004 USA (Texas) English	Full Article	Objective Measures	13	3/8 (37.50)	33	SPK: 33	KTA: 15	Yes	>6 months	n/a	Employment Status, Clinical Outcomes as surrogate markers of QOL

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Langenbach, Stippel et al. 2004 Germany (Cologne) English	Full Article	Qualitative	n/a	n/a n/a	8	SPK: 8	0	No	1 year	Interview	**INTERVIEW:** Experiences of Transplantation
Lo, Stratta et al. 2001 USA (Tennessee) English	Full Article	Quantitative	14	3/8 (37.50)	45	SPK, enteric drained (both functioning): 26 SPK, bladder drained (both functioning): 19	0	No	Mean: 18.5 months Range: 6-24 months	Affection Deficity Hyperactivity Disorder Simptoms Infrequency Scale (ASIS), Sickness Impact Profile (SIP), Spitzer Quality of Life Index (QLI), Minnesota Multiphasic Personality Inventory (MMPI)	**ASIS**: Psyco-Emotional Status, **SIP**: Health Status, Disability, Physical And Psycosocial, **QLI**: Health Perception, Self Care, Work, Social, **MMPI:** personality and psychopathology scales

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Koznarova 2001 Czech Republic (Prague) English	Full Article	Quantitative	10	2/8 (25.00)	79	SPK (both functioning): 66	KTA (functioning): 15 SPK (failed pancreas): 13	No	SPK Mean: 44+/- 4 months KTA (functioning) Mean: 72 +/- 36 months SPK (failed pancreas) Mean: 53 +/- 31 months	Short Form 36 (SF 36), Muthney modified	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **MUTHNEY MODIFIED:** Physical and Mental Health Status, Emotional Situation, Partnership and Family Life, Sexual wellbeing, Leisure Time, Vocational, Burden of Treatment + Diabetes Related Items
Kwiatkowski, Michalak et al. 2005 Poland (Warsaw) English	Full Article	Quantitative	8	2/8 (25.00)	19	SPK (both functioning): 19	0	No	4.2 +/- 3.6 years	Ad hoc	Physical,Psychological and Social Wellbeing, Daily Activities, Level Of Functioning, Global QOL Expectations, Burden Of Treatment

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Martell, Rice et al. 2015 USA (Wisconsin) English	Full Article	Qualitative	n/a	n/a n/a	70	SPK: 70	KTx for all causes: 143	No	> 6 months	Qualitative	Sexual Wellbeing
Martin 2001 USA (Ohio) English	Full Article	Quantitative	10	1/8 (12.50)	15	SPK: 15 + Liver : 19 + Heart: 17+ Ktx all causes: 97	0	No	Mean: 2.6 +/- 1.4 years	Short Form 36 (SF-36), Cincinnati Transplant Questionnaire	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **CTQ**: Transplant
Martins, Outerelo et al. 2015 Portugal (Multicentre) English	Full Article	Quantitative	12	2/8 (25.00)	126	SPK (both functioning): 106 SPK (both failed): 20	0	Yes	Mean: 4.8 +/- 3.5 years	Euroqol-5D-3L, Gastrointestinal Quality of Life (GIGLI)	**EQ-5D-**: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression **GIQLI:** GastroIntestinal Symptoms, **Ad hoc questions**: Burdein Of Treatment

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Matas, McHugh et al. 1998 USA (Minnesota) English	Full Article	Quantitative	12,00	3.8 (37.50)	1138	SPK, KTA and KT all causes: 1138	Population Normative Values	No	Range: 1-10 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Mosca, Dumbill et al. 2019 UK (Oxford) English	Conference Abstract	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mosca, Mittal et al. 2018 UK (Oxford) English	Conference Abstract	Quantitative	n/a	n/a n/a	200	SPK, PTA, PAK: 200	0	Yes	Unspecified	Euroqol-5D-3L (EQ-5D-3L)	**EQ-5D-3L**: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression **GIQLI:** GastroIntestinal Symptoms, **Ad hoc questions**: Burdein Of Treatment

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Martell, Rice et al. 2015 USA (Wisconsin) English	Full Article	Qualitative	n/a	n/a n/a	70	SPK: 70	KTx for all causes: 143	No	> 6 months	Qualitative	Sexual Wellbeing
Martin 2001 USA (Ohio) English	Full Article	Quantitative	10	1/8 (12.50)	15	SPK: 15 + Liver : 19 + Heart: 17+ Ktx all causes: 97	0	No	Mean: 2.6 +/- 1.4 years	Short Form 36 (SF-36), Cincinnati Transplant Questionnaire	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **CTQ**: Transplant
Martins, Outerelo et al. 2015 Portugal (Multicentre) English	Full Article	Quantitative	12	2/8 (25.00)	126	SPK (both functioning): 106 SPK (both failed): 20	0	Yes	Mean: 4.8 +/- 3.5 years	Euroqol-5D-3L, Gastrointestinal Quality of Life (GIGLI)	**EQ-5D**-: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression **GIQLI:** GastroIntestinal Symptoms, **Ad hoc questions**: Burdein Of Treatment

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Matas, McHugh et al. 1998 USA (Minnesota) English	Full Article	Quantitative	12,00	3.8 (37.50)	1138	SPK, KTA and KT all causes: 1138	Population Normative Values	No	Range: 1-10 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Mosca, Dumbill et al. 2019 UK (Oxford) English	Conference Abstract	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mosca, Mittal et al. 2018 UK (Oxford) English	Conference Abstract	Quantitative	n/a	n/a n/a	200	SPK, PTA, PAK: 200	0	Yes	Unspecified	Euroqol-5D-3L (EQ-5D-3L)	**EQ-5D-3L**: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression **GIQLI:** GastroIntestinal Symptoms, **Ad hoc questions**: Burdein Of Treatment

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Muehrer 2009 USA (Wisconsin) English	Full Article	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Muehrer, Keller et al. 2006 USA (Wisconsin) English	Full Article	Quantitative	11	n/a n/a	65	Female SPK, (both functioning): 65	0	No	Median: 5 years Range: 6 months-15 years	Arizona Sexual Experience Scale (ASEX), SEXUAL SELF-ESTEEM SCALE, Open Ended Questions	**ASEX:** Sexual Functioning, **SEXUAL SELF-ESTEEM SCALE, OPEN ENDED QUESTIONS:** Illness related

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Muehrer, Brown et al. 2013 USA (Wisconsin) English	Conference Abstract	Quantitative	n/a	n/a n/a	145	SPK: 145	0	Yes	Unspecified	Short Form 12 (SF-12) , QOL Uniscale, Social Communication Questionnaire (SCQ)	**SF 12** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **QOL UNISCALE**: Quality of Life, **Sexual Concern Questionnaire:** Sexual Wellbeing
Najarian, Gruessner et al. 1998 USA (Minnesota) English	Full Article	Quantitative	6	2/8 (25.00)	14	SPK (both functioning): 14		Yes	Range: 10-17 years	Karnowsky, Spitzer Quality of Life Index, Index (QLI), Reintegration to Normal Life Index (RNLI)	**KARNOWSKY:** Performance Status**, QLI:** Health Perception, Self Care, Work, Social, **RNLI:** Activity, Daily Living, Perception Of Self, Rehabilitation, Physical Ablilities, Mobility, Social, Family, Personal Relationships

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Nakache, Tyden et al. 1989 Sweden (Carolinska) English	Full Article	Quantitative	9	4/8 (50.00)	16	SPK (both functioning): 8 SPK (failed pancreas): 8	KTA (living donor: 4 Non-listed DM type1: 4	No	>2 years	Mixed Methods, Spitzer Quality of Life Index (QLI) , Reintegration to Normal Life Index (RNLI)	**INTERVIEW|:** physical , mental, social role functioning, health perception **QLI:** Health Perception, Self Care, Work, Social **RNLI:** Activity, Daily Living, Perception Of Self, Rehabilitation, Physical Ablilities, Mobility, Social, Family, Personal Relationships,
Nakache, Tyden et al. 1994 Sweden (Carolinska)	Full Article	Quantitative	8	3/8 (37.50)	8	SPK (both functioning)	KTA (functioning) + SPK (failed pancreas): 10	No	>7 years	Spitzer Quality of Life Index (QLI) , Rehabilitation to Normal Life Index (RNLI)	**QLI:** Health Perception, Self Care, Work, Social, **RNLI**: Activity, Daily Living, Perception Of Self, Rehabilitation, Physical Ablilities, Mobility, Social, Family, Personal Relationships

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Nathan, Fogel et al. 1991 USA (Boston) English	Full Article	Quantitative	11	3/8 (37.50)	12	SPK (both functioning): 12	KTA + SPK (failed pancreas): 18	Yes	Mean: 18 +/- 11 months	Diabetes Quality of Life (DQOL)	**DQOL:** Satisfaction, Impact, Diabetes Worry, Social/Vocational Worry
Nijhoff, Hovens et al. 2020 Netherlands (Leiden) English	Full Article	Quantitative	13	2/8 (25.00)	72	SPK: 72	WL: 47 Non-listed DM type-1 without renal failure: 42	No	> 1 years; SPK Median: 7 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

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Nyumura, Babazono et al. 2017 Japan (Tokio) English	Full Article	Quantitative	14	3/8 (37.50)	16	SPK: 16	KTA: 25 DM type 1 (no renal failure): 10 DM type 1 (on dialysis): 52	No	SPK Mean: 3.5+/- 4.6 years KTA Mean: 3.5 +/- 3.4 years	Short Form 36 v2 (SF 36 v2), Problem Areas in Diabetes (PAID), Clarke hypogycemic score	**SF 36v2:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Phillips, Walker et al. 2001 USA (Ohio) English	Full Article	Quantitative	7	1/8 (12.50)	20	SPK: 20 + Liver: 83 + KTx all causes: 115		No	Unspecified	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

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Piehlmeier, Bullinger et al. 1994 Germany (Munich) English	Full Article	Quantitative	13	2/8 (25.00)	32	SPK (both functioning): 15 SPK (both functioning longitudinal cohort): 8 SPK (failed pancreas): 9	WL: 6	Yes	SPK (functioning) Mean: 27.7 +/- 5.9 months SPK functioning (longitudinal) Mean: 22 +/- 4 months SPK (failed pancreas) Mean: 36.4 +/- 5.7 months	Muthney Modified	Physical and Mental Status, Emotional Wellbeing, Partnership and Family Life, Sexual wellbeing, Leisure Time, Vocational, Treatment-related Burden

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									PTA Mean: 22.7 +/- 1.6 months		
Posegger, Linhares et al. 2020 Brasil (Sao Paulo) English	Full Article	Quantitative	15	2/8 (25.00)	103	SPK: 103	WL: 57	No	<1 year, 1 to 3 years, >3 years	Kidney Disease Quality of Life Short Form (KDQOL-SF), Problem Areas in Diabetes (PAID)	**KDQOL-SF:** SF-36 Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning + Renal related domains: Symptoms/Problem, Work, Effects of Kidney Disease, Burden of Kidney Disease, Social Interactions, Sleep, Social Support, Dialysis Staff, Satisfaction, **PAID:** Diabetes Distress

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Radosevich McHugh et al. 2013 USA (Minnesota) English	Conference Abstract	Quantitative	n/a	n/a n/a	Unspecified	SPK, PTA, Liver, Heart, Lung, Ktx all causes: 1012	Population Normative Values	Yes	1 year, 3 years	Short Form 12 (SF-12)	**SF12** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **IPAQ_SHORT**: Physical Activity
Rajkumar, Mazid et al. 2019 Australia (Westmead) English	Full Article	Quantitative	17	3/8 (37.50)	18	SPK: 18	KTx all causes: 57	Yes	1 year	Kidney Disease Quality of Life Short Form (KDQOL-SF),	**KDQOL-SF:** SF-36 Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning + Renal related domains: Symptoms/Problem, Work, Effects of Kidney Disease, Burden of Kidney Disease, Social Interactions, Sleep, Social Support, Dialysis Staff, Satisfaction,

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Reilly-Spong, Park et al. 2013 USA (Minnesota) English	Full Article	Quantitative	16	2/8 (25.00)	16	SPK: 16	Liver: 25, Heart: 13, Lung: 12, Ktx all causes: 77	No	SPK, Mean: 5.9 +/- 5.1 years	Pitssburg Sleep Quality Index (PSQI), Short Form 36 v2 (SF 36 v2), Center for Epidemiological Studies-Depression Scale (CES-D), State trait anxiety Inventory (STAI)	**PSQI:** sleep quality **SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **CES-D** depression, **STAI** anxiety

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Salonia, D'Addio et al. 2011 Italy (Milan) English	Full Article	Quantitative	16	2/8 (25.00)	10	SPK: 10	KTA: 10 Non-listed DM type-1 (with renal failure): 9 Healthy control: 11	No	SPK Mean: 4.2 +/- 1.0 years KTA Mean: 6.3 +/- 3.9	BECK'S Depression Inventory, Clinical Assesment Of Sexual Function	**BECK'S Inventory:** Depression
Sansalone, Aseni et al. 2003 Italy (Milan) Italian	Full Article	Quantitative	9	2/8 (25.00)	30	SPK (both functioning): 30	0	No	1 year	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

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Satterly, Cox et al. 1991 USA (Iowa) English	Full Article	Quantitative	12,00	2/8 (25.00)	23	SPK (both functioning): 16 SPK (failed pancreas): 7	0	No	>6 months	Iowa Transplant Activities Questionnaire	Symptoms, Rehabiitation
Scalea, Pettinato et al. 2018 USA (Maryland) English	Full Article	Quantitative	13	2/8 (25.00)	32	PTA (functioning) 18 PTA (failed) 14	0	No	Unclear	Ad hoc, mixed methods	Demographic, Health Staus, Symptoms, Hypoglicaemia Fear, Daily Activities

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Schareck, Hopt et al. 1994 Germany (Tubinga) English	Full Article	Quantitative	11	3/8 (37.50)	45	SPK: 45	0	No	>1 years	Mixed Methods	Symptoms, Subjective Well-being, Attitude on transplantation/retransplantation
Scheuermann, Rademacher et al. 2020 Germany (Leipzig) English	Full Article	Quantitative	15	2/8 (25.00)	83	SPK (pre-tx HD): 64 SPK (pre-tx PD): 19	0	No	>1 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

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Secchi, Martinenghi et al. 1998 Italy (Milan) English	Full Article	Quantitative	16	1/8 (12.50)	34	SPK (both functioning): 29	KTA + SPK (failed pancreas): 9+5 WL (on dialysis): 48	No	SPK Mean: 42 +/- 0.5 months Range 6-93 KTA: Mean 48.1 +/- 0.4 months Range: 6-960 WL: Mean 47.3 +/- 5.1 months after RRT start, Range: 7-180	Simmons questionnaire, Diabetes and Transplant Items	Renal Related Physical and Psycological, Diabetes and Transplant Specific Items.

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Shahabeddin Parizi, Krabbe et al. 2019 Netherlands (Gorningen) English	Full Article	Review	n/a	n/a n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Smith, Trauer et al. 2010 Australia (Sydney)) English	Full Article	Quantitative	19	2/8 (25.00)	37	SPK: 37	Population Normative Values	Yes	4 months, 1-2-3 years	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Speight, Reaney et al. 2010 UK (Uxbridge) English	Full Article	Review	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Speight, Woodcock et al. 2010 UK (Uxbridge) English	Conference Abstract	Quantitative	n/a	n/a	n/a	n/a	n/a	n/a		Diabetes Quality of Life Questionnaire (QOL-Q)	**QOL-Q:** Social, Sexual, Family, Physical, Vocational, Sleep, Control, Freedom

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Stonnington, Darby et al. 2016 USA (Minnesota) English	Full Article	Quantitative	18	3/9 (33.00)	4	SPK: 4	Bone marrow: 4, Liver: 6, Heart: 17	No	6 weeks, 3 months	Short Form -36 (SF-36), Pereceived Stress Scale-10 Item, Connor Davidson Resilience Scale, Patient Health Questionnaire-9 (PHQ-9), Genrealised Anxiety Disorder (GAD-7), Positive And Negative Afffect Scale (PANAS), Mindful Attention Awareness Scale	**SF 36**: Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning . **PERCEIVED STRESS SCALE-10 ITEM**: Stress, **CONNOR-DAVIDSON RESILIENCE SCALE**: Resilience, **PHQ-9**: Depression, **GAD-7**: Anxiety HRQOL, **PANAS**: Afffect Scale, **MINDFUL ATTENTION AWARENESS SCALE** : Midfulness, Sleep Quality

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Stratta, Taylor et al. 1994 USA (Nebraska) English	Full Article	Quantitative	14	1/8 (12.50)	102	SPK (previous RRTt): 38 SPK (pre-RRT): 44 PTA: 20	0	No	SPK (previous RRT) Mean: 31 +/-13 months; SPK (pre-RRT) Mean: 25 +/ 11 months PTA Mean 12 +/- 9 months	Non Validated Questionnaire And Qualitative	Social, Vocational, Disability/Rehabilitation

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Stratta, Weide et al. 1997 USA (Nebraska) English	Full Article	Quantitative	11	1/8 (12.50)	57	PTA: 38 PAK: 19	0	No	Mean: 28 months Range: 1-60	Non Validated Questionnaire and Qualitative	Social, Vocational, Disability/Rehabilitation
Sugitani and Yoshida 2011 Japan (Fukuoca) Japanese	Full Article	Quantitative	9	3/8 (37.50)	10	SPK (both functioning): 10	WL: 19 Population Normative Values	No	Unspecified	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Sureshkumar, Mubin et al. 2002 USA (Pennsylvania) English	Full Article	Quantitative	12	4/8 (50.00)	27	SPK: 27	KTA: 27	No	SPK Mean: 3.1 +/- 2.4 years KTA Mean: 4.1 +/- 3.2 years	Short Form 36 (SF 36), Diabetes Quality of Life (DQOL), Quality of Wellbeing (QWB)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **DQOL:** Mobility, Social Activity, Social Functioning Satisfaction, Impact, Worry **QWB**: Wellbeing

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Stratta, Weide et al. 1997 USA (Nebraska) English	Full Article	Quantitative	11	1/8 (12.50)	57	PTA: 38 PAK: 19	0	No	Mean: 28 months Range: 1-60	Non Validated Questionnaire and Qualitative	Social, Vocational, Disability/Rehabilitation
Sugitani and Yoshida 2011 Japan (Fukuoca) Japanese	Full Article	Quantitative	9	3/8 (37.50)	10	SPK (both functioning): 10	WL: 19 Population Normative Values	No	Unspecified	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Sureshkumar, Patel et al. 2006 USA (Pennsylvania) English	Full Article	Quantitative	14	6/9 (67.00)	43	SPK (enteric drained): 19 SPK (bladder drained): 24	KTA (living donor): 11 KTA (deceased donor): 43 WL: 23	No	SPK Mean: 2.8 +/-2.0 years KTA (living donor) Mean: 4.9 +/-3.5 years KTA (deceased donor) Mean: 3.3 +/- 2/9 years)	Short Form 36 (SF 36), Diabetes Quality of Life (DQOL), Quality of Wellbeing (QWB)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **DQOL:** Mobility, Social Activity, Social Functioning Satisfaction, Impact, Worry **QWB**: Wellbeing

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Sureshkumar, Patel et al. 2006 USA (Pennsylvania) English	Full Article	Quantitative	14	6/9 (67.00)	17	SPK (both functioning): 17	KTA: 12	No	SPK and KTA at an average of 3 years from Sureshkumar, Mubin et al. 2002	Short Form 36 (SF 36), Diabetes Quality of Life (DQOL), Quality of Wellbeing (QWB)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **DQOL:** Mobility, Social Activity, Social Functioning Satisfaction, Impact, Worry **QWB**: Wellbeing
Sutherland, Gruessner et al. 2001) USA (Minnesota) English	Full Article	Quantitative	14	2/8 (25.00)	618	SPK: 316, PAK:(204), PTA: 98	0	Yes	1-2-4 years	Karnowsky	**KARNOWSKY:** Performance Status

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Suzuki, Kenmochi et al. 2012 Japan (Chiba) English	Conference Abstract	Quantitative	n/a	n/a	16	SPK (living-donor): 16	0	Yes	6-12-24-36 months	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Suzuki, Kenmochi et al. 2008 Japan (Chiba) English	Full Article	Quantitative	11	1/8 (12.50)	8	SPK (living-donor): 8	0	Yes	6-12-24 months	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Tai, He et al. 2010 China (Guangzhou) English	Full Article	Quantitative	12,00	2/8 (25.00)	7	SPK: 7	Population Normative Values	Yes	Mean: 23.3 months	Short Form 36 (SF 36)	**SF 36:** Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning
Triscornia, Nardi et al. 2017 Italy (Pisa) English	Conference Abstract	Quantitative	n/a	n/a n/a	37	PTA (functioning) 25 PTA (failed) 12	0	No	PTA (functioning) Mean: 10 +/- 4 years PTA (failed) Mean: 1.7+/- 2.3 years	Short Form 12 (SF 12), International Physical Activity Questionnaire Short Form (IPAQ_SHORT)	**SF12_**Vitality, Bodily Pain, General Health Perception, Physical Health, Role Physical, Mental Health, Role Emotional, Social Functioning **IPAQ_SHORT**: Physical Activity

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Vergani, Orsenigo et al. 2011 Italy (Milan) English	Conference Abstract	Quantitative	n/a	n/a	SPK + KTA : 50	SPK: unspecified	KTA: unspecified	No	Mean: 34 months	Gastrointestinal Symptoms Rating Scale	Gastrointestinal Symptoms
Vistoli, Croce et al. 2010 Italy (Pisa) English	Conference Abstract	Quantitative	n/a	n/a	187	SPK: 99, PTA: 57, PAK: 8	0	No	Unspecified	Unspecified	Unspecified

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Voruganti and Sells 1989 UK (Liverpool) English	Full Article	Quantitative	10,00	2/8 (25.00)	10	SPK: 10	KTA: 6	No	Unclear	Generic Questionnaire	Multidimensional Quality of Life
Winsett, Stratta et al. 2001 USA (Tennessee) English	Full Article	Quantitative	9	6/9 (56.00)	32	SPK: 32	Liver: 147, Heart: 101, Ktx all causes: 225	No	Mean: 5.5 +/- 3.3 years Range: 1-21 years	Ad hoc, multidimensional	Emotional Burden, Gastrointestinal Distress, Life/Role Involvement, Mobility

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehr, Mide et al. 1994 USA (Iowa) English	Full Article	Quantitative	13	5/9 (56.00)	54	SPK (both functioning): 41	KTA: 28 + SPK (failed pancreas): 13	No	> 6 months	Karnofsky, Myers, Pafrey, Simmons, Beck's Depression Inventory (BSI), Multiple Affect Adjective Checklist (MAACL-R), Gill, Walston, Cantril Questionnaires, Spitzer Quality of Life Index (QLI), Campbell Life Satisfaction Questionnaire, Pearson Fatigue Checklist	**KARNOFSKY**: Performance Status **MYERS:** social support, **PARFREY**: renal symptoms, **SIMMONS**: psychological burden of renal symptoms, **BECK'S INVENTORY:** depression, **MAACL-R**: mood disorders/anxiety, **GILL**: happiness and wellbeing, **WALSTON**: control, self esteem, **CANTRIL**: perception of past, present future QOL, **SPITZER**: activity, daily-living, activity, daily living, general health perception, support, outlook on life**, CAMPBELL:** life satisfaction, **PEARSON**: fatigue

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehr, Milde et al. 1991 USA (Iowa) English	Full Article	Quantitative	7	2/8 (25.00)	32	SPK (both functioning): 24 PAK: 8	0	No	> 6 months	Ad hoc	Depression/Fatigue + Chronic Complications Of Iddm

