

# Developing and Understanding the Use of Patient Reported Outcomes in Advanced Renal Disease.

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## **Publications**

### **Peer-reviewed Paper**

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Pittman Z, John S, McIntyre C. Daily Patient Reported Outcome Reporting Is Practical And Demonstrates Differential Patient Experience In CKD: Use Of A

Novel Dynamic Pro. Paper Presented At: British Renal Society, 2013; Manchester.

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## List of abbreviations

|        |                                                                       |
|--------|-----------------------------------------------------------------------|
| APD:   | Automated Peritoneal Dialysis                                         |
| AVF:   | Arteriovenous Fistula                                                 |
| BDI:   | Beck Depression Inventory                                             |
| BMI:   | Body Mass Index                                                       |
| Ca:    | Serum Levels Of Calcium                                               |
| CAPD:  | Continuous Ambulatory Peritoneal Dialysis                             |
| Cids:  | Clinically Important Differences                                      |
| CRP:   | C Reactive Protein                                                    |
| CV:    | Cardiovascular                                                        |
| CVC:   | Central Venous Catheter                                               |
| DOPPS: | The Dialysis Outcomes And Practice Patterns Study                     |
| DTI:   | Dialysis Thirst Inventory                                             |
| EQ 5D: | European Quality Of Life Instrument                                   |
| Esas:  | Erythropoietin Stimulating Agents                                     |
| ESRD:  | End Stage Renal Disease                                               |
| ESS:   | Epworth Sleepiness Scale                                              |
| FSS:   | Fatigue Severity Scale                                                |
| GFR:   | Glomerular Filtration Rate, eGFR Estimated Glomerular Filtration Rate |
| GP:    | General Practice                                                      |
| GWB:   | General Well Being used in Derby Evaluation of Illness Website        |

|         |                                                                   |
|---------|-------------------------------------------------------------------|
| HADS:   | Hospital Anxiety and Depression Scale                             |
| Hb:     | Haemoglobin                                                       |
| HD:     | Haemodialysis                                                     |
| HDF:    | Hemodiafiltration                                                 |
| HPL:    | Human Population Laboratory                                       |
| HSI:    | Health Status Index                                               |
| HUI:    | Health Utilities Index                                            |
| IDWG:   | Inter Dialytic Weight Gain                                        |
| IW:     | % Importance Weights For Outcome Preferences                      |
| KDCS:   | Kidney Disease Component Summery                                  |
| Mcids:  | Minimal Clinically Important Differences                          |
| MCS:    | Mental Component Scale, Derived from SF 12 or SF 36               |
| MDRD:   | Modification of Diet in Renal Disease                             |
| MHLC:   | Multidimensional Health Locus of Control                          |
| MOS:    | Medical Outcomes Study                                            |
| MTSOSD: | Modified Transplant Symptom Occurrence and Symptom Distress Scale |
| N-C:    | Necessity Minus Concerns Score for BMQ                            |
| NHS:    | National Health Service                                           |
| NICE:   | National Institute Of Health And Care Excellence                  |
| PCS:    | Physical Component Scale, Derived from SF 12 or SF 36             |
| PD:     | Peritoneal Dialysis                                               |
| PHQ 9:  | Patient Health Questionnaire                                      |

|                   |                                    |
|-------------------|------------------------------------|
| PO <sup>4</sup> : | Serum Phosphate                    |
| POS:              | Palliative Care Outcome Scale      |
| PSQI:             | Pittsburgh Sleep Quality Index     |
| PTH:              | Parathyroid Hormone                |
| QALY's:           | Quality-Adjusted Life Years        |
| QLI D:            | Quality of Life Index Dialysis     |
| QOL:              | Quality Of Life                    |
| QWB:              | Quality Of Wellbeing Questionnaire |
| QWB-SA:           | Quality Of Wellbeing               |
| RCT:              | Randomised Controlled Trial        |
| RRT:              | Renal Replacement Therapy          |
| SD:               | Standard Deviation                 |
| SF 36:            | Short Form 36                      |
| SIP:              | Sickness Impact Profile            |
| SSL:              | Social Support List                |
| TDS:              | Thirst Distress Scale              |
| Tx:               | Kidney Transplant                  |
| UK:               | United Kingdom                     |
| VAS:              | Visual Analogue Scale              |
| WHOQOL-BREF:      | World Health Organisation - Brief  |