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehr, Milde et al. 1992 USA (Iowa) English	Full Article	Quantitative	14	4/8 (50.00)	44	SPK (both functioning): 31 SPK (failed pancreas): 13	0	No	> 6 months	Karnofsky, Myers, Pafrey, Simmons, Beck's Depression Inventory (BSI), Multiple Affect Adjective Checklist (MAACL-R), Gill, Walston, Cantril Questionnaires, Spitzer Quality of Life Index (QLI), Campbell Life Satisfaction Questionnaire, Pearson Fatigue Checklist	**KARNOFSKY**: Performance Status **MYERS:** social support, **PARFREY**: renal symptoms, **SIMMONS**: psychological burden of renal symptoms, **BECK'S INVENTORY:** depression, **MAACL-R**: mood disorders/anxiety, **GILL**: happiness and wellbeing, **WALSTON**: control, self esteem, **CANTRIL**: perception of past, present future QOL, **SPITZER**: activity, daily-living, activity, daily living, general health perception, support, outlook on life**, CAMPBELL:** life satisfaction, **PEARSON**: fatigue

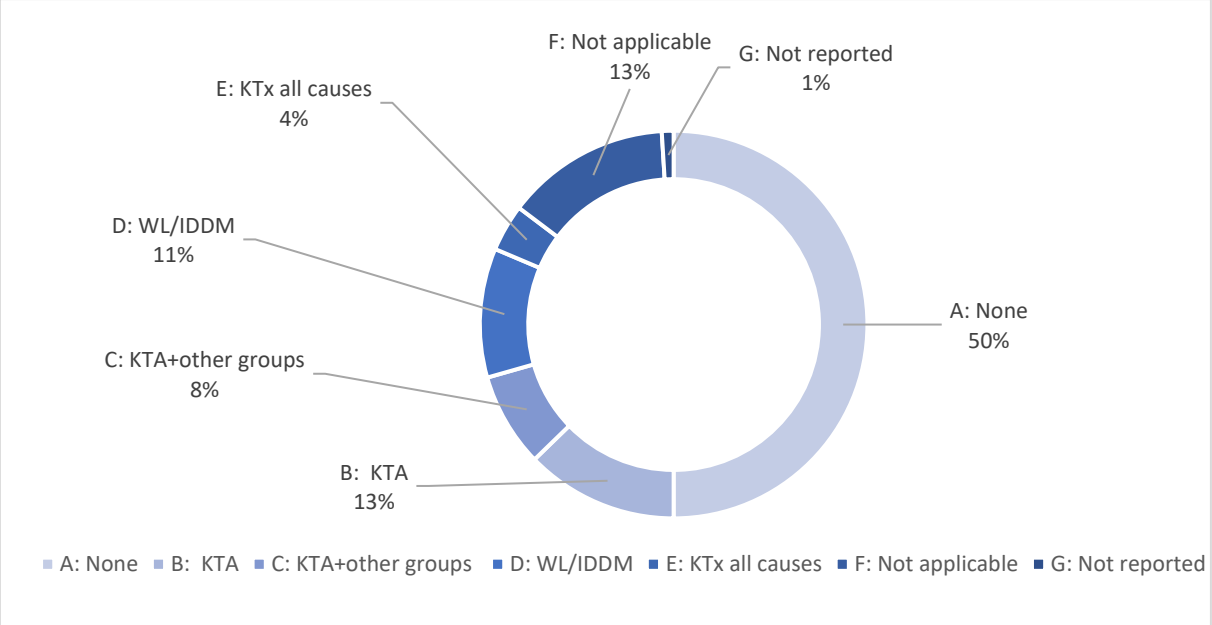
REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehr, Milde et al. 1991 USA (Iowa) English	Full Article	Quantitative	7	4/8 (50.00)	44	SPK (both functioning): 31 SPK (failed pancreas): 13	0	Yes	> 6 months	Karnofsky, Myers, Pafrey, Simmons, Beck's Depression Inventory (BSI), Multiple Affect Adjective Checklist (MAACL-R), Gill, Walston, Cantril Questionnaires, Spitzer Quality of Life Index (QLI), Campbell Life Satisfaction Questionnaire, Pearson Fatigue Checklist	**KARNOFSKY**: Performance Status **MYERS:** social support, **PARFREY**: renal symptoms, **SIMMONS**: psychological burden of renal symptoms, **BECK'S INVENTORY:** depression, **MAACL-R**: mood disorders/anxiety, **GILL**: happiness and wellbeing, **WALSTON**: control, self esteem, **CANTRIL**: perception of past, present future QOL, **SPITZER**: activity, daily-living, activity, daily living, general health perception, support, outlook on life**, CAMPBELL:** life satisfaction, **PEARSON**: fatigue

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehr, Milde et al. 1991 USA (Iowa) English	Full Article	Quantitative	7	4/8 (50.00)	44	SPK (both functioning): 31 SPK (failed pancreas): 13	0	Yes	> 6 months	Karnofsky, Myers, Pafrey, Simmons, Beck's Depression Inventory (BSI), Multiple Affect Adjective Checklist (MAACL-R), Gill, Walston, Cantril Questionnaires, Spitzer Quality of Life Index (QLI), Campbell Life Satisfaction Questionnaire, Pearson Fatigue Checklist	**KARNOFSKY**: Performance Status **MYERS:** social support, **PARFREY**: renal symptoms, **SIMMONS**: psychological burden of renal symptoms, **BECK'S INVENTORY:** depression, **MAACL-R**: mood disorders/anxiety, **GILL**: happiness and wellbeing, **WALSTON**: control, self esteem, **CANTRIL**: perception of past, present future QOL, **SPITZER**: activity, daily-living, activity, daily living, general health perception, support, outlook on life**, CAMPBELL:** life satisfaction, **PEARSON**: fatigue

REFERENCE YEAR COUNTRY LANGUAGE	REFERENCE TYPE	METHODS	DOWNS & BLACK SCORE	NUMBER OF GILL & FEINSTEIN CRITERIA (GILL & FEINSTEIN SCORE)	N OF PT	STUDY POPULATION	COMPARATOR	PROSPECTIVE*	FOLLOW-UP	PROMS	DOMAINS
Zehrer and Gross 1993 USA (Minnesota) English	Full Article	Quantitative	13,00	4/8 (50.00)	129	SPK (both functioning): 62 SPK (failed pancreas): 67	0	No	> 1 year	Ad Hoc on Diabetes, Karnowsky	Hypoglicaemia and diabetes items, **KARNOWSKY:** Performance Status
Zehrer, Cr et al. 1991 USA (Minnesota) English	Full Article	Quantitative	13	4/8 (50.00)	131	SPK (both functioning): 65 SPK (failed pancreas): 66	0	No	Range: 1-11	Index Of Wellbeing (IWB), Life Satisfaction Items, Index Of General Affect, Karnowsky, Transplant Items	Wellbeing, Satsfaction, **KARNOWSKY:** Performance Status, Transplant
Zehrer and Gross 1994 USA (Minnesota) English	Full Article	Quantitative	13	5/9 (56.00)	131	SPK (both functioning): 64 SPK (failed pancreas): 67	0	No	> 1 year	Diabetes Quality of Life (DQOL) modified, Ad Hoc on Transplantation	Diabetes, Transplant QOL

*(Pre-Transplant and Post-Transplant Assessment of HRQOL)

Abbreviations: PT (Pancreas Transplant), SPK (Simultaneous Pancreas Kidney Transplant), PTA (Pancras Transplant Alone), PAK (Pancreas After Kidney), PASPK (Pancreas After SPK), KTA (Kidney Tranpslant Alone), KTx (Kidney Transplant), Tx (Transplant), WL: patients on Pancreas Waiting List, HD: Hamodialysis, PD: Peritoneal Dialysis, QOL: Quality of Life, n/a: not-applicable



- **A2.6** Diagram of included studies, by control group

A: Any form of PT. **B:** Simultaneous Pancreas Kidney (SPK) vs Kidney Transplant Alone (KTA) with or without other control groups. **C:** Pancreas Transplant (PT) vs Waiting List (WL) and/or other patients with Insulin Dependent Diabetes Mellitus (TYPE 1 DIABETES), not transplanted. **D:** PT included in broader "transplant recipients" category. **E:** PT vs Kidney Transplant for all causes. **F:** unclear

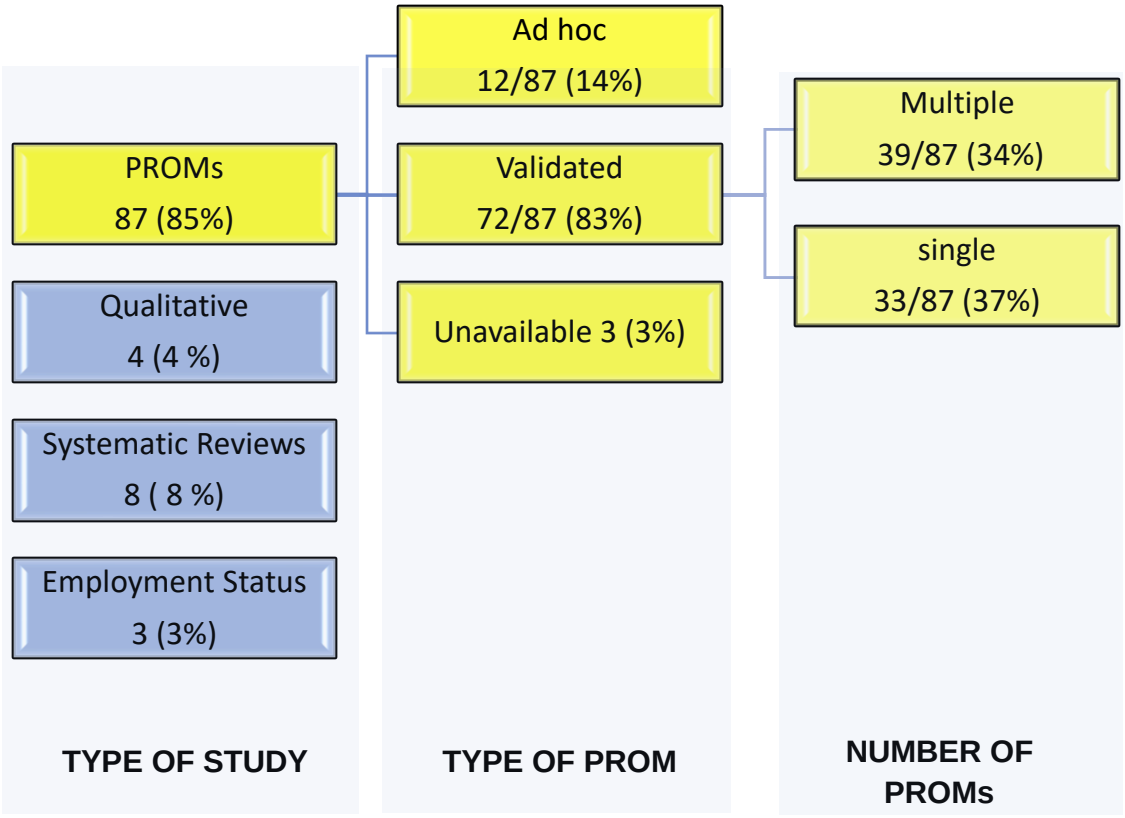
- A2.7 List of Validated PROMS and frequency of use

PROMS USED AND FREQUENCY		
	NAME (ACRONYM)	**NUMBER OF STUDIES**
	GENERIC/HRQOL/HEALTH STATUS	
1	EuroQoL 5 Dimension 3 Level (EQ-5D-3L)	1
2	EuroQoL 5 Dimension 5 Level (EQ-5D-5L)	2
3	International Physical Activity Questionnaire Short Form (IPAQ-SF)	2
4	Karnofsky Performance Status Scale (KPS)	10
5	Nottingham Health Profile 1 (NHP-1)	1
6	Nottingham Health Profile 2 (NHP-2)	2
7	Pearson Fatigue Checklist	1
8	Roland Morris Disability Questionnaire	1
9	Short Form 36 (SF 36)	3
10	Short Form 36 version 2 (SF 36v2)	2
11	Short Form 20 (SF 20)	1
12	Short Form 12 (SF 12)	1
13	Short Form 12 version 2 (SF 12v2)	4
14	Sickness Impact Profile (SIP)	6
15	Symptoms Checklist-90 (SCL-90)	3
16	Visual Analogue Scale for Health Utility (EQ-VAS)	2
	REHABILITATION/VOCATIONAL	
17	Reintegration to Normal Life Index (RNLI)	6
18	Muthny modified (Rehabilitation)	3
19	Work and Social Adjustment Scale (WSAS)	1
	GLOBAL QOL	
20	Spitzer QOL Index (QLI)	12
21	Visual Analogue Scale (VAS) for QOL	3
22	WHOQOL-BREF	1
23	Past, Present and Future QOL Evaluation (Cantril)	3
	WELLBEING	
24	Index of wellbeing (IWB)	2
25	Total well-being	1

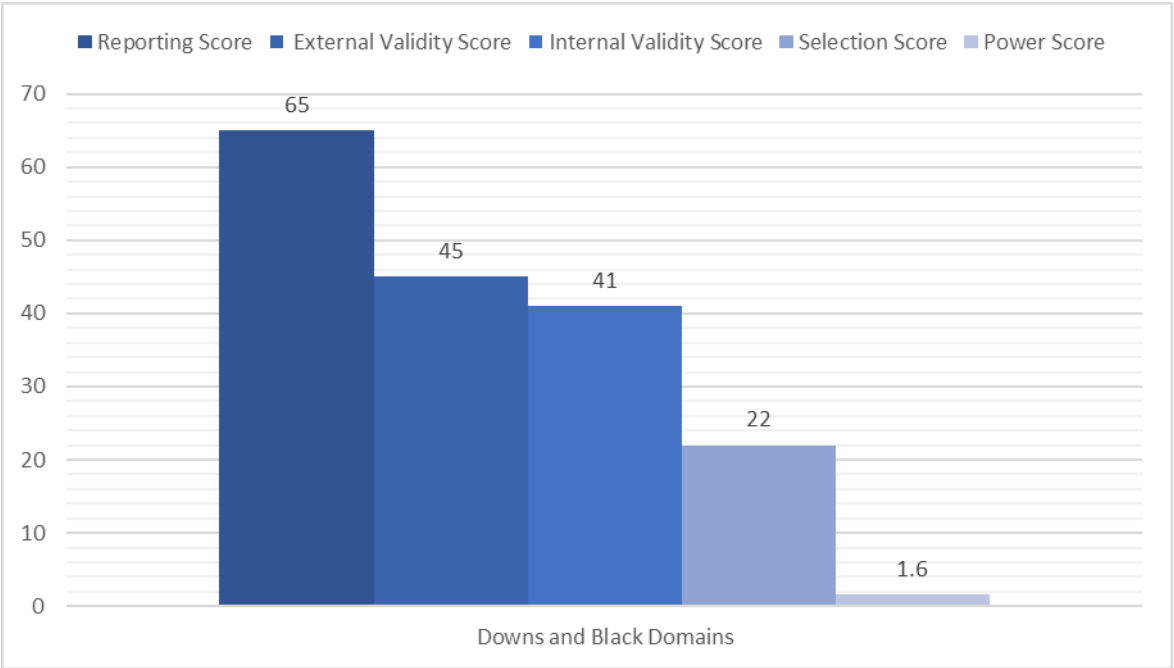
26	Quality of Wellbeing (QWB)	1
27	Well-being Questionnaire (W-BQ12)	1
	PSYCHOLOGICAL /PSYCHOSOCIAL	
28	ADHD Symptom Infrequency Scale (ASIS)	3
29	Affect Balance Scale	1
30	Beck's Depression Inventory	4
31	Brief Symptom Inventory (BSI)	1
32	Center for Epidemiological Studies - Depression Scale (CES-D)	3
33	Clinical Outcomes in Routine Evaluation (CORE-10)	1
34	Connor-Davidson Resilience Scale	1
35	Generalised Anxiety Disorder (GAD-7)	2
36	Hospital Anxiety and Depression Scale (HADS)	1
37	Index of General Affect	1
38	Mindful attention awareness scale	1
39	Minnesota Multiphasic Personality Inventory (MMPI)	1
40	Multiple Affect Adjective Check List (MAACL-R)	1
41	Patient Health Questionnaire-9 (PHQ-9)	2
42	Perceived Stress Scale 10-Item	3
43	Positive and Negative Affect Schedule (PANAS)	1
44	Social Communication Questionnaire (SCQ)	1
45	State trait anxiety Inventory (STAI-D1)	1
	TRANSPLANT SPECIFIC	
46	Cincinnati Transplant Questionnaire	2
47	Iowa Transplant Activities Questionnaire	1
	DIABETES SPECIFIC	
48	Audit of Diabetes-Dependent Quality of Life modified (ADDQoL)	1
49	Diabetes Quality of Life (DQOL)	6
50	Diabetes Quality of Life modified (DQOL modified)	1
51	Diabetes Quality of Life questionnaire (QOL-Q Diabetes)	1
52	Diabetes Treatment Satisfaction Questionnaire status (DTSQs)	1
53	Diabetes Treatment Satisfaction Questionnaire change version (DTSQc)	1
54	Problem Areas in Diabetes (PAID)	1

	RENAL FAILURE SPECIFIC	
55	Kidney Disease Quality of Life Short Form (KDQOL-SF)	3
56	Renal-Dependent Quality of Life Questionnaire (RDQoL)	1
57	Renal Questionnaire- Parfrey	3
58	Renal Treatment Satisfaction Questionnaire status version (RTSQs)	1
59	Renal Treatment Satisfaction Questionnaire change version (RTSQc)	1
60	Simmons	4
	OTHER DOMAIN SPECIFIC	
61	Arizona Sexual Experience Scale (ASEX)	1
62	Family Impact Questionnaire	1
63	Gastrointestinal Quality of Life Index (GIQLI)	1
64	Gastrointestinal Symptom Rating Scales	1
65	Happiness and Energy (Gill)	3
66	Life Satisfaction Questionnaire (Campbell)	3
67	Locus of Control (Walston)	3
68	Pittsburgh Sleep Quality Index (PSQI)	1
69	Sexual Concern Questionnaires (SCQ)	1
70	Sexual Self-Esteem Scale	1
71	Social Support (Myers)	3

- **A2.8** Studies stratified by type of study, type of PROM and number of PROMs utilised.



- **A2.9** Downs and Black checklist outcomes, stratified by section.



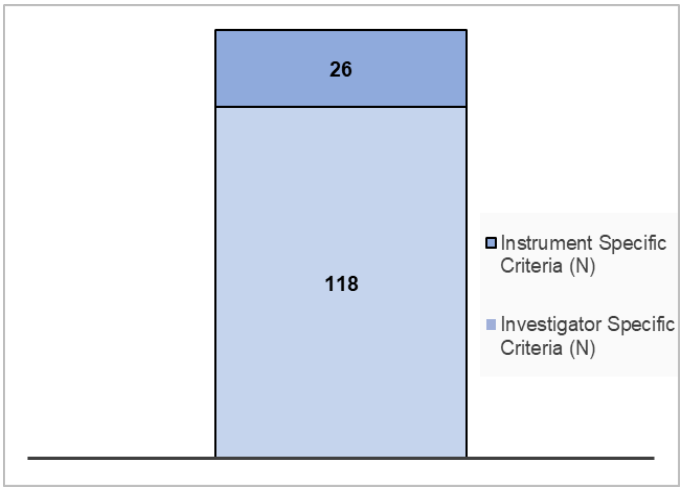
- **A2.10** Distribution of summary scores for Compliance with Gill and Feinstein's criteria in eligible articles

SUMMARY SCORE	ARTICLES (%)
75-100	0
50-74	27%
25-49	56%
0-24	17%

- **A2.11** Frequency of Compliance for each Gill and Feinstein's Criteria

	CRITERIA	NUMBER OF STUDIES	COMPLIANCE (%)
	Investigator Specific		
1	Meaning of quality of life	2	3.1%
2	Constituents of quality of life	56	87.5%
3	Selection of instruments	26	40.6%
4	Aggregate Score	34	53.1%
	Instrument Specific		
5	Patient rating	15	23.4%
6	Distinguish quality of life	7	10.9%
7	Supplemental responses	3	4.7%
8	incorporated	1	1.6%
9	Rating of importance	6	9.4%
10	incorporated	4	6.2%

A2.12 Distribution of Gill and Feinstein's Criteria, stratified by type.



- **A2.13** Comparison with Population Normative Values

Reference	Country	Time from Transplant	Number and Type of transplant (functional status)	SF-36: mental domains	SF-36: physical domains	Quality of Wellbeing
Anderson	USA	3-12-24 months	A) 40 SPK B) 48 KTA C) 119 Ktx all causes	= population norms, all categories, all timepoints	< population norms, all categories, all timepoints	
Drognitz	Germany	Mean 9.1 years (range 5.9-12.9)	A) SPK (functioning) B) SPK (failed kidney)	A) = population norms B) < population norms	A) = population norms B) < population norms	
Jurgensen	Germany	Unclear	101 SPK (male)	Unspecified	Unspecified	Similar to German Population Norm
Smith	Australia	4 months, 1-2-3 years	37 SPK (functioning)	= population norms at all timepoints	= population norms from 2 years onwards	
Sugitani	Japan	Unclear (2 years?)	10 SPK (functioning)	= population norms	= population norms	
Tai	China	Mean 23.2 months	10 SPK (functioning)	= population norms	= population norms	
Bolesta	Germany	Unclear	146 SPK (functioning)	= 10 years older population norms	= 10 years older population norms	
Isla Pera	Spain	Unclear (2-7 years?)	69 SPK (functioning)	< population norms	< population norms	
Matas	USA	Range 1-10 years	SPK+ KTA+ Ktx all causes (functioning)	< population norms	< population norms	
Radosevich	USA	1 yr., 3 yrs.	Liver, Heart, Lung, Kidney and Pancreas Transplant Recipients, (functional status unspecified)	= population norms at 3 years from transplant	< population norms at all timepoints	

A2.14 Predictors of HRQOL/QOL, as reported in the literature.

PREDICTORS OF QUALITY OF LIFE			
POSITIVE	Authors	NEGATIVE	Authors
Pancreas Transplantation	Isla-Pera P, 2009 Bozek-Pajak D 2016	**Insulin Dependence**	Bozek-Pajak D 2016
Meeting one's transplant goals	Zehr PS,1992	**Dialysis**	Nijhoff MF, 2020
Preserved Function of both grafts	Martins LS, 2015	**Loss of either graft**	Scheurmann U, 2020
Recent transplant	Bolesta K, 2016	**Duration of diabetes**	Bozek-Pajak D 2016
Older Age	Isla-Pera P, 2009	**High BMI**	Bozek-Pajak D 2016 Mosca I, 2018
Biological male gender	Bolesta K, 2016 Isla-Pera P, 2009	**Biological Female gender**	Smith GC, 2010
		Past cardiovascular events	Bozek-Pajak D 2016 Mosca I, 2018
		Vascular disease (ICH, stroke, peripheral disease/amputations)	Bozek-Pajak D 2016 Mosca I., 2018 Nijhoff MF, 2020
		Retinopathy	Nijhoff MF, 2020
		History of Psychological disorders	Smith GC, 2010 Nijhoff MF, 2020
		HTN	Bozek-Pajak D 2016
		Malignancies except melanoma	Nijhoff MF, 2020

APPENDIX 3: Supplementary material for Chapter 3

- **A3.1** Study Objectives and Outcome Measures

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective To assess the impact of Pancreas Transplantation on Quality of Life	PROMS Clinical Data	T0 pre-Transplant T1 6 weeks post-Transplant T2 6 months post-Transplant T3 1-year post-Transplant
Secondary Objectives To identify which clinical phenotypes correspond to higher QoL gain after transplantation. To compare changes in quality-of-life outcomes for waiting-list and post-transplant populations To evaluate differences in QoL gain within cohorts of Pancreas Transplant Recipients: SPK: Simultaneous Pancreas Kidney Transplant PTA: Pancreas Transplant Alone PAK: Pancreas Transplant after Kidney	PROMS Clinical Data	As above
Tertiary Objectives To estimate the resource-use and costs for waiting-list and post-transplant populations	PROMS Clinical Data Collection of Clinical Data	As above

A3.2 KDQOL-SFTM v1.3: summary of structure

SCALE	N OF ITEMS/SCALES
RENAL SPECIFIC	**43**
Symptoms/Problems	12
Effects of kidney disease on daily life	8
Burden of kidney disease	4
Work Status	2
Cognitive function	3
Quality of social interactions	3
Sexual Function	2
Sleep	4
Social Support	2
Dialysis staff encouragement	2
Patient satisfaction	1
GENERIC ITEMS (SF-36)	**36**
Physical Functioning	10
Role limitation caused by physical health problems	4
Role limitation caused by emotional health problems	3
Social functioning	2
Emotional well-being	5
Pain	2
Energy/fatigue	4
General health perceptions	5
Overall, Health Rating Scale	**1**

- **A3.3** DQOL: Summary of structure

SCALE	N OF ITEMS	ACCEPTABLE MISSING ITEMS	POSSIBLE SCORES
DIABETES SPECIFIC			
Satisfaction	15	3/15	1-5
Impact	20	4/20	1-5
Worry	11	2/4	1-5
1 GENERIC HEALTH ITEM that doesn't contribute to the DQOL scales			

- **A3.4** Kidney Disease and Quality of Life Short Form v1.3 (KDQOL-SFTM 1.3)

Your Health
– *and* –
Well-Being

Kidney Disease and Quality of Life (KDQOL-SF™ 1.3)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.



Thank you for completing these questions!

Kidney Disease and Quality of Life™ Short Form (KDQOL-SF™)
English Version 1.3
Copyright © 1993, 1994, 1995 by RAND and the University of Arizona

Study of Quality of Life For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. **In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]**

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

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

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

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

		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	☐ 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

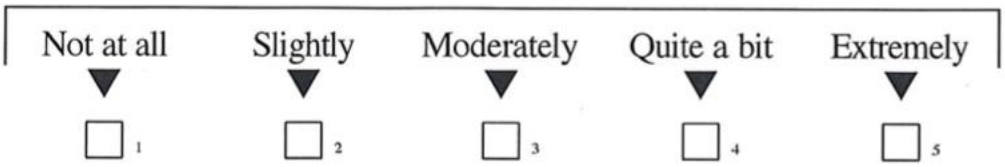
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	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 Were limited in the kind of work or other activities	☐ 1	☐ 2
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

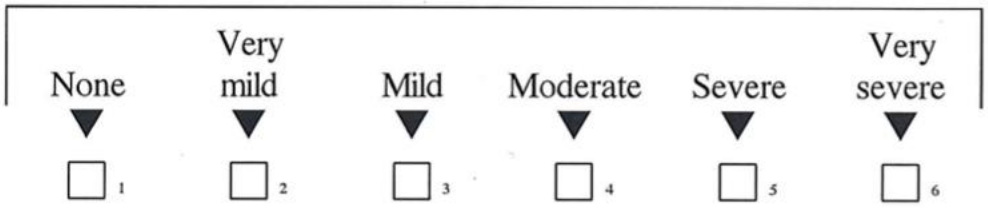
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	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

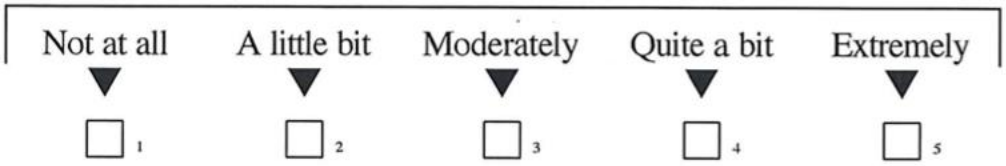
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…

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

Your Kidney Disease

12. How true or false is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

11. Please choose the answer that best describes how true or false each of the following statements is for you.

	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

13. These questions are about how you feel and how things have been going during the <u>past 4 weeks</u>. 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 <u>past 4 weeks</u>…

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
a Did you isolate yourself from people around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Did you react slowly to things that were said or done?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Did you act irritable toward those around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d Did you have difficulty concentrating or thinking?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e Did you get along well with other people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f Did you become confused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

14. During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
		▼	▼	▼	▼	▼
a	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Effects of Kidney Disease on Your Daily Life

15. Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
a	Fluid restriction?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Dietary restriction?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Being dependent on doctors and other medical staff?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

16. Have you had any sexual activity in the <u>past 4 weeks</u>?

(Circle One Number)

No .....1 → If no, please skip to Question 17

Yes 2

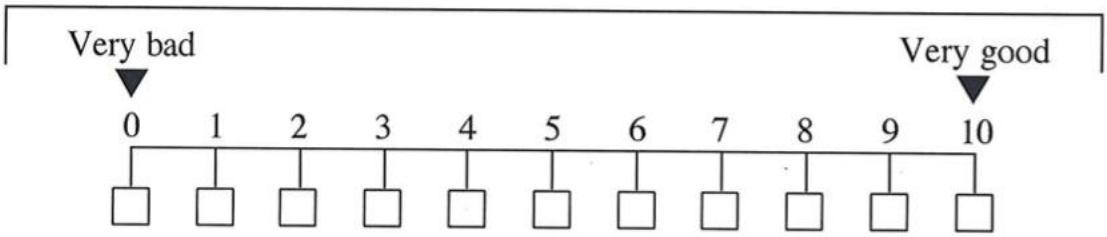
How much of a problem was each of the following in the <u>past 4 weeks</u>?

		Not a problem	A little problem	Somewhat of a problem	Very much a problem	Severe problem
a	Enjoying sex?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Becoming sexually aroused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **For the following question, please rate your sleep using a scale ranging from 0 representing "very bad" to 10 representing "very good."**

If you think your sleep is half-way between "very bad" and "very good," please mark the box under the number 5. If you think you sleep is one level better than 5, mark the box under 6. If you think your sleep is one level worse than 5, mark the box under 4 (and so on).

On a scale from 0 to 10, how would you rate your sleep overall? [Mark an ☒ in one box.]



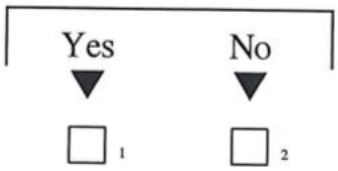
18. How often during the <u>past 4 weeks</u> did you...

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
	▼	▼	▼	▼	▼	▼
a Awaken during the night and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Get the amount of sleep you need?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

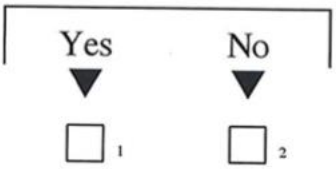
19. Concerning your <u>family and friends</u>, how satisfied are you with...

	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied
	▼	▼	▼	▼
a The amount of time you are able to spend with your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4
b The support you receive from your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4

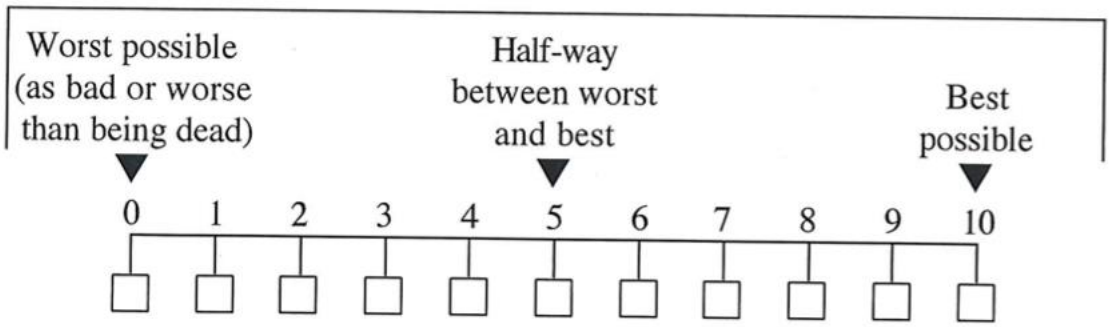
20. During the <u>past 4 weeks</u>, did you work at a paying job?



21. Does your health keep you from working at a paying job?



22. Overall, how would you rate your health?



Satisfaction With Care

23. Think about the care you receive for kidney dialysis. In terms of your satisfaction, how would you rate the friendliness and interest shown in you as a person?

Very poor	Poor	Fair	Good	Very good	Excellent	The Best
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

24. How true or false is each of the following statements?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a Dialysis staff encourage me to be as independent as possible	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Dialysis staff support me in coping with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

- **A3.5** Short Form 12 v2 (SF-12 v2TM)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

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

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

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

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(IQOLA SF-12v2 Standard, English (United Kingdom) 8/02)

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

Thank you for completing these questions!

- **A3.6** EQ-5D-5L®



Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

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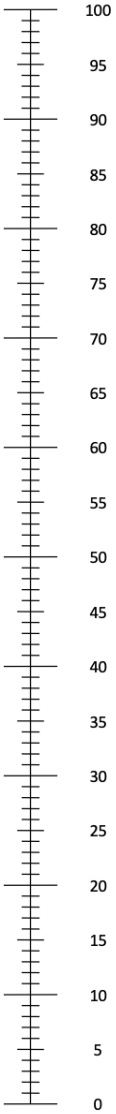
PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

- NOW PLEASE WRITE THE NUMBER YOU MARKED ON THE SCALE IN THE BOX BELOW

YOUR HEALTH TODAY= ☐

The worst health you can imagine

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- **A3.7** Interpretation of effect sizes, stratified by type.

EFFECT SIZE	MEASURE				
	Cohen's d	**Pearson's r**	**Cohen's W**	**f^2**	**η^2**
Small	0.2	0.1	0.1	0.02	0.01
Medium	0.5	0.3	0.3	0.15	0.06
Large	0.8	0.5	0.5	0.35	0.14

- **A3.8**Proportion of participants who responded 1,2,3,4 timepoints.

Questionnaires returned	**Participants (%)**	**Status**
0	2%	Non-Responders
1 timepoint	21%	
2 timepoints	18%	
3 timepoints	16%	
4 timepoints	44%	Full Completers

- **A3.9** Demographics and clinical characteristics of Recruited Individuals, stratified by Transplant Status: Transplanted (Study Participants) and Not-transplanted.

PARTICIPANT'S CHARACTERISTICS			
			Two-tailed Sig
Total Recruited **Transplanted** **Not-transplanted**	79 62 17		
Age (yrs.)	Mean	(SD)	
Transplanted **Not-transplanted**	43.19 45.29	(9.06) (7.36)	t (55) =.87837 p = .382476 NS
Gender	F	M	
Transplanted **Not-transplanted**	31 10	31 7	χ^2 = .4161 p = .518896 NS
Ethnicity	Caucasian	B.A.M.E.	
Transplanted Not-transplanted	49 17	7 0	Fisher exact test < .0001 Significant at p< .05
BMI	Mean	(SD)	
Transplanted Not-transplanted	25.39 26.28	(3.71) (4.12)	t (77) = .85338 p = .396097. NS
Age of diagnosis (yrs.)	Mean	(SD)	
Transplanted Not-transplanted	15.47 13.47	(9.4) (7.6)	Mann-Whitney U= 472.55 Z = -.651 p = .515 NS
Cigarette Smoke (N)	History of Smoking	Never Smoker	
Transplanted Not-transplanted	29 2	33 15	Fisher exact statistic = .0109 Significant at p< .05
Alcohol (N)	Yes	No	
Transplanted Not-transplanted	30 9	27 6	χ^2 = .2597 p = .61032 NS
Duration of WL (days)	Average (SD)	SD	
Transplanted Not-transplanted	464.31 824.06	(247.84) (1104.94)	Mann-Whitney U = 450.00 z = -.919 p = .358 NS
Preserved Sexual function (N)	Yes	No	
Transplanted Not-transplanted	12 5	50 5	Fisher exact test = .049 Significant at p < .05
Working Status (N)	Unemployed	Full-time/ Housework/ Student	
Transplanted Not-transplanted	27 6	35 11	χ^2 =. 3737 p = .54098 NS

History of Common Psychiatric Disorder (N)	Yes	No	
Transplanted Not-transplanted	18 6	44 11	χ^2 = .2473 p = .618952 NS
On psychotropic medications (N)	Yes	No	
Transplanted Not-transplanted	21 6	41 11	χ^2 = .012 p = .912729 NS
Type of transplant (N)	SPK	Other	
Transplanted Not-transplanted	55 13	7 4	Fisher exact test = .238 NS
Duration of diabetes (years)	Mean	(SD)	
Transplanted Not-transplanted	27.93 31.41		t (77) = 1.280 p = .205 NS
Insulin requirement (Units)	Mean	(SD)	
Transplanted Not-transplanted	42.35 48.21	(17.46) (26.84)	Mann-Whitney U = 510 z = -.203 p = .839 NS
End stage renal failure (N)	Yes	No	
Transplanted Not-transplanted	55 12	7 5	Fisher exact test = .119 NS
Renal Replacement Therapy (N)	HD	PD	
Transplanted Not-transplanted	29 6	14 6	χ^2 = 1.2334 p = .266749 NS
Renal Replacement Therapy duration (days)	Mean	(SD)	
Transplanted Not-transplanted	617.60 1067.80	350.959 (1538.259)	Mann-Whitney U = 200.000 z = -.232 p = .816 NS
Residual Urinary Output (N)	Yes	No	
Transplanted Not-transplanted	54 13	6 2	Fisher exact test = .6566 NS
HLA sensitization (N)	Mean	(SD)	
Transplanted Not-transplanted	32.92 48.12	(30.210) (44.585)	Mann-Whitney U = 428.000 z = 0 1.185 p = .235 NS
Hypoglycaemia crisis (N)	Frequent	Rare	
Transplanted Not-transplanted	32 17	30 0	Fisher exact test = .0001 SS
Hypoglycaemia Unawareness (N)	Yes	No	
Transplanted Not-transplanted	22 8	40 9	χ^2 =.7589 p = .38367 NS
Cardio/cerebro-vascular events (N)	Yes	No	
Transplanted **Not-transplanted**	48 11	12 6	χ^2 = 1.7299 p = .188427 NS
Cardiac procedures (N)	Yes	No	
Transplanted Not-transplanted	5 4	57 13	Fisher exact test = .0941. NS
Hypertension (N)	Yes	No	
Transplanted Not-transplanted	57 15	5 2	Fisher exact test = .6395. NS
Retinopathy (N)	Yes	No	

Transplanted Not-transplanted	57 14	5 3	Fisher exact test = .6947. NS
Registered blind (N)	Yes	No	
Transplanted Not-transplanted	8 1	54 16	Fisher exact test =1. NS
Neuropathy (N)	Yes	No	
Transplanted Not-transplanted	33 10	29 7	$\chi^2$0.1685. P=0.681407. NS.
Gastro-intestinal symptoms (N)	Yes	No	
Transplanted Not-transplanted	24 3	38 14	Fisher exact test = 0.1504. NS
Amputations (N)	Yes	No	
Transplanted Not-transplanted	9 4	53 13	Fisher exact test = .4611 NS
Claudication (N)	Yes	No	
Transplanted Not-transplanted	4 1	57 16	χ^2 0.0101. p = 0.919958. NS
Diabetes chronic complications (N)	1-2	3+	
Transplanted Not-transplanted	22 7	40 11	χ^2 .011. p =.915. NS
Comorbidities (N)	Yes	No	
Transplanted Not-transplanted	54 11	8 6	χ^2 4.5874 p = .032207 Significant at p < .05
Previous abdominal surgery (N)	Yes	No	
Transplanted Not-transplanted	36 12	26 5	Fisher exact test = .5517 NS
Previous transplant (N)	Yes	No	
Transplanted Not-transplanted	8 5	54 12	Fisher exact test = .139 NS

- **A3.10** Transplant Data

TRANSPLANT DATA	
Donor's type	
Donation after Brain Death	48 (77.4%)
Donation after Circulatory Death	14 (22.6%)
Donor's gender	
F	33 (53.2%)
M	29 (46.8%)
Donor's age (years)	
Mean ± SD	32.71±13.462
Donor's cause of death	
Hypoxic Brain Damage	22 (36.7%)
Intracranial Haemorrhage	31 51.7%)
Cerebrovascular Accident	1 (1.7%)
Trauma	5 (8.3%)
Meningitis	1 (1.7%)
CIT Pancreas (minutes)	
Mean ± SD	636.80± 124.036
WIT Pancreas (minutes)	
Mean ± SD	35.02 ±11.763
CIT Kidney (minutes)	
Mean ± SD	634.34 ±306.209
WIT Kidney (minutes)	
Mean± SD	36.11 ±21.168
Pancreas Exocrine Drainage	
Bladder	3 (4.8%)
Enteric	59 (95.2%)
Forearm Donor's Skin Flap	
No	58 (93.5%)
Yes	4 (6.5%)
Blood Transfusions	
No	6 (25.8%)
Yes	46 (74.2%)

- **A3.11** Frequency of Post-operative CT abdomen/angiogram

POST-OPERATIVE CT SCANS		
Number of CTs	n	Valid Percent
Zero	19	30.6
One	18	29.0
Two	12	19.4
Three	7	11.3
Five	1	1.6
Six	2	3.2
Seven	1	1.6
Twelve	2	3.2

- **A3.12** CT results

CT OUTCOMES		
CT findings	N	Valid Percentage
Normal Scan	11	25.6
Complications	32	74.4
Pancreatitis		
No	34	81.0
Yes	8	19.0
Pancreas Perfusion		
No Defects	27	65.9
Modest Thrombosis	12	29.3
Extensive Thrombosis	2	4.9
Collections/Haematomas		
No	25	61.0
Yes	16	39.0
Kidney Perfusion		
No Defects	34	81.0
Hypoperfusion	2	4.8
Infarcts	6	14.3
Bowel complications		
No	42	95.5
Yes	2	4.5

- **A3.13** Classification of surgical complications (Dindo, Demartines et al. 2004)

SEVERITY OF SURGICAL COMPLICATIONS		
CLAVIEN-DINDO GRADE	n	Valid Percent
Grade I (No change in management)	2	7.1
Grade II (Requiring additional medical management)	6	21.4
Grade III (Requiring surgical, endoscopic, radiological intervention)	17	60.7
Grade IV (Life threatening complication)	3	10.7
Death	0	
Total	28	100.0

- **A3.14** Summary of Transplant Data and Early Post-operative Course

POST-OPERATIVE COURSE					
ITU admission duration (days) N (%)	Mean (SD): 1.95 (2.26)	Median: 1	Range: 1-15		
Post-operative course N (%)	Uneventful: 21 (33.9%)	Complicated: 41(66.1%)			
Complications Clavien-Dindo III or above* N (%)	No: 42 (67.7%)	Yes: 20 (32.2%)			
Relaparotomies N (%)	No: 44(71 %)	Yes: 16(29%)	Multiple: 5(8%)		
Pancreas Thrombosis N (%)	No: 46 (77.4%)	Yes: 14 (22.6%)	Partial: 12 (19.4%)	Occlusive: 2(3.2%)	
Pancreatitis N (%)	No: 55 (89%)	Yes: 7 (11%)			
Duodenal leak N (%)	No: 60 (96.8%)	Yes: 2 (3.2%)			% Calculated on 59 enteric drained pancreases
Early Graft Pancreatectomy N (%)	No 59 (95%)	Yes: 3 (5%)			
Early Graft nephrectomy N (%)	No: 60 (97%)	Yes:	N/A: 2 (3 %)		
Primary Pancreatic Function N (%)	Yes: 59 (95%)	No: 3(5%)	Primary Non function: 0		
Primary Kidney Function N (%)	Yes: 41 (74%)	No: 3 (24%)	Primary Non function: 1 (2%)		% Calculated on N of functioning kidneys at discharge
Pancreas Status at Discharge N (%)	Functioning: 58 (93.5%)	Non-Functioning: 1 (1.6%)	Explanted: 3 (4.8%)		
Kidney Status at Discharge N (%)	Functioning: 58 (93.5%)	Non-Functioning: 2 (3.2%)	Explanted: 0	N/A: 2 (3.2%)	
Glucose tolerance test at discharge N (%)	At target: 32 (54%)	Sub-optimal: 1(2%)	High: 16 (27%)	Not done: 10 (17%)	Calculated on N of functioning pancreas at discharge
Creatinine at discharge (umol/L)	Mean (SD): 162 (135.22)	Median: 120	Range: 55-744		% Calculated on N of functioning kidneys at discharge
Haemoglobin at discharge (g/L) N (%)	Mean (SD): 86.29 (11.42)	Median: 86	Range: 67-112		
Hospital admission duration (days)	Average (SD): 20.13 (32.09)	Median: 11.5	Range: 6-211		

*(Dindo D, Demartines N, Clavien PA, 2004

- **A3.15** Progression of blood test results

Blood Tests	N	Mean	Range	SD
PANCREATIC FUNCTION				
OGGT T_0 at discharge (mmol/L)	49	4.967	3.8-7.0	.6587
OGGT $T_{120'}$ at discharge (mmol/L)	49	7.418	3.4-16.8	2.6971
Hba1c at 6 weeks (%)	22	5.3455	4.10-7.20	0.89108
HbA1c at 6 months (%)	31	5.103	4.1-6.2	.4231
1 Y HbA1c (%)	24	5.358	4.5-9.7	.9784
RENAL FUNCTION				
Creatinine at discharge (umol/L)	53	162.00	55-744	135.218
Creatinine at 6 weeks (umol/L)	42	108.48	48-188	34.778
Creatinine at 6 months (umol/L)	44	121.84	50-730	99.700
Creatinine at 1 year (umol/L)	27	112.93	57-200	38.737
HAEMOGLOBIN LEVEL				
Hb at discharge (g/L)	62	86.29	67-112	11.515
Hb at 6 weeks (g/L)	44	99.41	67-126	12.872
Hb at 6 months (g/L)	47	118.40	72-164	23.774
Hb at 1 year (g/L)	27	127.74	99-169	18.287

- **A3.16** Differences in baseline EQ-5D-5L L1-2 severity levels across domains

Differences in L 1-2 severity levels

	Mobility	Self-care	Activity	Pain	Anxiety
Mobility		$\chi^2 = 6.98$ p = .008	$\chi^2 = 3.14$ p = .077	$\chi^2 = .009$ p = .921	$\chi^2 = 1.81$ p = .178
Self-Care	SS		$\chi^2 = 20.35$ p < .00001	$\chi^2 = 8.59$ p = .003	$\chi^2 = 1.25$ p =.264
Activity	NS	SS		$\chi^2 = 2.24$ p = .134	**$\chi^2 = 10.70$ p = .001**
Pain	NS	SS	NS		$\chi^2 = 2.68$ p = .101
Anxiety	NS	NS	**SS**	NS	

X^2= chi-square statistics with Yates correction

- **A3.17** EQ-5D-5L normative values from non-UK populations, stratified by age.

EQ-index normative values					
Country	**Authors, year**	**Manuscript**	**Age range**	**Sample size**	**Mean EQ Index ± SD**
Alberta, Canada	Alberta PROMs & EQ-5D Research & Support Unit (APERSU) 2018	Alberta Population Norms for EQ-5D-5L	45-64		**0.83 ± 0.11**
Germany	Grochtdreis T et al 2019	Health-related quality of life measured with the EQ-5D-5L: estimation of normative index values based on a representative German population sample and value set	45-54 54-64	996 787	**0.87 ± 0.17** **0.87 ± 0.20**
Denmark	Jensen MB et al 2021	Danish population health measured by the EQ-5D-5L.	40-49 50-59	159 214	**0.90 ± 0.16** **0.88 ± 0.19**
Spain	Garcia-Gordillo MA et al 2016	Normative values of EQ-5D-5L in a Spanish representative population sample from Spanish Health Survey, 2011	40-49 50-59	3822 3312	**0.95 ± 0.11** **0.91 ± 0.19**

- **A3.18** KDQOL: trajectory of changes across time points for “full-responders”.

	KDQOL: TRAJECTORY OF CHANGES			
Timepoint	Baseline	6 Weeks	6 Months	1 Year
Mean ± SD	59.25±14.82	59.94±18.66	71.01±21.08	71.81±19.16
ANOVA	Number = 20 Wilk’s λ = .464 F (3,17) = 6.557 Sig. = .004 Partial η^2 = .536			

- **A3.19** DQOL: trajectory of changes across time points for “full-responders”

	DQOL: TRAJECTORY OF CHANGES			
Timepoint	Baseline	6 Weeks	6 Months	1 Year
Mean ± SD	50.18 ± 14.47	66.98 ± 16.71	71.11 ± 17.53	67.73 ±15.53
ANOVA	Number = 24 Wilk’s λ = .339 F (3,21) = 13.649 Sig. <.004 Partial η^2 = .661			

- **A3.20** KDQOL: linear mixed modelling outcomes.

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	60
Total		9		9		

a. Dependent Variable: DQOL.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	53.620	837.139	<.001
time	3	74.146	22.964	<.001

a. Dependent Variable: DQOL.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	65.653131	2.409638	50.236	27.246	<.001	60.813795	70.492467
[time=1]	-17.529395	2.834302	99.029	-6.185	<.001	-23.153244	-11.905546
[time=2]	-2.176880	2.629908	83.416	-.828	.410	-7.407276	3.053517
[time=3]	4.221091	2.158685	57.282	1.955	.055	-.101141	8.543322
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: DQOL.

b. This parameter is set to zero because it is redundant.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	48.124	2.577	57.322	42.963	53.284
2	63.476	2.674	42.629	58.082	68.871
3	69.874	2.853	45.045	64.128	75.620
4	65.653	2.410	50.236	60.814	70.492

a. Dependent Variable: DQOL.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Repeated Measures	Var: [time=1]	382.450319	72.232260	5.295	<.001	264.125974	553.782139
	Var: [time=2]	329.096025	79.289670	4.151	<.001	205.230162	527.720646
	Var: [time=3]	340.090555	80.224887	4.239	<.001	214.191544	539.991372
	Var: [time=4]	258.789008	54.121389	4.782	<.001	171.763655	389.906414
	ARH1 rho	.753060	.050801	14.824	<.001	.635141	.836676

a. Dependent Variable: DQOL.

- **A 3.21** DQOL: linear mixed modelling outcomes

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	60
Total		9		9		

a. Dependent Variable: DQOL.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	53.620	837.139	<.001
time	3	74.146	22.964	<.001

a. Dependent Variable: DQOL.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	65.653131	2.409638	50.236	27.246	<.001	60.813795	70.492467
[time=1]	-17.529395	2.834302	99.029	-6.185	<.001	-23.153244	-11.905546
[time=2]	-2.176880	2.629908	83.416	-.828	.410	-7.407276	3.053517
[time=3]	4.221091	2.158685	57.282	1.955	.055	-.101141	8.543322
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: DQOL.

b. This parameter is set to zero because it is redundant.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	48.124	2.577	57.322	42.963	53.284
2	63.476	2.674	42.629	58.082	68.871
3	69.874	2.853	45.045	64.128	75.620
4	65.653	2.410	50.236	60.814	70.492

a. Dependent Variable: DQOL.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Repeated Measures	Var: [time=1]	382.450319	72.232260	5.295	<.001	264.125974	553.782139
	Var: [time=2]	329.096025	79.289670	4.151	<.001	205.230162	527.720646
	Var: [time=3]	340.090555	80.224887	4.239	<.001	214.191544	539.991372
	Var: [time=4]	258.789008	54.121389	4.782	<.001	171.763655	389.906414
	ARH1 rho	.753060	.050801	14.824	<.001	.635141	.836676

a. Dependent Variable: DQOL.

- **A 3.22** PCS: longitudinal changes

Baseline	6 Weeks
Mean (SD) = 31.67 ± 9.76	Mean (SD) = 34.17 ± 10.22
Number = 22 t (25) = -1.111 p = .277	

Baseline	6 Months
Mean (SD) =29.92 ± 9.86	Mean (SD) =39.90 ± 12.84
Number = 18 t (17) = -3.160 p = .007 Cohen's d = -.719	

Baseline	1 Year
Median =30.03	Median = 43.72
Number = 26 Z = -3.592 p < .001 Cohen's d = .1.985	

- **A3.23** PCS: linear mixed modelling outcomes.

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	53
Total		9		9		

a. Dependent Variable: PCS.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	50.772	741.873	<.001
time	3	42.498	6.967	<.001

a. Dependent Variable: PCS.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
1	31.481	1.488	44.649	28.484	34.479
2	33.761	1.748	35.431	30.214	37.308
3	38.804	2.147	31.904	34.429	43.178
4	40.999	1.850	39.567	37.258	44.740

a. Dependent Variable: PCS.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	40.999063	1.850245	39.567	22.159	<.001	37.258303	44.739824
[time=1]	-9.517881	2.140606	73.066	-4.446	<.001	-13.784038	-5.251725
[time=2]	-7.237758	2.104426	61.254	-3.439	.001	-11.445466	-3.030050
[time=3]	-2.195285	2.004529	38.369	-1.095	.280	-6.251962	1.861393
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: PCS.

b. This parameter is set to zero because it is redundant.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Repeated Measures	Var: [time=1]	103.157664	22.221483	4.642	<.001	67.630372	157.347997
	Var: [time=2]	108.416295	27.891576	3.887	<.001	65.480398	179.505522
	Var: [time=3]	128.207165	34.627252	3.702	<.001	75.511439	217.676653
	Var: [time=4]	122.676182	28.098039	4.366	<.001	78.306725	192.185863
	ARH1 rho	.640994	.073623	8.706	<.001	.473773	.763600

a. Dependent Variable: PCS.

- **A3.24** MCS: longitudinal changes

Baseline	6 Weeks
Mean (SD) = 42.77 ± 11.43	Mean (SD) = 45.53 ± 13.46
Number = 26 t (25) = - 1.18 p = .249 NS	

Baseline	6 Months
Mean (SD) = 42.71 ± 10.88	Mean (SD) = 45.61 ± 13.13
Number = 18 t (17) = - 1.09 p = .292 NS	

Baseline	1 Year
Mean (SD) = 31.68 ± 10.86	Mean (SD) = 42.63 ± 11.49
Number = 26 Z = -1.628 p = .104 NS	

- **A3.25** MCS: "full responders" longitudinal changes

MCS: TRAJECTORY OF CHANGES				
Timepoint	Baseline	6 Weeks	6 Months	1 Year
Median	Median = 43.86	Median = 43.31	Median =52.95	Median = 52.53
Friedman Test	χ^2 (3, Number = 13) = 2.672 Sig. = .445 NS			

- **A3.26** MCS: linear mixed modelling outcomes.

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	54
Total		9		9		

a. Dependent Variable: MCS.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	46.817	722.310	<.001
time	3	43.235	2.195	.102

a. Dependent Variable: MCS.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	47.289166	2.087602	40.238	22.652	<.001	43.070742	51.507589
[time=1]	-6.343098	2.488173	76.003	-2.549	.013	-11.298720	-1.387476
[time=2]	-4.064825	2.660852	62.399	-1.528	.132	-9.383114	1.253465
[time=3]	-1.613772	2.383832	34.913	-.677	.503	-6.453640	3.226096
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: MCS.

b. This parameter is set to zero because it is redundant.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	40.946	1.809	47.234	37.308	44.585
2	43.224	2.433	32.955	38.275	48.174
3	45.675	2.604	28.908	40.350	51.001
4	47.289	2.088	40.238	43.071	51.508

a. Dependent Variable: MCS.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Repeated Measures	Var: [time=1]	152.634413	31.926931	4.781	<.001	101.298835	229.985507
	Var: [time=2]	210.814208	57.506359	3.666	<.001	123.511463	359.825957
	Var: [time=3]	190.108620	54.310017	3.500	<.001	108.600420	332.791412
	Var: [time=4]	160.600887	36.557721	4.393	<.001	102.798833	250.904064
	ARH1 rho	.642483	.076858	8.359	<.001	.466713	.769427

a. Dependent Variable: MCS.

- **A3.27** EQ-VAS: progression at all time-points

Baseline	6 Weeks
Mean (SD) = 42.77 ± 11.43	Mean (SD) = 45.53 ± 13.46
NUMBER = 29 t (28) = - 4.668 p < .001 Cohen's d = -.867	

Baseline	6 Months
Mean (SD) = 42.66 ± 23.40	Mean (SD) = 67.08 ± 23.54
NUMBER = 24 Z = -3.962 p < .001 Cohen's d = 2.75	

Baseline	1 Year
Mean (SD) = 42.66 ± 23.40	Mean (SD) = 71.85 ± 21.59
NUMBER = 35 Z = -4.153 p < .001 Cohen's d = 1.971	

- **A3.28** EQ.VAS: linear mixed modelling outcomes.

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	59
Total		9		9		

a. Dependent Variable: VAS.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	57.545	615.808	<.001
time	3	66.461	20.071	<.001

a. Dependent Variable: VAS.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	71.429967	3.121488	47.036	22.883	<.001	65.150469	77.709464
[time=1]	-29.120320	4.185054	102.013	-6.958	<.001	-37.421342	-20.819298
[time=2]	-7.072551	3.794134	70.929	-1.864	.066	-14.637970	.492868
[time=3]	-6.094597	3.277503	46.991	-1.860	.069	-12.688115	.498920
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: VAS.

b. This parameter is set to zero because it is redundant.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	42.310	3.434	47.936	35.405	49.214
2	64.357	3.333	43.900	57.640	71.075
3	65.335	3.490	43.053	58.297	72.373
4	71.430	3.121	47.036	65.150	77.709

a. Dependent Variable: VAS.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Repeated Measures	Var: [time=1]	639.538034	132.387201	4.831	<.001	426.249512	959.552763
	Var: [time=2]	442.398078	101.900888	4.341	<.001	281.675812	694.827352
	Var: [time=3]	411.718449	94.933446	4.337	<.001	262.018228	646.947669
	Var: [time=4]	405.632165	84.807964	4.783	<.001	269.256715	611.080223
	ARH1 rho	.622039	.070591	8.812	<.001	.464197	.741589

a. Dependent Variable: VAS.

- **A3.29** EQ-index: progression at all time-points

Baseline	6 Weeks
Mean ± SD =.559 ± .276	Mean ± SD =.605 ± .293
NUMBER = 31 Z = -.1.195 p = .232 NS	

Baseline		6 Months
Mean ± SD =.559 ± .276		Mean ± SD =.635 ± .676
	NUMBER = 28 Z = -.1.025 p = .305 NS	

Baseline		1 Year
Mean ± SD =.559 ± .276		Mean ± SD =.730 ± .268
	NUMBER = 39 Z = -1.982 p = .0.48 Cohen's d= .669	

- **A3.30** EQ-Index: linear mixed modelling outcomes.

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables	Number of Subjects
Fixed Effects	Intercept	1		1		
	time	4		3		
Repeated Effects	time	4	Heterogeneous First-Order Autoregressive	5	Recipients	60
Total		9		9		

a. Dependent Variable: EQindex.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	49.912	6.027	.018
time	3	49.846	.764	.520

a. Dependent Variable: EQindex.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	.641266	.052878	48.236	12.127	<.001	.534960	.747571
[time=1]	1.872532	1.742561	49.946	1.075	.288	-1.627600	5.372664
[time=2]	-.040009	.061140	73.531	-.654	.515	-.161847	.081828
[time=3]	-.003690	.052763	50.746	-.070	.945	-.109628	.102248
[time=4]	0[b]	0	.	.	.	.	.

a. Dependent Variable: EQindex.

b. This parameter is set to zero because it is redundant.

time[a]

time	Mean	Std. Error	df	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
1	2.514	1.749	49.649	-.999	6.027
2	.601	.046	40.458	.507	.695
3	.638	.050	43.590	.537	.738
4	.641	.053	48.236	.535	.748

a. Dependent Variable: EQindex.

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Repeated Measures	Var: [time=1]	175.323725	35.324339	4.963	<.001	118.124516	260.220396
	Var: [time=2]	.082066	.019194	4.276	<.001	.051889	.129792
	Var: [time=3]	.082481	.018170	4.539	<.001	.053559	.127020
	Var: [time=4]	.115921	.023718	4.888	<.001	.077625	.173109
	ARH1 rho	.545548	.071273	7.654	<.001	.391132	.670089

a. Dependent Variable: EQindex.

- **A3.31** EQ-5D-5L. Severity level progression

Dimension	Level	BASELINE	%	L1-2 vs L3-4-5	6 WEEKS	%	L1-2 vs L3-4-5	6 MONTHS	%	L1-2 vs L3-4-5	1 YEAR	%	L1-2 vs L3-4-5
Mobility	L1 (no problem)	19	33%		13	38%		13	43%		20	48%	
	L2 (slight problem)	12	21%	31 (54%)	11	32%	24 (70%)	7	23,00%	20 (67%)	8	19%	28 (67%)
	L3 (moderate problem)	17	29%		5	15%		6	20%		8	19%	
	L4 (severe problem)	9	15%		5	15%		3	10%		6	1%	
	L5 (extreme problem/unable to)	1	2%	26 (46%)	0	0	10 (30%)	1	3,30%	10 (33%)	0	0	14 (33%)
	Total	58			34			30			42		
Self Care	L1 (no problem)	34	59%		21	62%		18	60%		30	71%	
	L2 (slight problem)	12	21%	46 (80%)	11	32%	32 (94%)	8	27%	26 (87%)	9	21%	39 (92%)
	L3 (moderate problem)	9	15%		1	3%		2	7%		3	7%	
	L4 (severe problem)	3	5%		1	3%		1	3%		0	0	
	L5 (extreme problem/unable to)	0	0	12 (20%)	0	0	2 (6%)	1	3%	4 (13%)	0	0	3 (8%)
	Total	58			34			30			42		
Activity	L1 (no problem)	12	21%		9	26%		12	40%		17	40%	
	L2 (slight problem)	9	16%	21 (37%)	8	24%	17 (50%)	8	27%	20 (67%)	11	26%	28 (67%)
	L3 (moderate problem)	18	31%		9	26%		7	23%		10	24%	
	L4 (severe problem)	13	22%		4	12%		2	7%		2	5	
	L5 (extreme problem/unable to)	6	10%	37 (79%)	4	12%	17 (50%)	1	3%	10 (33%)	2	5	14 (33%)
	Total	58			34			30			42		
Pain	L1 (no problem)	10	17%		9	27%		11	38%		15	37%	
	L2 (slight problem)	20	34%	30 (51%)	12	36%	21 (63%)	7	24%	18 (62%)	12	29%	27 (66%)
	L3 (moderate problem)	19	33%		7	21%		6	21%		8	20	
	L4 (severe problem)	8	14%		5	15%		4	14%		5	12	14 (34%)
	L5 (extreme problem/unable to)	1	2%	28 (49%)	0		12 (37%)	1	3%	11 (38%)	1	2	
	Total	58			33			29			41		
Anxiety	L1 (no problem)	16	28%		14	41%		12	41%		15	37%	
	L2 (slight problem)	23	40%	39 (68%)	10	29%	24 (70%)	10	34%	22 (75%)	17	41%	32 (78%)
	L3 (moderate problem)	12	21%		5	15%		4	14%		4	10	
	L4 (severe problem)	4	7%		5	15%		2	7%		4	10	
	L5 (extreme problem/unable to)	2	4%	18 (32%)	0		10 (30%)	1	4%	7 (25%)	1	2	9 (12%)
	Total	57			34			29			41		

- **A3.32** PCS and MCS: scores stratified by timepoints and UK normative values (Jenkinson, 1998)

	Baseline		6 Weeks		6 Months		1 Year		UK Norm	
	PCS	MCS	PCS	MCS	PCS	MCS	PCS	MCS	PCS	MCS
25%	23.59	33.13	23.46	33.23	28.85	33.70	30.12	35.45	47.06	46.09
50%	30.03	39.63	34.19	47.99	39.11	50.22	43.72	53.12	53.20	53.24
75%	37.42	51.05	41.33	57.45	49.98	58.93	51.85	57.83	56.14	56.93
Mean	31.82	41.41	35.56	45.06	39.26	45.62	41.9	47.6		
(SD)	(9.74)	(12.34)	(10.12)	(13.09)	(12.14)	(27.74)	(11.42)	(13.78)		

- **A3.33** Predictors of baseline KDQOL

PREDICTORS OF BASELINE KDQOL				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-10.50	Inverse		.001
Gi symptoms	-5.86	Inverse		.051
Pre-Transplant transfusions	-9,81	Inverse		.002
Claudication	-8.69	Inverse		.121
Work Satus	4.10	Direct		.180
Constant	94.58			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.745	.555	8.880	5,40	< .001

A3.34 Predictors of baseline DQOL

PREDICTORS OF BASELINE DQOL				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Gi symptoms	-13.60	Inverse		.002
Pre-Transplant transfusions	-11.74	Inverse		.007
Constant	85.44			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.539	.290	9.810	2,48	< .001

- **A3.35** Predictors of baseline PCS

PREDICTORS OF BASELINE PCS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Previous cardiac revascularisation	15.58	Direct		.002
Peripheral Neuropathy	-4.99	Inverse		.060
Constant	22.64			.002
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.526	.277	7.850	2,41	.001

A3.36 Predictors of baseline MCS

PREDICTORS OF BASELINE MCS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-10.47	Inverse		.004
Cigarette Smoke	-10.18	Inverse		.002
Constant	69.86			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.599	.359	11.499	2,41	< .001

- **A3.37** Predictors of baseline DQOL Generic Health Item

PREDICTORS OF BASELINE DQOL Generic Health Item				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
GI symptoms	-13.04	Inverse		.016
Cigarette Smoke	-11.45	Inverse		.034
Preserved Urinary Output	-10.39	Inverse		.241
WL Duration	.017	Direct		.124
Constant	53.63			.007
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.574	.330	5.169	4,42	.002

- **A3.38** Predictors of baseline EQ-VAS

PREDICTORS OF BASELINE EQ-VAS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Blindness	-17.38	Inverse		.069
Cigarette Smoke	-14.86	Inverse		.019
Constant	83.81			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.430	.185	5.666	2,50	.006

- **A3.39** Predictors of baseline EQ-index

PREDICTORS OF BASELINE EQ-index				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-.141	Inverse		.060
Gi symptoms	-215	Inverse		.003
Constant	1.04			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.491	.241	8.559	2,54	< .001

- **A3.40** Baseline: Factors influencing HRQOL before transplant, stratified by scales.

PREDICTORS OF HRQOL AT BASELINE							
KDQOL	DQOL	PCS	MCS	DQOL generic health item	EQ-VAS	EQ-Index	KDQOL overall health item
Common Psychiatric Disorders	Gi symptoms	Neuropathy	Cigarette Smoke	Gi symptoms	Blindness	Gi Symptoms	
Previous blood transfusions	Previous blood transfusions	Cardiac Revascularisation	Common Psychiatric Disorders	Cigarette Smoke	Cigarette Smoke	Common Psychiatric Disorders	
Gi symptoms				Preserved Urinary Output			
Claudication				WL time			
MULTIPLE REGRESSION RESULTS							
R^2 = .555 F (5,40) = 8.880 p < .001	R^2 = .290 F (4,28) = 9.810 p < .001	R^2 = .277 F (2,41) = 7.85 p = .001	R^2 = .359 F (2,41) = 11.499 p < .001	R^2 = .330 F (4,41) = 5.169 p = .002	R^2 = .185 F (2,50) = 5.666 p = .006	R^2 = .241 F (2,54) = 8.559 p < .001	n/a

- A3.41 Predictors of KDQOL at 6 Weeks

PREDICTORS OF KDQOL AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	--13.50	Inverse		.027
Psychotropic Medications	-7.07	Inverse		.234
Blindness	-21.49	Inverse		.015
Work Status	5.65	Direct		.323
Constant	103.40			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.682	.465	5.647	4,26	.002

- A3.42 Predictors of DQOL at 6 Weeks

PREDICTORS OF DQOL AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Age at transplantation	-.76	Inverse		.006
BMI	1.17	Direct		.115
Daily Insulin Requirement (dichotomised: < 40, 41+ Units	7.09	Direct		.181
Shorter Waiting List Time	.021	Direct		.034
Constant	1.04			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.676	.457	5.884	4,28	.001

- **A3.43** Predictors of PCS at 6 Weeks

PREDICTORS OF PCS AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Gender	4.206	Direct		.203
Psychotropic Medications	-8.09	Inverse		.029
GI symptoms	-6.47	Inverse		.059
Constant	1.04			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.647	.419	6.015	3,25	.003

- **A3.44** Predictors of MCS at 6 Weeks

PREDICTORS OF MCS AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Registered Blind	-.15.67	Inverse		.041
Constant	62.49			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.382	.146	4.611	1,27	.041

- **A3.45** Predictors of EQ-VAS at 6 Weeks

PREDICTORS OF EQ-VAS AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Registered Blind	-28.44	Inverse		..005
GI symptoms	-18.35	Inverse		.005
Preserved Urinary Output	27.59	Direct		.009
Constant	1.04			.004
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.715	.511	9.750	4,26	< .001

- **A3.46** Predictors of EQ-index at 6 Weeks

PREDICTORS OF EQ-Index AT 6 WEEKS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Gender	.118	Direct		.088
GI Symptoms	-.205	Inverse		.007
OGTT at discharge (dichotomised: normal, high)	.216	Direct		.003
Haemoglobin at discharge	.007	Direct		.022
Hospital Stay (dichotomised: <12, 13+ days)	-.197	Inverse		.003
Constant	1.04			.004
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.839	.704	11.422	5,24	< .001

- **A3.47** Predictors of HRQOL at six weeks, stratified by scale.

PREDICTORS OF HRQOL AT 6 WEEKS							
KDQOL	**DQOL**	**PCS**	**MCS**	**DQOL generic health item**	**EQ-VAS**	**EQ-Index**	**KDQOL overall health item**
History of Common Psychiatric Disorders	Age	Psychotropic medications	Registered blind		Preserved Urinary Output	Gender	Psychotropic medications
Psychotropic medications	BMI	Gi symptoms			Gi symptoms	GI Symptoms	Gi symptoms
						OGTT at discharge	
Work Status	Insulin requirement	Gender			Registered blind	Haemoglobin at discharge	Age
Registered blind						Hospital Stay	Work Status
MULTIPLE REGRESSION RESULTS							
R^2 = .465 F (4.26) = 5.647 p = .002	R^2 = .457 F (4,28) = 5.884 p < .001	R^2 = .419 F (2.26) = 6.015 p = .003	R^2 = .146 F (1,27) = 4.611 p = .041	n/a	R^2 = .511 F (3,28) = 9.750 p < .001	R^2 = .704 F (5,24) = 11.422 p < .001	R^2 = .422 F (4.26) = 4.742 p = .005

- **A3.48** Predictors of KDQOL at 6 Months

PREDICTORS OF KDQOL AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
GI symptoms	-17.95	Inverse		.002
Psychotropic Medications	-7.24	Inverse		.169
Registered Blind	-16.97	Inverse		.032
Work Status	.19.56	Direct		.001
Constant	92.61			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.883	779	17.608	4,20	< .001

- **A3.49** Predictors of DQOL at 6 Months

PREDICTORS OF DQOL AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
GI symptoms	-14.88	Inverse		.011
HLA sensitisation	.265	Direct		.006
Retinopathy	-18.96	Inverse		.023
Constant	11.8.04			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.682	.466	7.554	3,26	< .001

- **A3.50** Predictors of PCS at 6 Months

PREDICTORS OF PCS AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Gender	7.65	Male: Direct		< .001
History of Common Psychiatric Disorders	-7,32	Inverse		< .001
GI Symptoms	-15.64	Inverse		< .001
Work	5.760	Direct		.002
Constant	92.61			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.968	.937	62.977	4, 17	< .001

- **A3.51** Predictors of MCS at 6 Months

PREDICTORS OF MCS AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-10.42	Inverse		.005
Psychotropic Medications	-4.05	Inverse		.229
GI Symptoms	-7.18	Inverse		.033
Registered Blind	-18.57	Inverse		< .001
Work Status	9.22	Direct		.010
Constant	80.71			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.914	.836	16.304	5,16	< .001

- **A3.52** Predictors of DQOL Generic Health Item at 6 Months

PREDICTORS OF DQOL Generic Health Item at 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Retinopathy	-48.58	Inverse		.015
Constant	135.12			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.471	.222	6.840	1,24	.015

- **A3.53** Predictors of EQ-VAS at 6 Months

PREDICTORS OF EQ-VAS AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
History of Common Psychiatric Disorders	-10.34	Inverse		.178
Psychotropic Medications	-10.81	Inverse		.157
GI Symptoms	-17.93	Inverse		.016
Registered Blind	-23.58	Inverse		.029
Gender	12.30	Direct		.080
Constant	127.56			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.798	637	7.022	5,20	< .001

- **A3.54** Predictors of EQ-index at 6 Months

PREDICTORS OF EQ-index AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Preserved Urinary Output	.404	Direct		.019
GI symptoms	-.235	Inverse		.029
Haemoglobin at discharge	.012	Direct		.011
Constant	-.841			.108
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.729	.531	9.063	3,24	< .001

- **A3.55** Predictors of KDQOL Overall Health Item at 6 Months

PREDICTORS OF KDQOL Overall Health Item AT 6 MONTHS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Psychotropic Medications	-15.55	Inverse		.053
GI Symptoms	-27.60	Inverse		.001
Registered Blind	-32.91	Inverse		.007
Constant	152.39			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.808	.653	12.546	3,20	< .001

- **A3.56** Predictors of HRQOL at six months, stratified by scales.

PREDICTORS OF HRQOL AT 6 MONTHS							
KDQOL	**DQOL**	**PCS**	**MCS**	**DQOL generic health item**	**EQ-VAS**	**EQ-Index**	**KDQOL overall health item**
Psychotropic medications	HLA sensitisation	History of Common Psychiatric Disorders	History of Common Psychiatric Disorders		History of Common Psychiatric Disorders	Preserved Urinary Output	Psychotropic medications
Gi symptoms	Gi symptoms	Gi symptoms	Gi symptoms		Gi symptoms	Gi symptoms	Gi symptoms
Registered blind	Retinopathy	Gender	Registered blind	Retinopathy	Registered blind	Haemoglobin at discharge	Registered blind
Work Status		Work Status	Work Status		Gender		
			Psychotropic medications		Psychotropic medications		
MULTIPLE REGRESSION RESULTS							
R^2 = .779 F (4,20) = 17.605 p < .001	R^2 = .466 F (3,26) = 7.554 p < .001	R^2 = .937 F (4,17) = 62.977 p < .001	R^2 = .836 F (5,16) = 16.304 p < .001	R^2 = .222 F (1,24) = 6.840 p = .015	R^2 = .637 F (5,20) = 7.022 p < .001	R^2 = .531 F (3,24) = 9.063 p < .001	R^2 = .653 F (3,20) = 12.546 p < .001

- **A3.57** Predictors of HRQL at one year, stratified by scales.

PREDICTORS OF HRQOL AT 1 YEAR							
KDQOL	**DQOL**	**PCS**	**MCS**	**DQOL generic health item**	**EQ-VAS**	**EQ-Index**	**KDQOL overall health item**
Psychiatric Disorders	Preserved sexual function	Gender	Psychiatric Disorders	Psychotropic medications	Psychiatric Disorders	Psychotropic medications	Hypoglycaemia unawareness
Work Status	BMI	Preserved Urinary Output	Retinopathy	Retinopathy	Age	1 Year creatinine	BMI
Registered blind	WL time	Number of Chronic complications	Registered blind			Medical complications within 1st year	Number of chronic complications
	GI symptoms						GI symptoms
MULTIPLE REGRESSION RESULTS							
R^2 = .332 F (3,33) = 5.461 p = .004	R^2 = .368 F (4,36) = 5.235 p = .002	R^2 = .558 F (3,28) = 11.779 p < .001	R^2 = .550 F (3,28) = 11.403 p < .001	R^2 = .262 F (2.34) = 6.049 p = .006	R^2 = .171 F (2.37) = 3.813 p = .031	R^2 = .315 F (3,25) = 3.827 p = .022	R^2 = .404 F (4.31) = 5.250 p = .002

A3.58 Pre-transplant predictors of HRQOL distribution across timepoints, stratified by PROMs.

	KDQOL				DQOL				PCS				MCS				DQOL generic				EQ-VAS				EQ-INDEX				KDQOL generic				TOT
	Pre-	Six	6	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	Pre-	Six Weeks	6 Months	1 Year	
GI symptoms	X			X	X		X	X		X	X				X		X					X	X		X	X	X			X	X	X	17
Blindness		X	X	X										X	X	X					X	X	X								X		10
Retinopathy							X									X			X	X													2
Psychiatric History	X	X		X							X		X		X	X							X	X	X								10
Psychotropic Medications		X	X							X					X					X			X				X				X	X	X		9
Work Status	X	X	X	X							X				X															X			6
Urinary Output												X					X					X					X							4
Gender										X	X	X											X			X								5
BMI						X		X																									X	3
Age at Tx						X																		X						X				3
Time on WL						X		X									X																	3
Pre-Tx Transfusions	X				X																													2
N chronic complications												X																					X	2
Claudication	X																																	1
Neuropathy									X																									1
Hypo-unaware																																	X	1
Insulin dose					X																													1
HLA sensitisation							X																											1
Cardiac Procedures									X																									1
Smoking													X				X				X													3

APPENDIX 4: Supplementary material for Chapter 4

- **A4.1** Study objectives and outcome measures

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective To assess long term Quality of Life after Pancreas Transplantation	PROMS “SF-36” “EQ-5D-5L®” `’The Hypoglycaemia Fear Survey-II Worry”. Clinical Data	Single time point at recruitment.
Secondary Objectives To evaluate differences in QoL within cohorts of Pancreas Transplant Recipients: SPK: Simultaneous Pancreas Kidney Transplant PAK: Pancreas after Kidney Transplant PASPK: Pancreas after SPK Transplant PTA: Pancreas Transplant Alone Failed Pancreas Failed Kidney Failed Pancreas and Kidney	As Above	As above
To identify predictors of Quality-of-Life gain after PT	As above	As above

-

A4.2 SF-36®: summary of structure

SF-36®	
SCALE	**N OF ITEMS/SCALES**
Physical Functioning	10
Role limitation caused by physical health problems	4
Role limitation caused by emotional health problems	3
Social functioning	2
Emotional well-being	5
Pain	2
Energy/fatigue	4
General health perceptions	5
Overall, Health Rating Scale	1

- **A4.3**Hypoglycaemia Fear Survey-Worry

Questionnaire

The Hypoglycaemia Fear Survey-II Worry (HFS-II W) scale

Instructions: Below is a list of concerns people with diabetes sometimes have about low blood glucose. Please read each item carefully (do not skip any). Place an X in the box that best describes how often in **the last six months** you **worried** about each item because of low blood glucose.

Because my blood glucose could go low, I worried about...	Never	Rarely	Sometimes	Often	Almost always
1 Not recognising/realising I was having low blood glucose	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2 Not having food, fruit or juice available	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3 Passing out in public	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4 Embarrassing myself or my friends in a social situation	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5 Having a hypo while alone	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6 Appearing stupid or drunk	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7 Losing control	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8 No one being around to help me during a hypo	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9 Having a hypo while driving	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10 Making a mistake or having an accident	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11 Getting a bad evaluation or being criticised	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12 Difficulty thinking clearly when responsible for others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13 Feeling lightheaded or dizzy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14 Accidently injuring myself or others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15 Permanent injury or damage to my health or body	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16 Low blood glucose interfering with important things I was doing	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17 Becoming hypoglycaemic during sleep	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18 Getting emotionally upset and difficult to deal with	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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- **A4.4** Short Form 36®

RAND HEALTH

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

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

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

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

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

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?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

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**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

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)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. 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?

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

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

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

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

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

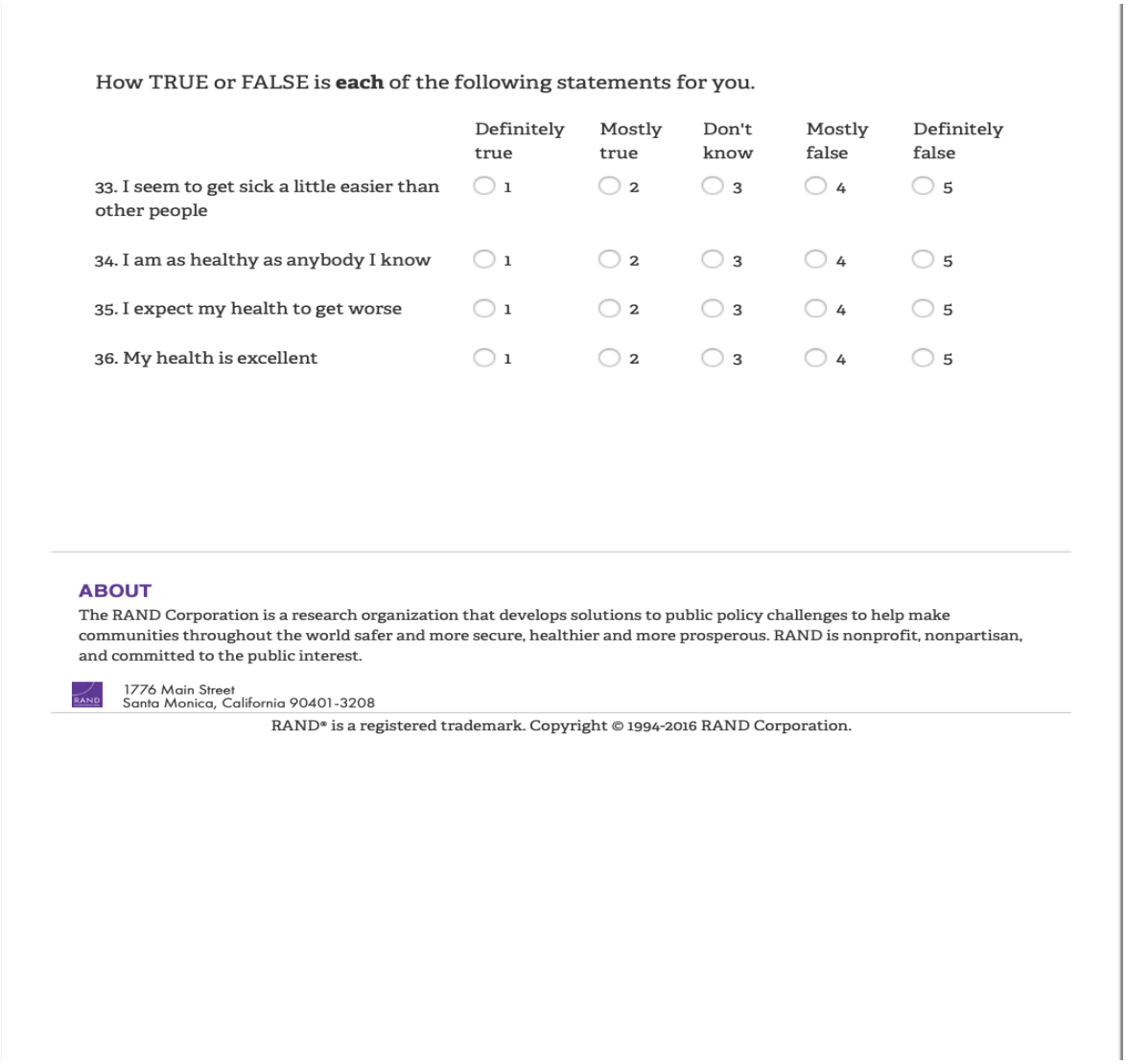
These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

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

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. 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.)?

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



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

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

ABOUT

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- **A4.5**Cross-sectional study enrolment rates, stratified by completion modality.

RECRUITMENT				
	Online	Paper	Total	Chi-Square Test
Enrolled	79	19	98	χ^2= 0.002, p= 0.89 NS
Not enrolled	20	6	26	

- **A4.6** Pre-operative variables, stratified by type of transplant.

	DESCRIPTIVE STATISTICS				Statistical Difference
Age at transplantation (yrs.)	N	Mean	Median	SD	T-Test
Total	98	46.36	45.50	8.66	
SPK, PAK, PaSPK	83	47.08	48	8.68	t (96) = 1.985
PTA	15	42.33	45	7.58	p=0.05 Cohen's d= 8.532
Gender		F		M	Chi-Square Test With Yates Correction
Total	98	45 (45.9%)		53 (54.1%)	
SPK, PAK, PaSPK	83	32 (38.55%)		51 (61.45%)	χ^2= 9.984, p= 0.002
PTA	15	13 (86.67%)		2 (13.33%)	Statistically Significant
Ethnicity		Caucasian		B.A.M.E.	Fisher Exact Test
Total	98	92 93.8%		6 6.1%	
SPK, PAK, PaSPK	83	77 (92.77%)		6 (7.23%)	Fisher = 0.5863
PTA	15	15 (100%)		0	NS
BMI	N	Mean	Median	SD	T-Test
Total	98	25.77	25.5	3.99	
SPK, PAK, PaSPK	83	25.9566	26.2	3.90	p = 0.321
PTA	15	24.7067	24.8	4.45	NS
Age of diagnosis (yrs.)	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	14.17	13	9.30	
SPK, PAK, PaSPK	83	14.92	13	9.70	p = - 0.093
PTA	15	10.07	11	5.24	NS
Cigarette Smoke (N)		History of Smoking		Never Smoker	Fisher Exact Test
Total	98	29 (29.6%)		69 (70.4%)	
SPK, PAK, PaSPK	83	29 (34.94%)		54 (65.06%)	Fisher = 0.0045
PTA	15	0		15 (100%)	Statistically Significant
Alcohol (N)		Yes		No	Fisher Exact Test
Total	86	47 (47.96%)		39 (39.80%)	
SPK, PAK, PaSPK	73	43 (51.81%)		30 (36.14%)	Fisher = 0.0749
PTA	13	4 (26.67%)		9 (60%)	NS
Duration of WL (days)	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	455.87	407	404.76	
SPK, PAK, PaSPK	83	476.98	423	408.22	p = 0.70
PTA	15	339.07	126	376.58	NS
Previous Tx		Yes		No	Fisher Exact Test
Total	98	15 (15.31%)		83 (84.69%)	
SPK, PAK, PaSPK	83	11 (13.25%)		72 (86.75%)	Fisher = 0.2377
PTA	15	4 (26.67%)		11 (73.33%)	NS
Working Status (N)		Unemployed		Full-time/ Housework/ Student	Chi-Square Test With Yates Correction
Total	97	44 (44.90%)		53(54.08%)	
SPK, PAK, PaSPK	82	39 (46.98%)		43(51.80%)	χ^2= 0.541, p= 0.462
PTA	15	5 (33.33%)		10(66.67%)	NS
Daily insulin requirement (UI)	N	Mean	Median	SD	Mann-Whitney U Test
Total	93	46.15	40	22.09	
SPK, PAK, PaSPK	80	46.61	40	23.20	p = 0.920
PTA	13	43.31	40	13.72	NS
HbA1c mmol/mol	N	Mean	Median	SD	T-Test
Total	92	68.39	68	19.28	
SPK, PAK, PaSPK	78	67.47	68	18.83	p=0.284
PTA	14	73.5	67.5	21.68	NS
Duration of IDDM (years)	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	32.40	32	9.28	
SPK, PAK, PaSPK	83	32.33	31	9.24	p = 0.630
PTA	15	32.8	34	9.79	NS

	DESCRIPTIVE STATISTICS				Statistical Difference
Pre-emptive		Yes		No	
Total	75	24 (32%)		51 (68%)	
SPK, PAK, PaSPK	75	24 (32%)		51 (68%)	N/A
PTA	n/a			n/a	
Type of Dialysis (N)		HD		PD	
Total	51	24 (47.06%)		27 (52.94%)	
SPK, PAK, PaSPK	51	24 (47.06%)		27 (52.94%)	N/A
PTA	n/a	n/a		n/a	
Dialysis duration (days)	N	Mean	Median	SD	
Total	57	634.58	486	567.24	
SPK, PAK, PaSPK	57	634.58	486	567.24	N/A
PTA	n/a	n/a	n/a	n/a	
Residual Urinary Output (N)		Yes		No	
Total	82	72 (86.75%)		10 (12.05%)	
SPK, PAK, PaSPK	82	72 (86.75%)		10 (12.05%)	N/A
PTA		n/a		n/a	
Sensitization (N)	N	Mean	Median	SD	Mann-Whitney U Test
Total	90	19.36	1	30.09	
SPK, PAK, PaSPK	75	17.85	1	27.93	p = 0.612
PTA	15	26.87	1	39.48	NS
Cardiac procedures (N)		Yes		No	Fisher Exact Test
Total	98	4 (4.1%)		94 (95.9%)	
SPK, PAK, PaSPK	83	4 (4.82%)		79 (95.18%)	Fisher = 1
PTA	15	0		15	NS
Hypertension (N)		Yes		No	Chi-Square Test With Yates Correction
Total	98	84 (85.71%)		14 (14.29%)	
SPK, PAK, PaSPK	83	77 (92.77%)		6 (7.23%)	χ^2= 18.449, p< 0.001
PTA	15	7 (46.67%)		8 (53.33%)	Statistically Significant

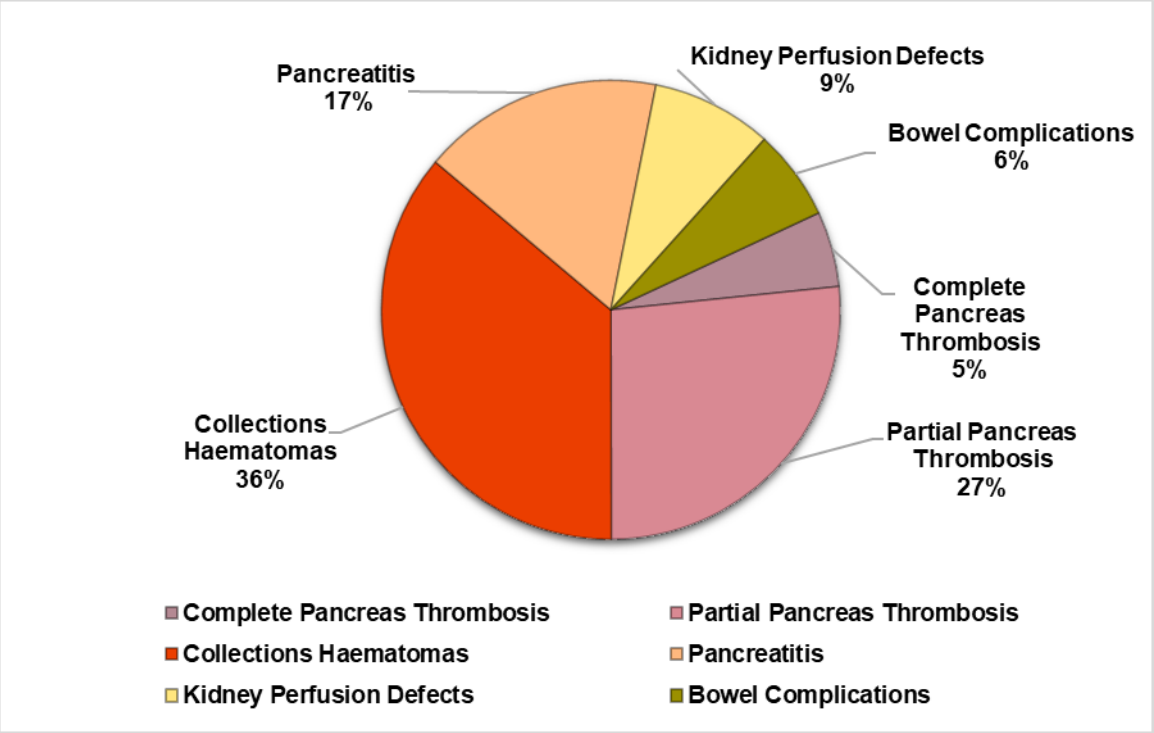
A4.5. Pre-operative diabetic complications, stratified by type of transplant.

	DESCRIPTIVE STATISTICS				Statistical Difference
End stage renal failure (N)		Yes		No	
Total	98	75 (76.53%)		23 (23.47%)	
SPK, PAK, PaSPK	83	75 (90.36%)		8 (9.64%)	N/A
PTA	15	0		15 (100%)	
Hypoglycaemia Unawareness (N)		Yes		No	Fisher Exact Test
Total	97	41 (41.84%)		56 (57.14%)	
SPK, PAK, PaSPK	82	26 (31.33%)		56(67.27%)	Fisher <0.00001
PTA	15	15 (100%)		0	Statistically Significant
Cardio/cerebro-vascular events (N)		Yes		No	Fisher Exact Test
Total	98	8 (8.2%)		90 (91.8%)	
SPK, PAK, PaSPK	83	7 (8.43%)		76 (91.57%)	Fisher = 1
PTA	15	1(6.67%)		14 (93.33%)	NS
Retinopathy (N)		Yes		No	Fisher Exact Test
Total	97	92 (93.88%)		5 (5.10%)	
SPK, PAK, PaSPK	83	79 (95.18%)		4 (4.82%)	Fisher = 0.549
PTA	14	13 (86.67%)		1 (6.67%)	NS
Registered blind (N)		Yes		No	Fisher Exact Test
Total	98	14 (14.3%)		84 (85.7%)	
SPK, PAK, PaSPK	83	10 (12.05%)		73 (87.95%)	Fisher = 0.220
PTA	15	4 (26.67%)		11 (73.33%)	NS
Neuropathy (N)		Yes		No	Fisher Exact Test
Total	98	65 (66.3%)		33 (33.7%)	
SPK, PAK, PaSPK	83	53 (63.86%)		30 (36.14%)	Fisher = 0.373
PTA	15	12 (80%)		3 (20%)	NS
Gastro-intestinal symptoms (N)		Yes		No	Chi-Square Test With Yates Correction
Total	98	35 (35.7%)		63 (64.3%)	
SPK, PAK, PaSPK	83	27 (32.53%)		56 (67.47%)	χ^2= 1.574, p= 0.210
PTA	15	8 (53.33%)		7 (46.67%)	NS
Amputations (N)		Yes		No	Fisher Exact Test
Total	98	11 (11.2%)		87 (88.8%)	
SPK, PAK, PaSPK	83	9 (10.84%)		74 (89.16%)	Fisher = 0.2377
PTA	15	3 (20%)		12 (80%)	NS
Claudication (N)		Yes		No	Fisher Exact Test
Total	98	7 (7.14%)		91 (92.86%)	
SPK, PAK, PaSPK	83	6 (7.23%)		77 (92.77%)	Fisher = 1
PTA	15	1 (6.67%)		14 (93.33%)	NS
Number of diabetes chronic complications (N)		1-2		3+	Fisher Exact Test
Total	98	14 (14.29%)		84 (85.71%)	
SPK, PAK, PaSPK	83	15		68	Fisher = 1
PTA	15	2 (13.33%)		13 (86.67%)	NS

A4.7: Summary of transplant variables

TRANSPLANT VARIABLES			
INDEPENDENT VARIABLES	**DESCRIPTIVE STATISTICS**		**STATISTICAL DIFFERENCE**
Donor-s type	DBD	DCD	Chi-Square with Yates Correction
Total	81 (82.7%)	16 (16.3%%)	
SPK, PAK, PaSPK	70 (84.3%)	12 (14.5%)	χ^2= 0.602
PTA	11 (73.3%)	4 (26.7%)	p= 0.805 NS
Donor's gender	Female	Male	Chi-Square with Yates Correction
Total	49 (50%)	48 (49%)	1 (1%)
SPK, PAK, PaSPK	41 (49.4%)	42 (50.6%)	χ^2= 0.061
PTA	8 (53.3%)	6 (40%)	p= 0.438 NS
Donor's age (years)	Mean	SD	Mann-Whitney U Test
Total	39.04	13.76	
SPK, PAK, PaSPK	38.69	14.095	P = 0.611 NS
PTA	41.14	11.831	
CIT Pancreas (minutes)	Mean	SD	T-Test
Total	651.18	137.47	
SPK, PAK, PaSPK	656.64	135.714	p = 0.381 NS
PTA	620.15	148.888	
Pancreas anastomotic time (minutes)	Mean	SD	Mann-Whitney U Test
Total	60.16	137.63	
SPK, PAK, PaSPK	52.82	113.148	P = 0.328 NS
PTA	101.17	235.246	
CIT Kidney (minutes)	Mean	SD	N/A
Total	709.33	257.44	
SPK, PAK, PaSPK	709.33	257.44	
PTA	N/A	N/A	
Kidney anastomotic time (minutes)	Mean	SD	N/A
Total	54.86	33.75	
SPK, PAK, PaSPK	54.86	33.75	
PTA	N/A	N/A	
Exocrine Drainage	Bladder	Enteric	Fisher Exact Test
Total	15 (15.3%)	83 (84.7%)	
SPK, PAK, PaSPK	4 (4.8%)	79 (95.2%)	Fisher < 0.001 Statistically Significant
PTA	11 (73.3%)	4 (26.7%)	

- **A4.8** Distribution of radiologically diagnosed complications.



A4.9 summary of post-transplant variables

POST TRANSPLANT					
Hospital Admission (days)	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	17.33	14	9.39	
SPK, PAK, PaSPK		17.22	14	9.206	P = 0.972 NS
PTA		17.93	14	10.620	
Blood Transfusions		No	Missing	Yes	
Total	98		43 (43.9%)	44 (4.9%)	
PTA			14	17.93	
SPK, PAK, PaSPK		9 (10.8%)	37	37 (44.6%)	
PTA		2 (13.3%)	6	7 (46.7%)	
Post-operative course N (%)		Complicated		Regular	Fisher Exact Test
Total	97	61 (62.24%)	98	36 (36.73%)	
SPK, PAK, PaSPK	82	49 (59.04%)	No	33 (39.76%)	Fisher = 0.159 NS
PTA	15	12(80%)		3 (20%)	
Post operative CT		Yes	No	No	Fisher Exact Test
Total	94	65 (66.33%)		29(29.59%)	
SPK, PAK, PaSPK	80	54 (65.06%)		26(31.33%)	Fisher = 0.538 NS
PTA	14	11 (73.33%)		3(20%)	
CT positive for complications		Yes		No	Fisher Exact Test
Total	65	42 (42.86%)		23(23.47%)	
SPK, PAK, PaSPK	54	33 (61.11%)		21(38.89%)	Fisher = 0.302 NS
PTA	11	9 (81.8%)		2 (18.18%)	
Pancreatitis *CT		Yes		No	Fisher Exact Test
Total	65	16 (16.3%		49 (50%)	
SPK, PAK, PaSPK	54	13 (15.67%		41 (49.40%)	Fisher = 1 NS
PTA	11	3 (20%		8 (53.33%)	
Pancreatic Thrombosis *CT		Yes		No	Fisher Exact Test
Total	65	30 (30.61%)		35 (35.71%)	
SPK, PAK, PaSPK	54	23 (27.71%)		31 (37.35%)	Fisher = 0.320 NS
PTA	11	7 (46.67)		4 (26.67%)	
Pancreas Thrombosis Severity		Complete		Partial	Fisher Exact Test
Total	30	5 (5.1%)		25 (25.5%)	
SPK, PAK, PaSPK	23	3 (3.6%)		20 (24.1%)	Fisher = 0.565 NS
PTA	7	2 (13.3%)		5 (33.3%	
Collections/Haematomas		Yes		No	Fisher Exact Test
Total	62	34 (34.69%)		28 (28.57%)	
SPK, PAK, PaSPK	51	28 (33.73%)		23 (27.71%)	Fisher = 1 NS
PTA	11	6 (40%)		5 (33.33%)	
Kidney Perfusion Defects *CT		Yes		No	
Total	54	8 (9.64%)		46 (55.42%)	
SPK, PAK, PaSPK	54	8 (9.64%)		46 (55.42%)	
PTA		N/A		N/A	
Bowel Complications *CT		Yes		No	Fisher Exact Test
Total	54	6 (6.12%)		59 (48.98%)	
SPK, PAK, PaSPK	54	6 (6.12%)		48 (48.98%)	Fisher = .579 NS
PTA	11	0		11 (73.33%)	

Medical Complications		Yes	missing	No	Fisher Exact Test
Total	93	41 (41.83%)	5	42 (42.86%)	
SPK, PAK, PaSPK	80	35 (42.17%)	3	45 (54.22%)	Fisher = 1 NS
PTA	13	6 (40%)	2	7 (46.67%)	
Surgical Complications		Yes		No	Chi-Square with Yates Correction
Total	97	47(48%)	1(1%)	50 (51%)	
SPK, PAK, PaSPK	82	38 (45%)	1(1%)	44 (53%)	χ^2= 0.479 p= 0.489 NS
PTA	15	9 (60%)		6 (40%)	
Return to theatre		Yes	missing	No	Chi-Square with Yates Correction
Total	97	22 (22%)	1 (1%)	75 (77%)	
SPK, PAK, PaSPK	82	15 (18 %)	1 (1%)	67 (8 %)	χ^2= 4.316 p= 0.038 Statistically Significant
PTA	15	7 (47%)		8 (53%)	
Early Graft Pancreatectomy N (%)		Yes		No	Fisher Exact Test
Total	98	5 (5.10%)		93 (94.90%)	
SPK, PAK, PaSPK	83	3 (3.61%)		80 (96.39%)	Fisher = 0.167 NS
PTA	15	2 (13.33%)		13 (86.67%)	
Early Graft nephrectomy N (%)		Yes		No	
Total	83	1 (1.20%)		82 (98.80%)	
SPK, PAK, PaSPK	83	1 (1.20%)		82 (98.80%)	N/A
PTA	n/a	n/a		n/a	
Pancreas Primary Function N (%)		Yes		No	Fisher Exact Test
Total	98	90 (91.84%)		8 (8.16%)	
SPK, PAK, PaSPK	83	75 (90.36%)		8 (9.64%)	Fisher = 0.352 NS
PTA	15	15 (100%)		0	
Insulin independent at Discharge N (%)		Yes		No	Fisher Exact Test
Total	98	91 (92.86%)		7 (7.14%)	
SPK, PAK, PaSPK	83	77 (92.77%)		6 (7.23%)	Fisher = 1 NS
PTA	15	14 (93.33%)		1 (6.67%)	
Normal Glucose tolerance test at discharge N (%)		Yes		No	Fisher Exact Test
Total	72	50 (51.02%)		22 (22.45%)	
SPK, PAK, PaSPK	60	41 (49.40%)		19 (22.90%)	Fisher = 0.738) NS
PTA	12	9 (60%)		3 (20%)	
OGTT 2h	N	Mean	Median	SD	T-test
Total	69	7.43	7.2	2.39	
SPK, PAK, PaSPK	58	7.5155	7.4	2.431	p = 0.487 NS
PTA	11	6.9636	6.2	2.20330	

Kidney Primary Function N (%)		**Yes**		**No**	
Total	80	66 (79.2%)		14 (16.87%)	
SPK, PAK, PaSPK	80	66 (79.2%)		14 (16.87%)	
PTA		N/A		N/A	
Dialysis free at Discharge N (%)		Yes		No	
Total	98	98 (100%)		0	
SPK, PAK, PaSPK	83	83 (100%)		0	
PTA	15	15 (100%)		0	
Creatinine at discharge (umol/L) N (%)	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	132.07	102.50	88.94	
SPK, PAK, PaSPK	83	139.89	107.	93.523	MWU= 329.5 Z= -2.891 p = 0.004 Statistically Significant
PTA	15	88.8	77	34.736	
Haemoglobin at discharge (g/L) N (%)	N	Mean	Median	SD	T-test
Total	98	91.97	90.5	12.60	
SPK, PAK, PaSPK	83	90.73	90	11.837	t (96) = -2.334 Cohen's d= 12.317 p =0.022 Statistically Significant
PTA	15	98.80	96	14.819	

- **A4.10** Summary of follow-up data

FOLLOW-UP					
Independent Variables					
Transplanted from over one years		Yes		No	
Total	98	95 (97%)		3 (3%)	
SPK, PAK, PaSPK	83	80 (96.4%)		3 (3.6%)	
PTA	15	15 (100%)		0	
Insulin independent at one year		Yes		No	Fisher Exact Test
Total	94	89 (93.68%)		5 (5.26%)	
SPK, PAK, PaSPK	79	76 (95%)		3 3.75%	Fisher = 0.179 NS
PTA	15	13 (86.67) %		2 (13.33%)	
missing	(1)				
HbA1c at one year	N	Mean	Median	SD	Mann-Whitney U Test
Total	71	35.14	34	(8.33)	
SPK, PAK, PaSPK	60	35.7	34.5	(8.045)	P = 0.627 NS
PTA	11	32.073	34	(9.5696)	
missing	(24)				
Dialysis free at one year		Yes		No	
Total	94	94 (98.95%)		0	
SPK, PAK, PaSPK	79	79 (98.75%)		0	
PTA	15	15 (100%)		0	
missing	(1)				
Creatinine at one year	N	Mean	Median	SD	T-test
Total	89	119.62	114	36.93	
SPK, PAK, PaSPK	76	119.82	114.5	37.646	P = 0.904 NS
PTA	13	118.46	114	33.790	
missing	(6)				
Hb at one year (g/L)	N	Mean	Median	SD	Mann-Whitney U Test
Total	67	126.27	128	28.03	
SPK, PAK, PaSPK	58	129.03	131.50	28.656	MWU= 83.000 Z= -3.274 p = 0.001 Statistically Significant
PTA	9	108.44	110	14.715	
missing	(28)				
Transplanted from 2+ years		Yes		No	
Total	98	90 (91.84%)		8 (8.16%)	
SPK, PAK, PaSPK	83	75 (90.36%)		8 (9.64%)	
PTA	15	15 (100%)		0	
Insulin independent at two years		Yes		No	Fisher Exact Test
Total	90	81 (90%)		8 (8.89%)	
SPK, PAK, PaSPK	83	68 (90.67%)		6 (8%)	Fisher = 0.618 NS
PTA	15	13 (86.67%)		2 (13.33%)	
HbA1c at two years	N	Mean	Median	SD	Mann-Whitney U Test
Total	63	37.89	35	9.78	
SPK, PAK, PaSPK	53	37.85	35	9.85549	P = 0.992 NS
PTA	10	38.1	35	9.91576	

Hb at five years	N	Mean	Median	SD	
Total	39	118.62	126	29.67	
SPK, PAK, PaSPK	35	120.94	127	30.35	MWU= 12.000 Z= -2.687
PTA	4	98.25	101.5	9.74	p = 0.004 Statistically Significant
Insulin independent 2022		Yes		No	Fisher Exact Test
Total	98	91 (92.85%)		7 (7.14%)	
SPK, PAK, PaSPK	83	78 (93.98%)		5 (6.02%)	Fisher = 0.291
PTA	15	13 (86.67%)		2 (13.33%)	ns
missing	(35)				
HbA1c 2021-22	N	Mean	Median	SD	Mann-Whitney U Test
Total	27	38.33	37	6.81	
SPK, PAK, PaSPK	22	38.18	37	6.59	p = 0.660
PTA	5	39	36	8.51	ns
missing	(71)				
Dialysis free 2022		Yes		No	Fisher
Total	72	59 (82%)		13 (18%)	
SPK, PAK, PaSPK	60	51 (85%)		9 (15%)	F = 0.210
PTA	12	8 (66.7%)		4 (33.3%)	ns
missing	(26)				
Creatinine 2022	N	Mean	Median	SD	Mann-Whitney U Test
Total	30	126.10	111	61.93	
SPK, PAK, PaSPK	24	123.63	110.5	67.09	p = 0.233
PTA	6	136	122	37.36	ns
missing	(58)				
Hb 2022	N	Mean	Median	SD	T-test
Total	28	126	130	18.80	
SPK, PAK, PaSPK	23	129.83	133	17.08	T (26) = 2.531 Cohen's
PTA	5	108.40	101	17.56	d= 17.1582 p =0.018 Statistically Significant
missing	(70)				
Enteric conversion					Fisher
Total	15	10		4	
SPK, PAK, PaSPK	4	3		1	F = 1
PTA	11	7	1	3	ns
missing	1				
Years from transplant	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	8.61	8	4.46	
SPK, PAK, PaSPK	83	8.54	8	4.68	P = 0.514
PTA	15	9	9	3.09	ns
missing					
Age at recruitment	N	Mean	Median	SD	Mann-Whitney U Test
Total	98	57.13	54	35.48	
SPK, PAK, PaSPK	83	58.77	54	37.30	P= .480
PTA	15	48.07	50	21.66	ns
missing	0				

Dialysis free at two years		**Yes**		**No**	
Total	95	87 (96.67%)		0	
SPK, PAK, PaSPK	81	73 (97.33%)		0	
PTA	14	14 (93.33%)		0	
missing	(3)				
Creatinine at two years	N	Mean	Median	SD	Mann-Whitney U Test
Total	86	120.71	112	48.46	
SPK, PAK, PaSPK	73	119.19	112	82.86	P = 0.947
PTA	13	129.23	111	74.21	NS
missing	(12)				
Hb at two years	N	Mean	Median	SD	Mann-Whitney U Test
Total	55	131.38	131	15.57	
SPK, PAK, PaSPK	47	133.30	133	15.34	MWU= 77.500 Z= -2.640
PTA	8	120.13	116	12.46	p = 0.007 Statistically Significant
missing	(35)				
Transplanted from over five years					
Total	98	74 (75.5%)		24 (24.5%)	
SPK, PAK, PaSPK	83	60 (72.3%)		23 (27.7%)	
PTA	15	14 (93.3%)		1 (6.7%)	
Insulin independent at five years		Yes		No	Fisher Exact Test
Total	74	63 (85.14%)		11 (14.86%)	
SPK, PAK, PaSPK	60	52 (86.66%)		8 (13.33%)	Fisher = 0.388
PTA	14	11 (78.57%)		3 (21.43%)	NS
missing	0				
HbA1c at five years	N	Mean	Median	SD	Mann-Whitney U Test
Total	56	37.17	36	12.61	
SPK, PAK, PaSPK	49	35.78	36	8.84	P = 0.147
PTA	7	46.86	38	26.60	NS
missing	(18)				
Dialysis free at five years		Yes		No	
Total	70	68		2	
SPK, PAK, PaSPK	59	57		2	
PTA	11	11		0	
missing	(4)				
Creatinine at five years	N	Mean	Median	SD	Mann-Whitney U Test
Total	64	137.98	119	65.35	
SPK, PAK, PaSPK	54	134.67	116.5	61.33	p = 0.296
PTA	10	155.90	136.5	85.53	ns
missing	(10)				

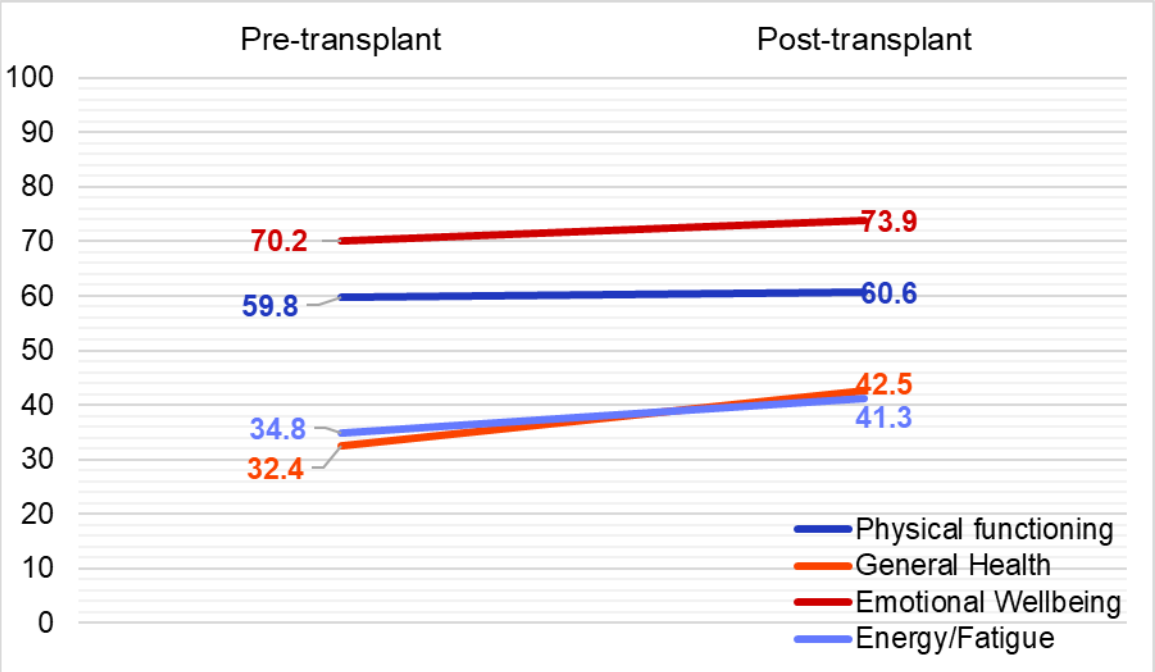
- **A4.11** SF-36, longitudinal study: pre-operative outcomes stratified by transplant type.

LONGITUDINAL STUDY: PRE-OPERATIVE SF-36®							
	Scale	**n**	**Mean**	**Median**	**SD**	**Distribution**	**Statistical Difference**
	Physical functioning						Independent t-test
	Total	29	59.8	65	28.6	Not Normal	
	SPK/PAK/PASPK	22	60	65	28.4	Normal	t (27) = .056
	PTA	7	59.3	45	31.8	Normal	p = .955 NS
	Role physical						Mann-Whitney U
	Total	29	70.7	25	182.7	Not Normal	
	SPK/PAK/PASPK	22	78.4	25	208.9	Not Normal	MWU = 71.500
	PTA	7	46.4	50	46.6	Normal	p = -.784 NS
	Pain						Mann-Whitney U
	Total	29	69.3	67.5	26.6	Not Normal	
	SPK/PAK/PASPK	22	69.4	73.5	26.9	Not Normal	MWU = 75.500
	PTA	7	68.9	67.5	27.9	Normal	p = -.940 NS
	General health						Independent t-test
	Total	29	32.4	35	20.1	Normal	
	SPK/PAK/PASPK	22	30.9	30	19.1	Normal	t (27) = -.918
	PTA	7	38.9	45	23.4	Normal	p = .366 NS
	Emotional well-being						Independent t-test
	Total	29	70.2	72	19.3	Normal	
	SPK/PAK/PASPK	22	69.9	74	18.2	Normal	t (27) = -.104
	PTA	7	71	68	23.9	Normal	p = .918 NS
	Role emotional						Mann-Whitney U
	Total	29	74.7	100	42.4	Not Normal	
	SPK/PAK/PASPK	22	74.2	100	43.6	Not Normal	MWU = 76.000
	PTA	7	76.2	100	41.8	Not Normal	p = -.980 NS
	Social function						Mann-Whitney U
	Total	29	71.6	75	24.5	Not Normal	
	SPK/PAK/PASPK	22	67.6	68.8	25.8	Not Normal	MWU = 47.500
	PTA	7	83.9	75	15.7	Not Normal	p = -.135 NS
	Energy/fatigue						Independent t-test
	Total	29	34.8	35	24.3	Normal	
	SPK/PAK/PASPK	22	32.5	35	22	Normal	t (27) = -.911
	PTA	7	42.1	40	31.5	Normal	p = .371 NS
SUMMARY SCALES	**PCS**						Independent t-test
	Total	25	36.8	34.1	10.8	Normal	
	SPK/PAK/PASPK	20	**36.8**	**35.6**	**10.8**	Normal	t (23) = .056
	PTA	5	**36.8**	**32.7**	**12**	Normal	p = .955 NS
	MCS						Independent t-test
	Total	25	**47.1**	**49.3**	**10.7**	Normal	
	SPK/PAK/PASPK	20	**47.1**	**49.6**	**10.9**	Normal	t (6) *= .056
	PTA	5	**47**	**48.6**	**11.27**	Normal	p = .981 NS

- **A4.12** SF-36, longitudinal study: post-operative outcomes, stratified by transplant type.

LONGITUDINAL STUDY: POST-OPERATIVE SF-36®							
	Scale	**n**	**Mean**	**Median**	**SD**	**Distribution**	**Statistical Differenc**
	Physical functioning						Independent t-test
	Total	29	60.6	65	28.7	Not Normal	
	SPK/PAK/PASPK	22	61.7	62.5	25.6	Normal	t (7.7) * = 0.29
	PTA	7	57.1	70	39	Normal	p = .80 ns
	Role physical						Mann-Whitney U
	Total	29	37.1	25	42.1	Not Normal	
	SPK/PAK/PASPK	22	39.8	25	42.7	Not Normal	MWU = 63.500
	PTA	7	28.6	0	41.9	Not Normal	p = -.47 ns
	Pain						Independent t-test
	Total	28	40.8	45	27.3	Normal	
	SPK/PAK/PASPK	21	55.4	47.5	27.1	Normal	t (10.6) * = 1.356
	PTA	7	39.6	32.5	26.4	Normal	p = .20 ns
	General health						Independent t-test
	Total	29	42.5	45	22.5	Normal	
	SPK/PAK/PASPK	22	43	45	19.8	Normal	t (27) = 0.17
	PTA	7	41.3	35	31.5	Normal	p = .87 ns
	Emotional well-being						Independent t-test
	Total	28	73.9	76	15.7	Normal	
	SPK/PAK/PASPK	21	74.5	76	15.7	Normal	t (9.7) * = -0.21
	PTA	7	72	76	17	Normal	p = .84 ns
	Role emotional						Mann-Whitney U
	Total	29	67.8	100	38.3	Not Normal	
	SPK/PAK/PASPK	22	65.2	83.4	40.5	Not Normal	MWU = 66.500
	PTA	7	76.2	100	31.7	Not Normal	p = .56 ns
	Social function						Mann-Whitney U
	Total	29	60.8	75	32.2	Not Normal	
	SPK/PAK/PASPK	22	64.2	75	31.2	Not Normal	MWU = 56.000
	PTA	7	50	50	35.4	Normal	p = -.28 ns
	Energy/fatigue						Independent t-test
	Total	28	41.3	42.5	27.1	Normal	
	SPK/PAK/PASPK	21	46.9	50	26.1	Normal	t (11.1) * = 2.1
	PTA	7	24.3	25	24.1	Normal	p = **.059** ns
SUMMARY SCALES	**PCS**						Independent t-test
	Total	**27**	**38.2**	**37.9**	**12.7**	Normal	
	SPK/PAK/PASPK	**21**	**39.3**	**40.6**	**11.9**	Normal	t (8.4) * = 0.79
	PTA	**6**	**34.2**	**35.4**	**15.7**	Normal	p = .45 ns
	MCS						Independent t-test
	Total	**27**	**48.3**	**50.8**	**9.6**	Normal	
	SPK/PAK/PASPK	**21**	**49**	**50.8**	**9.4**	Normal	t (9.4) *= 0.74
	PTA	**6**	**45.7**	**46**	**10.6**	Normal	p = .48 ns

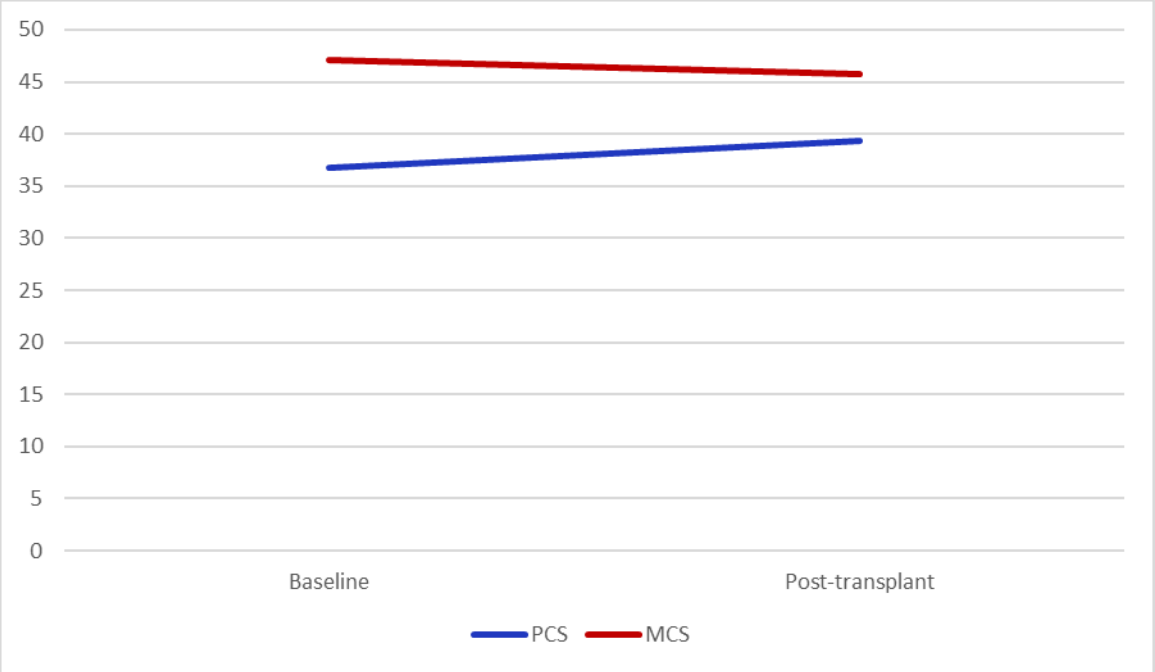
- **A4.13** Longitudinal SF-36 results: domains with an upward trajectory



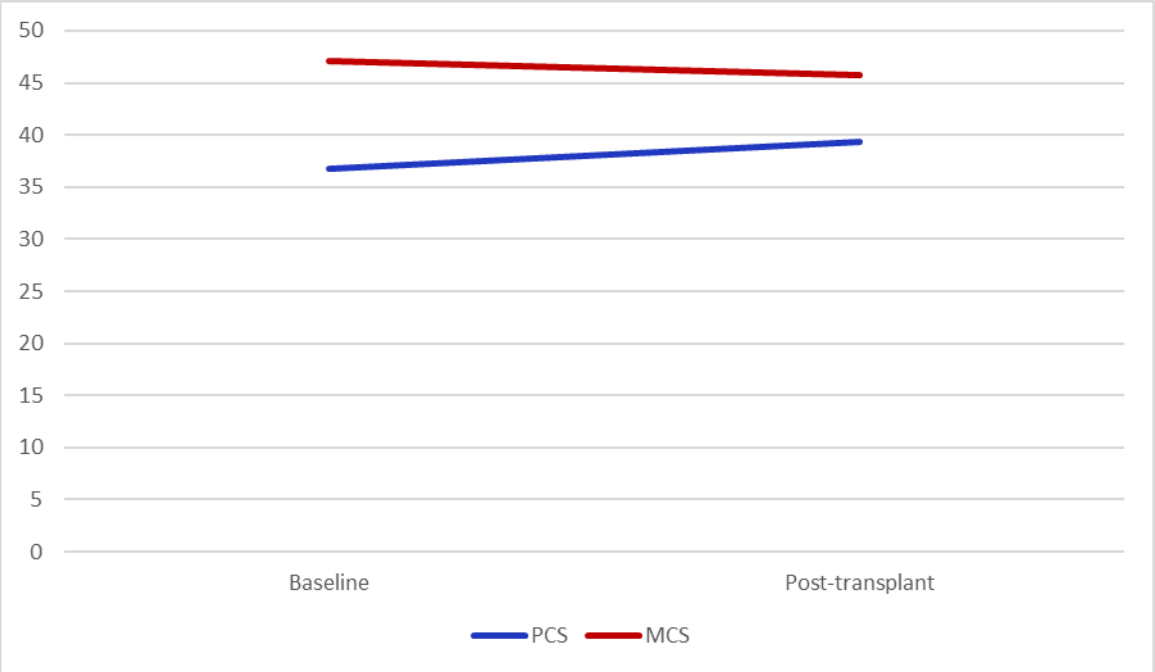
- **A4.14** SF-36: longitudinal changes

	Scale	Pre-Tx	Post-Tx	Statistical Significance	
	Physical functioning	Mean	Mean		
	Total	59.8	60.6	Z = -.129 p = 898	ns
	SPK/PAK/PASPK	60	61.7	t = -.207 p = .838	ns
	PTA	59.3	57.1	t = .091 p = .930	ns
	Role physical				
	Total	70.7	37.1	Z = -.324 p = .746	ns
	SPK/PAK/PASPK	78.4	39.8	Z = -.057 p = .954	ns
	PTA	46.4	28.6	Z = -.552 p = .581	ns
	Pain				
	Total	69.3	40.8	Z = -2.277 p = .023 Cohen's d = .933	ss
	SPK/PAK/PASPK	69.4	55.4	**Z = 1.9 p = .057**	ns
	PTA	68.9	39.6	t = 1.675 p = .145	ns
	General health				
	Total	32.4	42.5	t = -.102 p = .079	ns
	SPK/PAK/PASPK	30.9	43	t (21) = 2.170 p = .042 Cohen's d = -.433	ss
	PTA	38.9	41.3	t = -.154 p = .883	ns
	Emotional well-being				
	Total	70.2	73.9	t = -.887 p = .383	ns
	SPK/PAK/PASPK	69.9	74.5	t = - 1.027 p = .317	ns
	PTA	71	72	t = -.091 p = .930	ns
	Role emotional				
	Total	74.7	67.8	Z = -.799 p = .424	ns
	SPK/PAK/PASPK	74.2	65.2	Z = - 1.029 p = .304	ns
	PTA	76.2	76.2	Z = 0 p = 1	ns
	Social function				
	Total	71.6	60.8	Z = -1.289 p = .197	ns
	SPK/PAK/PASPK	67.6	64.2	Z = -.132 p = .897	ns
	PTA	83.9	50	Z = -1.897 p = .058	ns
	Energy/fatigue				
	Total	34.8	41.3	t = -.940 p = .356	ns
	SPK/PAK/PASPK	32.5	46.9	t (20) = -2.178 p = .042 Cohen's d = -.475	ss
	PTA	42.1	24.3	t = 1.161 p = .290	ns
SCALES	**PCS**				
	Total	36.8	**38.2**	t = -.206 p = .839	ns
	SPK/PAK/PASPK	**36.8**	**39.3**	t = -.132 p = .897	ns
	PTA	**36.8**	**34.2**	t = -.154 p = .887	ns
	MCS				
	Total	**47.1**	**48.3**	t = -.1.221 p = .235	ns
	SPK/PAK/PASPK	**47.1**	**49**	t = -.930 p =. 365	ns
	PTA	**47**	**45.7**	t = -.838 p = .463	ns

- **A4.15** Long term longitudinal progression of PCS and MCS after SPK



- **A4.16**Long term longitudinal progression of PCS and MCS after PTA



- **A4.17** SF-36: longitudinal MCS and PCS outcomes and UK population norms (Jenkinson, 1998) for the totality of study participants

	TOTAL SAMPLE				UK	
	Pre-operative		Post-operative		Population Norm	
Percentiles	**PCS**	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
25%	27.92	35.66	29.34	39.86	47.06	46.09
50%	34.07	49.25	37.94	50.75	53.20	53.24
75%	45.75	54.98	46.26	56.47	56.14	56.93
Mean (SD)	36.80 (10.78)	47.09 (10.72)	38.18 (12.72)	48.27 (9.61)		

- **A4.18** SF-36: longitudinal MCS and PCS outcomes and UK population norms (Jenkinson, 1998) for SPK/PAK/PASPK recipients

	SPK/PAK/PASPK				UK	
	Pre-operative		Post-operative		Population Norm	
Percentiles	**PCS**	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
25%	28.01	37.01	30.65	42.74	47.06	46.09
50%	35.59	49.60	40.59	50.75	53.20	53.24
75%	45.97	54.82	48.98	57.46	56.14	56.93
Mean (SD)	36.80 (10.80)	47.12 (10.88)	39.31 (11.94)	49.02 (9.44)		

- **A4.19**SF-36: longitudinal MCS and PCS outcomes and UK population norms (Jenkinson, 1998) for PTA recipients

	PTA				UK	
	Pre-operative		Post-operative		Population Norm	
Percentiles	**PCS**	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
25%	26.47	35.36	20.28	37.23	47.06	46.09
50%	32.68	48.56	35.42	45.96	53.20	53.24
75%	49.16	57.81	47.05	56.03	56.14	56.93
Mean (SD)	36.79 (11.97)	46.98 (10.72)	34.21 (15.69)	45.70 (10.63)		

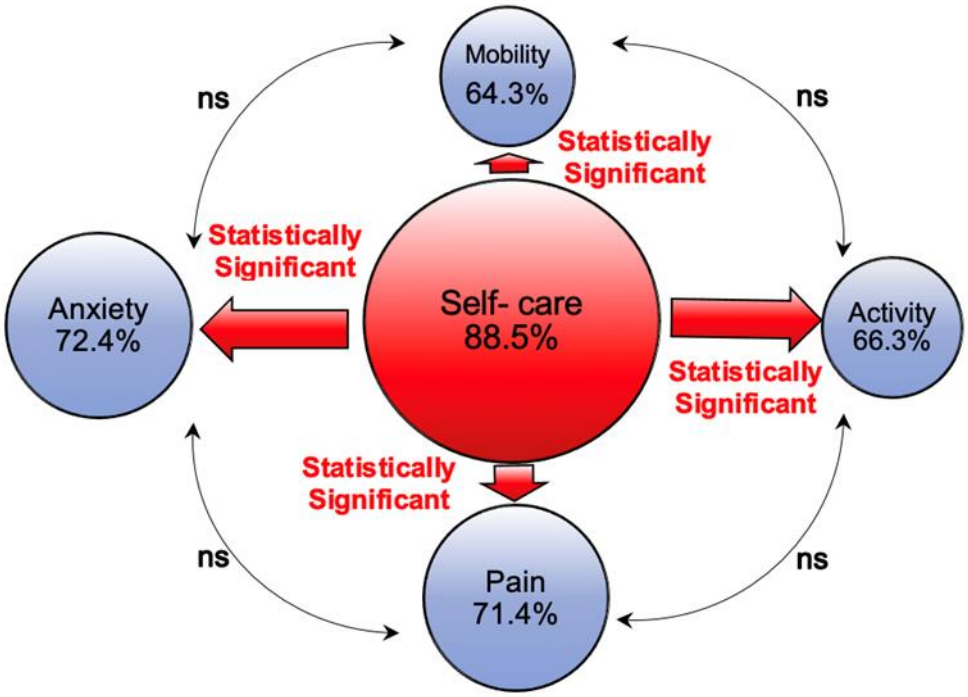
- **A4.20** SF-36, cross-sectional study: post-operative outcomes

	CROSS-SECTIONAL STUDY: SF-36®						
	Scale	**n**	**Mean**	**Median**	**SD**	**Distribution**	**Statistical Difference**
	Physical functioning						Mann-Whitney U
	Total	97	57.4	60	30.9	Not Normal	
	SPK/PAK/PASPK	82	58	60	30.2	Not Normal	MWU = 568.500
	PTA	15	54	65	35.1	Not Normal	p = .642 ns
	Role physical						Mann-Whitney U
	Total	97	42.8	25	43.4	Not Normal	
	SPK/PAK/PASPK	82	44.5	25	44.1	Not Normal	MWU = 521.000
	PTA	15	33.3	25	39.7	Not Normal	p = .323 ns
	Pain						Mann-Whitney U
	Total	96	61.9	66.3	28.1	Not Normal	
	SPK/PAK/PASPK	82	64.1	67.5	27.9	Normal	MWU = 400.500
	PTA	14	49.5	51.3	26.8	Not Normal	p = .070 ns
	General health						Mann-Whitney U
	Total	98	42.3	45	23.3	Normal	
	SPK/PAK/PASPK	83	42.7	45	22.7	Normal	MWU = 565.000
	PTA	15	39.6	35	26.9	Not Normal	p = .570 ns
	Emotional well-being						Mann-Whitney U
	Total	96	71.6	76	19.5	Not Normal	
	SPK/PAK/PASPK	82	71	76	20	Not Normal	MWU = 529.500
	PTA	14	75.1	80	16.4	Not Normal	p = .643 ns
	Role emotional						Mann-Whitney U
	Total	96	68.6	100	40.2	Not Normal	
	SPK/PAK/PASPK	81	65.6	100	41.5	Not Normal	MWU = 463.500
	PTA	15	84.4	100	27.8	Not Normal	p = .105 ns
	Social function						Mann-Whitney U
	Total	98	64.3	75	30.6	Not Normal	
	SPK/PAK/PASPK	83	65.7	75	30.4	Not Normal	MWU = 506.000
	PTA	15	56.7	75	31.3	Normal	p = .245 ns
	Energy/fatigue						Mann-Whitney U
	Total	96	45.03	50	25.1	Not Normal	
	SPK/PAK/PASPK	82	47.6	50	24.6	Not Normal	MWU = 344.500
	PTA	14	30	27.5	23.4	Normal	Z = -2.341 p = .019 Cohen's d = .494 ss
SUMMARY SCALES	**PCS**						Mann-Whitney U
	Total	**88**	**39.6**	**40.7**	**12.4**	Not Normal	
	SPK/PAK/PASPK	**75**	**40.5**	**42.1**	**12.1**	Not Normal	MWU = 365.000
	PTA	**13**	**34.4**	**33.7**	**13.2**	Normal	p = .150 ns
	MCS						Mann-Whitney U
	Total	**88**	**47.3**	**50.1**	**10.6**	Not Normal	
	SPK/PAK/PASPK	**75**	**46.9**	**49.3**	**10.8**	Not Normal	MWU = 393.000
	PTA	**13**	**49.9**	**52.7**	**9.7**	Not Normal	p = .266 ns

- **A4.21** EQ-5D-5L Dichotomised severity level distribution

LEVEL 1-2 DISTRIBUTION	
	Total Study Population
L1-2	40 (41%)
L 3-5	58 (59%)

- **A4.22** EQ-5D-5L: proportion of Level 1-2 distribution s across domains.



- **A4.23** EQ-5D-5L: Dichotomised severity level distribution for each domain for the totality of study participants

EQ-5D-5L Health States			
Dimensions	**Total N**	**Levels**	**Distribution**
Mobility	**98**	**L1 -L2**	63 (64.3%)
		L3-L4-L5	35 (35.7%)
		Missing	0
Self-care	**96**	**L1 -L2**	85 (88.5%)
		L3-L4-L5	11 (9.4%)
		Missing	2 (2.1%)
Usual Activities	**98**	**L1 -L2**	65 (66.3%)
		L3-L4-L5	33 (33.7%)
		Missing	0
Pain/ Discomfort	**98**	**L1 -L2**	70 (71.4%)
		L3-L4-L5	28 (28.6%)
		Missing	0
Anxiety/ Depression	**98**	**L1 -L2**	71 (72.4%)
		L3-L4-L5	27 (27.6%)
		Missing	0

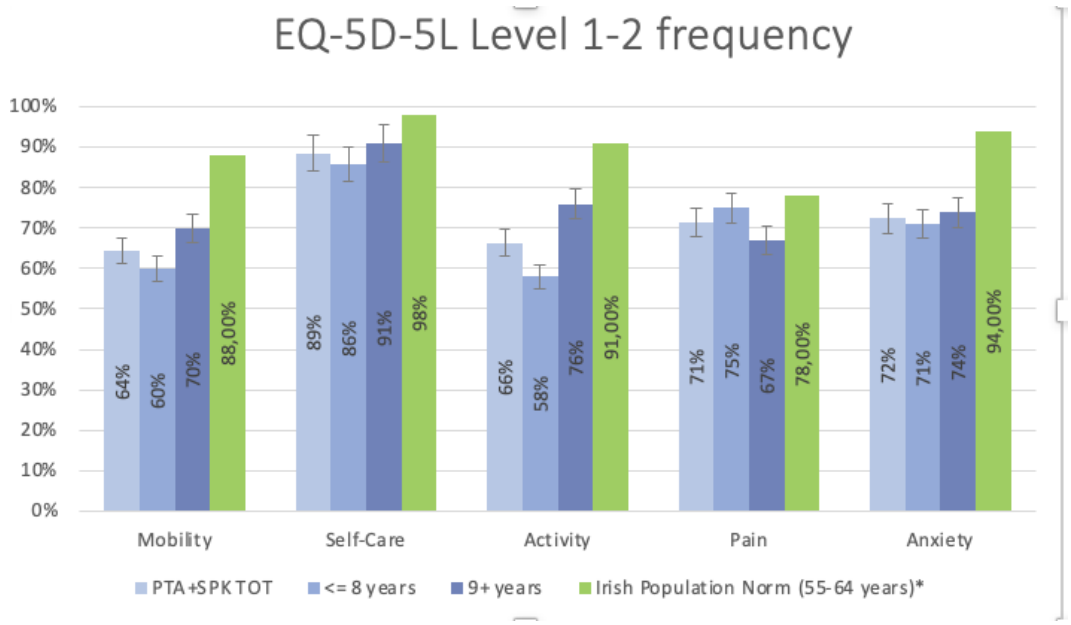
- **A4.24**EQ-5D-5L: Severity level distribution for each dimension, stratified by type of transplant.

	SPK, PAK, PASPK				PTA				
EQ-5D	**EQ -5L**	**N (%)**	**EQ-5L binary**	**N (%)**	**EQ -5L**	**N (%)**	**EQ-5L binary**	**N (%)**	**L1-2 SPK vs PTA**
Mobility	**L1**	32 (38.6%)	**L 1-2**	55 (66.3%)	**L1**	5 (33.3%)	**L 1-2**	8 (53.3%)	χ^2 = .406 P = .525 ns
	L2	23 (27.7%)			**L2**	3 (20%)			
	L3	20 (24.1%)	**L 3-5**	28 (33.7%)	**L3**	6 (40%)	**L 3-5**	7 (46.7%)	
	L4	2 (2.4%)			**L4**	1 (6.7%)			
	L5	0 (0%)			**L5**	0 (0%)			
Self-care	**L1**	56 (67.5%)	**L 1-2**	70 (84.4%)	**L1**	12 (80%)	**L 1-2**	15 (100%)	Fisher exact test = .2039 ns
	L2	14 (16.9%)			**L2**	3 (20%)			
	L3	9 (10.8%)	**L 3-5**	11 (13.2%)	**L3**	0 (0%)	**L 3-5**	0 (0%)	
	L4	2 (2.4%)			**L4**	0 (0%)			
	L5	0 (0%)			**L5**	0 (0%)			
(missing)	**?**	2 (2.4%)	?	2		0 (0%)			
Usual Activities	**L1**	35 (42.2%)	**L 1-2**	55 (66.3%)	**L1**	4 (26.7%)	**L 1-2**	10 (66.7%)	Fisher exact test = .1 ns
	L2	20 (24.1%)			**L2**	6 (40%)			
	L3	18 (21.7%)	**L 3-5**	28 (33.7%)	**L3**	2 (13.3%)	**L 3-5**	5 (33.3%)	
	L4	8 (9.6%)			**L4**	3 (20%)			
	L5	2 (2.4%)			**L5**	0 (0%)			
Pain	**L1**	28 (33.7%)	**L 1-2**	63 (75.9%)	**L1**	3 (20%)	**L 1-2**	7 (46.7%)	χ^2 = 3.985 P = .0459 ss
	L2	35 (42.2%)			**L2**	4 (26.7%)			
	L3	12 (14.5%)	**L 3-5**	20 (24.1%)	**L3**	5 (33.3%)	**L 3-5**	8 (43.3%)	
	L4	5 (6%)			**L4**	3 (20%)			
	L5	3 (3.6%)			**L5**	0 (0%)			
Anxiety-Depression	**L1**	40 (48.2%)	**L 1-2**	62 (74.7%)	**L1**	7 (46.7%)	**L 1-2**	9 (60%)	χ^2= .7373 P = .391 ns
	L2	22 (26.5%)			**L2**	2 (13.3%)			
	L3	17 (20.5%)	**L 3-5**	21 (25.3%)	**L3**	5 (33.3%)	**L 3-5**	6 (40%)	
	L4	3 (3.6%			**L4**	1 (6.7%)			
	L5	1 (1.2%)			**L5**	0 (0%)			

- **A4.25**. EQ-5D-5L: dichotomised severity level distribution, stratified by time from surgery.

LEVEL 1-2 DISTRIBUTION		
	< = 8 years from surgery	**9 + years from surgery 46**
	Total Study Population	Total Study Population
L1-2	18	22
L 3-5	34	24
Comparison	$\chi^2 = 1.26$ p = .262 ns	

- **A4.26** EQ-5D-5L: Level 1-2 distributions across domains: comparison between total outcomes and Irish population norms, stratified by time from surgery.



- **A4.27**EQ-5D-5L, Dichotomised severity level distribution: comparison across transplant cohorts, stratified by time from surgery.

LEVEL 1-2 DISTRIBUTION				
	< = 8 years from surgery 52		9 + years from surgery 46	
	SPK/PAK/PASPK	PTA	SPK/PAK/PASPK	PTA
L1-2	17	1	19	3
L 3-5	29	5	18	6
Comparison	Fisher Exact Test = .651 ns		Fisher Exact Test = .464 ns	

- **A4.28** EQ-5D-5L, Dichotomised severity level distribution: comparison within transplant cohorts, stratified by time from surgery.

LEVEL 1-2 DISTRIBUTION				
	SPK/PAK/PASPK (83)		PTA (15)	
	<8 years	9+ years	<8 years	9+ years
L1-2	17	19	1	3
L 3-5	29	18	5	6
	χ^2 = 1.19 p = .275 ns		Fisher Exact Test = .464 ns	

- **A4.29** EQ-5D-5L: Proportion of total participants reporting level 1-2 and difference with aged matched Irish normative data.

TOTAL PARTICIPANTS: LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 55-64*	**88.4%**	**97.8%**	**91.2%**	**78.1%**	**94%**
Total Study Sample	64.3%	88.5%	66.3%	71.4%	72.4%
Statistical Significance	p < .00001	p < .00001	p < .00001	p = .279	p < .00001

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

- **A4.30**. Distribution of level 1-2 across EQ-5D-5L domains: comparison between study outcomes and Irish population norms, stratified by age.

	STUDY POPULATION	IRISH NORMATIVE DATA*				
EQ-5D-5L DOMAINS	**(Mean age 57 years)**	35-44	45-54	55-64	65-74	75+
Mobility	**64.3%**	96.4%	93%	88.4% p < .0001	80.1% p = .008	**74.4% p = .178**
Self-Care	**88.5%**	100%	98.2%	97.8% p < .0001	96.1% p = .037	97.7% p = .014
Activity	**66.3%**	96.8%	93.4%	91.2% p < .0001	85.2% p = .0007	**74.5% p = .291**
Pain	**71.4%**	90.1%	79.1%	**78% p = .279**	72.4%	72.2%
Anxiety/Depression	**72.4%**	91.9%	89.5%	94% p < .0001	93.6% p < .0001	92.2% p = .0009

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

- **A4.31** EQ-5D-5L: Proportion of SPK/PAK/PASPK recipients reporting level 1-2 and difference with aged matched Irish normative data.

SPK/PAK/PASPK: LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 55-64*	**88.4%**	**97.8%**	**91.2%**	**78.1%**	**94%**
SPK/PAK/PASPK	64.3%	88.5%	66.3%	71.4%	72.4%
Statistical Significance	p < .000034	p < .0013	p < .000034	p = .822	p < .00001

* ***Data extrapolated from*** Hobbins A et al. HRB Open Res 2018

- **A4.32** EQ-5D-5L: Proportion of PTA recipients reporting level 1-2 and difference with aged matched Irish normative data.

PTA: LEVEL 1-2 FREQUENCY (%)					
	Mobility	Self-Care	Activity	Pain	Anxiety/Depression
Irish Norm age 45-54*	**93%**	**98.2%**	**93.4%**	**79.1%**	**89.5 %**
PTA	53.3%	100%	66.7%	46.7%	60%
Statistical Significance	p < .00001	p = 1	p = .0039	p = .0101	p = .0030

***** *Data extrapolated from* **Hobbins** A et al. HRB Open Res 2018

- **A4.33** EQ-VAS results stratified by type of transplant.

CROSS-SECTIONAL STUDY: POST-OPERATIVE EQ-VAS						
Scale	**n**	**Mean**	**Median**	**Stan. Dev.**	**Distribution**	**Comparison**
EQ-VAS						Mann-Whitney U Test
Total	97	67.7	72	21.2	Not Normal	
SPK/PAK/PASPK	82	68.7	75	21.3	Not Normal	MWU = 507.500 p = .282 ns
PTA	15	62.3	63	20.4	Normal	

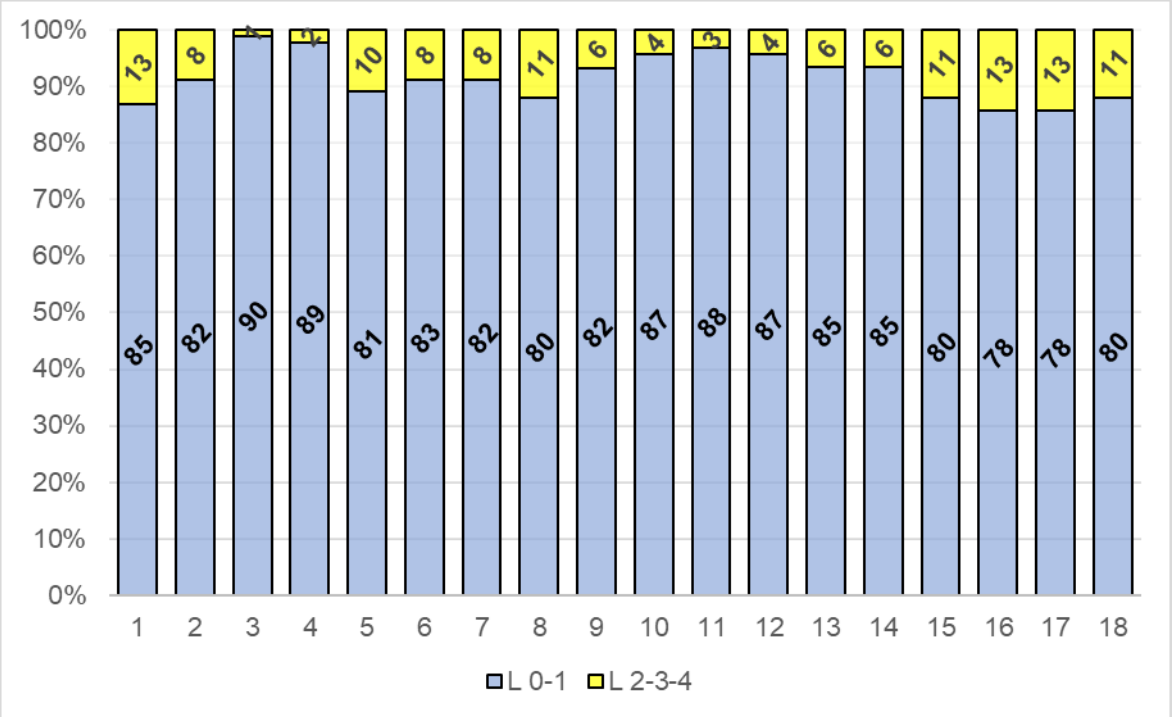
- **A4.34** EQ-index results stratified by type of transplant.

CROSS-SECTIONAL STUDY: POST-OPERATIVE EQ-Index						
EQ-Index	**n**	**Mean**	**Median**	**Stan. Dev.**	**Distribution**	Mann-Whitney U Test
Total	96	0.675	0.689	0.258	Not Normal	
SPK/PAK/PASPK	81	0.684	0.707	0.259	Not Normal	MWU = 485.000 p = .216 ns
PTA	15	0.629	0.641	0.253	Normal	

- **A4.35** HFS-II W results stratified by type of transplant.

CROSS-SECTIONAL STUDY: POST-OPERATIVE HFS-II Worry						
Scale	**n**	**Mean**	**Median**	**Stan. Dev.**	**Distribution**	**Comparison**
HSF-II Worry						Mann-Whitney U Test
Total	96	12.1	4	14.7	Not Normal	
SPK/PAK/PASPK	81	10.8	3	14.1	Not Normal	MWU = 426.000 p = .063 ns
PTA	15	19.1	26	16.1	Not Normal	

- **A4.36** HFS-II Worry: Hypoglycaemia Worry concerns, stratified by dichotomised frequency levels: “Never-Rarely” (L 0-1), “Sometimes-Often-Almost Always” (L 2-3-4)



- **A4.37** HFS-II W: Ranking of worries based on frequency.

	HFS-II WORRY		
	Item	**Level 0-1**	**Levels 2-3-4**
1	Passing out in public	99%	1%
2	Embarrassing myself or my friends in a social occasion	98%	3%
3	Getting a bad evaluation or being criticised	97%	3%
4	Making a mistake or having an accident	96%	4%
5	Difficult thinking clearly when responsible for others	96%	4%
6	Feeling lightheaded or dizzy	93%	7%
7	Accidentally injuring myself or others	93%	7%
8	Having a hypo while driving	93%	7%
9	Appearing stupid or drunk	91%	9%
10	Not having food, fruit, or juice available	91%	9%
11	Losing control	91%	9%
12	Having a hypo while alone	89%	11%
13	No one being around to help me during a hypo	88%	12%
14	Permanent injury or damage to my health or body	88%	12%
15	Getting emotionally upset and difficult to deal with	88%	12%
16	Not recognising/realising I was having low blood glucose	87%	13%
17	Low blood glucose interfering with important things I was doing	86%	14%
18	Becoming hypoglycaemic during sleep	86%	14%

- **A4.38** Predictors of long-term PCS

PREDICTORS OF LONG-TERM PCS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Work status at transplantation	7.89	Direct		.008
Creatinine at 5 years, binary: 1) <119 umol/L, 2) 120+ umol/L	-8.42	Inverse		.005
Constant	40.02			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.487	.238	8.566	2,55	< .001

- **A4.39** Predictors of long-term MCS

PREDICTORS OF LONG TERM MCS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Type of dialysis at transplantation	6.99	Direct		.024
Constant	36.62			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.332	.110	5.451	1,44	.024

- **A4.40** Predictors of EQ-VAS

PREDICTORS OF LONG-TERM EQ-VAS				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Claudication	-19.28	Inverse		.018
Pancreas exocrine drainage, binary: 1) bladder 2) enteric	15.42	Direct		.009
Constant	59.93			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.332	.110	5.815	2,94	< .001

- **A4.41** Predictors of long-term EQ-index

PREDICTORS OF LONG-TERM EQ-Index				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Working status	.198	Direct		.001
Creatinine at 5 years, binary: 1) <119 umol/L, 2) 120+ umol/L	-.131	Inverse		.029
Constant	.566			< .001
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.479	.229	8.764	2,59	< .001

- **A4.42** Predictors of long term HFS-II W Summary Score

PREDICTORS OF LONG TERM HFS-II Summary Score				
Predictor	**Unstandardised coefficient B**	**Direction of relationship**		**Sig.**
Hypoglycaemia unawareness at transplantation	10.65	Inverse		< .001
Cardiovascular/cerebrovascular disease	11.26	Direct		.029
Constant	-15.20			.033
MODEL OF BEST FIT				
R	**R^2**	**F**	**(df)**	**Sig**
.412	.170	9.390	2,92	< .001

- **A4.43** Pre-Transplant clinical factors: differences between the Prospective Longitudinal Study (Chapter 3) and the Cross-sectional study (Chapter 4)

PRE-OPERATIVE FACTORS					
Independent Variables	Participants with available data N (%)	Descriptive Statistics			Difference
Gender		F		M	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	29		31	χ^2= 0.991, p= 0.32 NS
Cross-sectional study	83 (100%)	32 38.55%		51 61.45%	
Ethnicity		Caucasian		B.A.M.E.	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	34	6		χ^2= 0.081, p= 0.78 NS
Cross-sectional study	83 (100%)	77 92.77%		6 7.23%	
BMI	N	Mean	Median	SD	Independent T-Test
Prospective Longitudinal Study	60 (100%)	25.43	25.3	3.71	p = .420 NS
Cross-sectional study	83 (100%)	25.96	26.2	3.90	
Age at diagnosis	N	Mean	Median	SD	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	15.65	15	9.49	p = 0.60 NS
Cross-sectional study	83 (100%)	14.92	13	9.7	
Age at transplantation (yrs.)	N	Mean	Median	SD	Independent T-Test
Prospective Longitudinal Study	60 (100%)	43.33	43	8.99	t (124.6) = - 2.95 p=0.013 Cohen's d = -.426 Statistically Significant
Cross-sectional study	83 (100%)	47.08	48	8.68	
Cigarette Smoke (N)		History of Smoking		Never Smoker	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	29		31	χ^2= 2.07, p= 0.15 NS
Cross-sectional study	83 (100%)	29 34.94		54 65.06	
Alcohol (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	55	29		26	χ^2= 0.267, p= 0.60 NS
Cross-sectional study	73	43 51.81%		30 36.14%	
Duration of WL (days)	N	Mean	Median	SD	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	472.52	495.5	245.75	p = 0.36 NS
Cross-sectional study	83 (100%)	476.98	423	408.22	
Type of Transplant	N (%)	PAK/PAS PK		SPK	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	5	55		F = 1 NS
Cross-sectional study	83 (100%)	8	75		
Previous Tx		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	7		53	χ^2= 0.007, p= 0.98 NS
Cross-sectional study	83 (100%)	11 13.25%		72 86.75%	

Working Status (N)		**Unemployed**		**Full-time/ Housework/ Student**	**Chi-Square Test With Yates Correction**
SPK, PAK, PaSPK	60 (100%)	26		34	χ^2= 0.108, p= 0.74 NS
PTA	82 (98.8%)	39 46.98%		43 51.80%	
Daily insulin requirement (UI)	N	Mean	Median	SD	Mann-Whitney U Test
SPK, PAK, PaSPK	60 (100%)	42.48	40	17.57	p = 0.39 NS
PTA	83 (100%)	46.61	40	23.20	
Duration of IDDM (years)	N	Mean	Median	SD	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	27.9	27	9.92	MWU = 1863.500 W= 3693.500 Z= -2.565 P = 0 .010 Statistically Significant
Cross-sectional study	83 (100%)	32.33	31	9.24	
End stage renal failure at transplantation(N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	55		5	χ^2= 2.941, p= 0.86 NS
Cross-sectional study	83 (100%)	75 90.36%		8 9.64%	
SPK: Pre-emptive transplantation		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	55 (100%)	12		43	χ^2= 1.174, p= 0.28 NS
Cross-sectional study	75 (100%)	24 32%		51 68%	
Type of Renal Replacement Therapy (N)		HD		PD	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	43 (100%)	29		14	χ^2= 3.156, p= 0.76 NS
Cross-sectional study	51 (100%)	24		27	
SPK: RRT duration (days)	N	Mean	Median	SD	Mann-Whitney U
Prospective Longitudinal Study	42 (97.7%)	617.6	567.00	350.96	p = 0.27 NS
Cross-sectional study	51 (100%)	623.8	505	559.1	
Preserved Urinary Output (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	58 (96.7%)	52		6	χ^2= 0.020, p= 0.89 NS
Cross-sectional study	82 (98.8%)	72 86.75%		10 12.05%	
HLA sensitization (N)	N*	Mean	Median	SD	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	32.4	28.5	29.25	MWU = 1422.000 W= 4272.000 Z= -3.747 P < 0.001 Statistically Significant
Cross-sectional study	75 (90.4%)	17.85	1	27.93	
Hypoglycaemia Unawareness (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60	20		40	χ^2= 0.0005, p= 0.98 NS
Cross-sectional study	82 (98.8%)	26 31.33%		56 67.27%	

- **A4.44** Transplant and post-Transplant factors: differences between the Prospective Longitudinal Study (Chapter 3) and the Cross-sectional study (Chapter 4)

TRANSPLANT AND POST-TRANSPLANT FACTORS					
Independent Variables	Participants N (%)	Descriptive Statistics			Difference
Pancreas Exocrine Drainage	N (%)	Bladder		Enteric	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	1		59	Fisher = 0.40 NS
Cross-sectional study	83 (100%)	4		79	
Peri-operative transfusions		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	46		14	χ^2= 0.052, p= 0.82 NS
Cross-sectional study	83 (100%)	37		9	
CT/MRI after surgery*	N*	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	42		18	χ^2= 0.017, p= 0.90 NS
Cross-sectional study	76 (91.5%)	54		26	
Abnormal CT findings	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	42 (100%)	31		11	χ^2= 1.190, p= 0.28 NS
Cross-sectional study	54 (100%)	33		21	
CT findings: Pancreatitis	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	41 (97.6%)	8		33	χ^2= 0.079, p= 0.78 NS
Cross-sectional study	54 (100%)	13		41	
CT findings: Pancreas Venous Thrombosis	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	40 (95.2%)	13		27	χ^2= 0.609, p= 0.44 NS
Cross-sectional study	54 (100%)	23		31	
CT findings: Pancreas Thrombosis Severity	N	Complete		Partial	Fisher Exact Test
SPK, PAK, PaSPK	13 (100%)	2		11	Fisher = 1 NS
PTA	23 (100%)	3		20	
CT findings: Collections	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	40 (95.2%)	16		24	χ^2= 0.567, p= 0.45 NS
Cross-sectional study	54 (100%)	27		27	
CT findings: Kidney Perfusion Defects	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	41 (97.6%)	8		33	χ^2= 0.108, p= 0.74 NS
Cross-sectional study	54 (100%)	8		46	
CT findings: Bowel Complications	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	42 (100%)	2		40	Fisher = 0.459 NS
Cross-sectional study	54 (100%)	6		48	
Post-Operative Complications	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	40		20	χ^2= 0.076, p= 0.78 NS
Cross-sectional study	81 (97.6%)	51		30	
Medical Complications	N	Yes		No	Chi-Square Test With Yates Correction
SPK, PAK, PaSPK	60 (100%)	26		34	χ^2= 0.015, p= 0.90 NS
PTA	80 (96.4%)	35		45	

Cardio/cerebro-vascular events (N)		**Yes**		**No**	**Chi-Square Test With Yates Correction**
Prospective Longitudinal Study	60 (100%)	54		6	χ^2= 0.0007, p= 0.98 NS
Cross-sectional study	83 (100%)	7 8.43%		76 91.57%	
Cardiac procedures (N)		Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	5		55	Fisher = 1 NS
Cross-sectional study	83 (100%)	4 4.82%		79 95.18%	
Hypertension (N)		Yes		No	Fisher Exact Test
SPK, PAK, PaSPK	60 (100%)	56		4	Fisher = 1 NS
PTA	83 (100%)	77 92.77%		6 7.23%	
Retinopathy (N)		Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	53		7	Fisher = 0.202 NS
Cross-sectional study	83 (100%)	79 95.18%		4 4.82%	
Registered blind (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	7		53	χ^2= 0.037, p= 0.85 NS
Cross-sectional study	83 (100%)	10 12.05%		73 87.95%	
Neuropathy (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	33		27	χ^2= 2.222, p= 0.14 NS
Cross-sectional study	83 (100%)	53 63.86%		30 36.14%	
Gastro-intestinal symptoms (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	24		36	χ^2= 0.553, p= 0.46 NS
Cross-sectional study	83 (100%)	27 32.53%		56 67.47%	
Amputations (N)		Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	9		51	χ^2= 0.234, p= 0.63 NS
Cross-sectional study	83 (100%)	9 10.84%		74 89.16%	
Claudication (N)		Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	4		55	Fisher = 1 NS
Cross-sectional study	83 (100%)	6 7.23%		77 92.77%	
Diabetes chronic complications (N)		1-2		3+	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	18		42	χ^2= 2.159, p= 0.14 NS
Cross-sectional study	83 (100%)	15		68	

Surgical Complications	**N**	**Yes**		**No**	**Chi-Square Test With Yates Correction**
Prospective Longitudinal Study	60 (100%)	27		33	χ^2= 0.062, p= 0.80 NS
Cross-sectional study	82 (98.8%)	34		48	
Return to theatre	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	60 (100%)	16		44	χ^2= 0.098, p= 0.32 NS
Cross-sectional study	82 (98.8%)	15		67	
Pancreatic Primary Function	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	58 (96.7%)	57		1	Fisher = 1 NS
Cross-sectional study	83 (100%)	75		8	
Renal Primary Function	N	Yes		No	Chi-Square Test With Yates Correction
Prospective Longitudinal Study	55 (100%)	41		14	χ^2= 0.817, p= 0.37 NS
Cross-sectional study	75 (100%)	61		14	
Graft Pancreatectomy	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	3		57	Fisher = 0.695 NS
Cross-sectional study	83 (100%)	3		80	
Duration of ITU admission* (days)	N*	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	1.88	1.00	2.26	p = 0.30 NS
Cross-sectional study	67 (80%)	1.8	2.00	1.4	
Duration of Hospital Stay (days)	N	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	60 (100%)	20.42	11.5	32.85	MWU = 1953.500 W= 3783.500 Z= -2.199 P = 0.028 Statistically Significant
Cross-sectional study	83 (100%)	17.2	14.0	9.2	
Insulin Independent at discharge	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	56		4	Fisher = 1 NS
Cross-sectional study	83 (100%)	77		6	
Dialysis-Free at discharge	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	58		2	Fisher = 0.174 NS
Cross-sectional study	83 (100%)	83		0	
Haemoglobin levels at discharge (g/L)	N	Mean	Median	Standard Deviation	Independent T-Test
Prospective Longitudinal Study	60 (100%)	85.7	85.5	11.2	t (141) = - 2.69 p=0.008 Cohen's d = -.456 Statistically Significant
Cross-sectional study	83 (100%)	90.7	90.0	11.8	
2 h Glucose Tolerance Test at discharge*	N	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	47 (78.3%)	7.52	7.30	2.69	p = 0.72 NS *Calculated on patients insulin independent at discharge
Cross-sectional study	58 (69.9%)	7.52	7.4	2.4	

Creatinine at discharge (patients dialysis-free at discharge) * (umol/L)	**N***	**Mean**	**Median**	**Standard Deviation**	**Mann-Whitney U Test**
Prospective Longitudinal Study	53 (81%)	162	120	135.2	p = 0.35 NS *Calculated on patients dialysis-free at discharge
Cross-sectional study	83 (100%)	139.9	107	93.5	
Patients who reached 1 Yr. from transplant		Yes		No	Fisher Exact Test
Prospective Longitudinal Study	60 (100%)	55		5	Fisher = 0.28 NS
Cross-sectional study	83 (100%)	80		3	
Insulin Independent at 1 Year	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	57 (68.7%)	50 (91%)			Fisher = 0.093 NS *Calculated on patients who reached 1 yr. follow-up
Cross-sectional study	79 (98.8)	40 (95%)		3	
Dialysis-Free at 1 Year	N	Yes		No	Fisher Exact Test
Prospective Longitudinal Study	51 (92.7%)	50		1	Fisher = 1 NS *Calculated on patients who reached 1 yr. follow-up
Cross-sectional study	79 (98.8%)	79		0	
Haemoglobin levels at 1 Year *(g/L)	N*	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	25 (45.5%)	129	127	18.3	p = 0.43 NS *Calculated on patients who reached 1 yr. follow-up
Cross-sectional study	58 (72.5%)	129	131.5	28.7	
HbA1c at 1 Year* (mmol/mol) *	N*	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	22 (40%)	35.5	33	11.2	p = 0.25 NS *Calculated on insulin-independent patients who reached 1 yr. follow-up
Cross-sectional study	60 (75%)	35.7	34.5	8.0	
Creatinine at 1 Year* (umol/L)	N*	Mean	Median	Standard Deviation	Mann-Whitney U Test
Prospective Longitudinal Study	44 (80%)	112	102.5	45	p = 0.18 NS *Calculated on dialysis-free patients who reached 1 yr. follow-up
Cross-sectional study	76 (91.6%)	119.8	114.5	37.7	
***Unreliable comparison due to statistically significant discrepancies in proportion of data available**					

- **A4.45** Pre- transplant PCS and MCS results stratified by study.

Pre-Transplant PCS								
	N	Mean	Median	SD	Distribution	t-test	Degrees of freedom	p
Prospective Longitudinal Study	44	31.82	30.03	9.74	Normal	t = .284	22	0.78 NS
Cross-sectional study	20	36.8	35.59	10.80	Normal			
Pre-Transplant MCS								
	N	Mean	Median	SD	Distribution	t-test	Degrees of freedom	p
Prospective Longitudinal Study	44	41.41	39.63	12.34	Normal	t = .681	22	0.55 NS
Cross-sectional study	20	47.12	49.6	10.88	Normal			

- **A4.46** Post-transplant SF-36 PCS and MCS results, stratified by study.

POST-TRANSPLANT HRQOL OUTCOMES								
	Time from transplant	Mean	Median	SD	Distribution	Mann Whitney U Test	Z	p
PCS								
Prospective Longitudinal Study	1 year	41.90	43.72	11.42	Not Normal	MWU= 1121.000	-.538	0.59 NS
Cross-Sectional Study	8.5 years	40.49	42.09	12.07	Not Normal			
MCS								
Prospective Longitudinal Study	1 year	47.6	42.63	13.77	Not Normal	MWU = 1069.000	-.891	0.37 NS
Cross-Sectional Study	8.5 years	46.86	49.33	10.76	Not Normal			

- **A4.47** Post-transplant EQ-VAS and EQ-index results, stratified by study.

POST-TRANSPLANT HRQOL OUTCOMES								
	Time from transplant	Mean	Median	SD	Distribution	Mann Whitney U Test	Z	p
EQ-VAS								
Prospective Longitudinal Study	1 Year	72.03	75	22.15	Not Normal	MWU = 1390.500	-.947	0.34 NS
Cross-Sectional Study	8.5 years	68.74	75	21.31	Not Normal			
EQ-index								
Prospective Longitudinal Study	1 year	.615	.713	.724	Not Normal	MWU = 1536.500	-.238	0.81 NS
Cross-Sectional Study	8.5 years	.684	.707	.259	Not Normal			

- **A4.48** Post-transplant EQ severity level distribution, stratified by study.

EQ-Levels Distribution							
	Time from transplant	L 1-2	%	L 3-5	%	Chi-Square Test With Yates Correction	p
Prospective Longitudinal Study	1 year	16	(41%)	23	(59%)	χ^2= 0.036,	p= 0.85 NS
Cross-Sectional Study	8.5 years	34	(41%)	49	(59%)		

- **A4.49** Predictors of early and long-term HRQOL

HRQOL PREDICTORS							
PCS		**MCS**		**EQ-VAS**		**EQ-INDEX**	
Prospective longitudinal Study (1 Yr.)	**Cross-Sectional Study (8.5 Yrs.)**	**Prospective longitudinal Study (1 Yr.)**	**Cross-Sectional Study (8.5 Yrs.)**	**Prospective longitudinal Study (1 Yr.)**	**Cross-Sectional Study (8.5 Yrs.)**	**Prospective longitudinal Study (1 Yr.)**	**Cross-Sectional Study (8.5 Yrs.)**
Pre-operative HRQOL predictors							
Gender	Work Status at transplant	Psychiatric Disorders	Type Of Dialysis at Transplant	Psychiatric Disorders	Claudication	Psychotropic Medications	Work Status at transplant
Preserved Urinary Output		Retinopathy		Age			
Number Of Chronic Complications		Registered Blind					
Transplant-related predictors							
					Pancreatic Exocrine Drainage	Glucose tolerance test at discharge	
	Creatinine at 5 Yrs.					Creatinine at 6 Weeks	Creatinine at 5 Yrs.