## Abstract

### *Introduction*

The number of patients receiving treatment for advanced chronic kidney disease (CKD) is increasing worldwide. Current treatments are imperfect and impose a number of restrictions on daily life, both physical and psychosocial. The psychosocial burdens of advanced CKD have been explored to varying degrees with the effects on quality of life and symptoms most extensively documented in cross sectional data. There are no data on changing symptoms over relatively short time periods or the factors that affect an individual patient's interaction with the disease and its treatments.

This thesis set out to explore the health related quality of life (HRQOL), symptom burden, the factors associated with understanding/decision making and the focus for outcome preferences in a cohort of patients with advanced CKD receiving a variety of different treatments. This was achieved with the use of a questionnaire-based study called the "Influence of illness beliefs and treatment outcome preferences in patients with end stage renal disease" (INTUITIVE) study. In addition I explored the specific question of frequent collection of symptom related data, with the design and implementation of a web based symptom scoring system.

### *Methods*

The INTUITIVE study recruited 58 individuals from prevalent dialysis, transplant and pre dialysis populations in a single renal unit. The study

comprised a number of patient reported outcome questionnaires that covered the areas of health related quality of life HRQOL, symptom and treatment burdens, impact on daily life and screening for depression. In addition questionnaires that explored individual's perceptions of their illness, beliefs about aspects of treatment and their outcome preferences were completed. All participants were asked to complete all relevant sections and a subset were asked to complete the questionnaires again after one year. For the frequent symptom tracking we designed and implemented a web based system for frequent tracking of symptoms (general well being (GWB), pain, sleep, breathing, energy and appetite) on a visual analogue scale. Participants from dialysis and pre dialysis populations were asked to complete the online form daily. Outcomes of interest were uptake, response rates, inter-modality variation and change in symptoms corresponding to predefined events.

## *Results*

I have shown that HRQOL is dependant to a large degree on the number and burden of symptoms but also on the burden of specific symptoms in particular restless legs, shortness of breath, tiredness, dry mouth and itching. Individuals in the pre dialysis setting had more symptoms than transplant recipients and attributed more of their symptoms to kidney disease than the other groups. People on haemodialysis (HD) attributed more symptoms to the dialysis than those on peritoneal dialysis (PD) In addition, participants had a complex psychological understanding through which they were able to interpret and make sense of their kidney disease and its treatments. Individuals on peritoneal dialysis had a greater feeling of personal control over their kidney disease and older individuals perceive less negative consequences from the condition. Stronger beliefs around the necessity of prescribed medicines were seen in the transplant (Tx) population and in dialysis patients who had lower serum phosphate. Individuals not on dialysis had a much stronger preference for survival than those on dialysis and all were prepared to trade improvements in survival or symptoms against increases in treatment burden. The results from the web-based system showed that we successfully introduced an online, patient acceptable, iterative patient reported outcome measure that discriminates symptom burden, cross-sectionally and longitudinally.

## *Discussion*

I have been able to demonstrate that poor HRQOL is related to symptom burden in advanced CKD and to identify the symptoms that are of most relevance. At the same time I have developed a methodology for frequent symptom tracking that is able to detect changes associated with relevant clinical events. I have been able to demonstrate that individuals are able to choose between symptoms, survival and symptom burden and that this balancing can be quantified in a meaningful way. In addition I have shown that treatment beliefs about necessity relate to behaviour and this has suggested further avenues for investigation in future work. Future work will focus on the use of these tools to inform interventions aimed at improving outcomes including HRQOL.

## Chapter 1. Introduction

Chronic Kidney Disease (CKD) is increasingly recognised as a public health concern and burden worldwide. There are now several large-scale population studies that try to address the question of prevalence. The prevalence of CKD in these studies varies between 7 and 40% depending on the population studied and the method of assessment <sup>2-8</sup>. An assessment in 2009 in the UK put the prevalence of CKD 1 -5 at 14% for males and 13% for females <sup>9</sup>.

### The consequences of CKD, an Overview

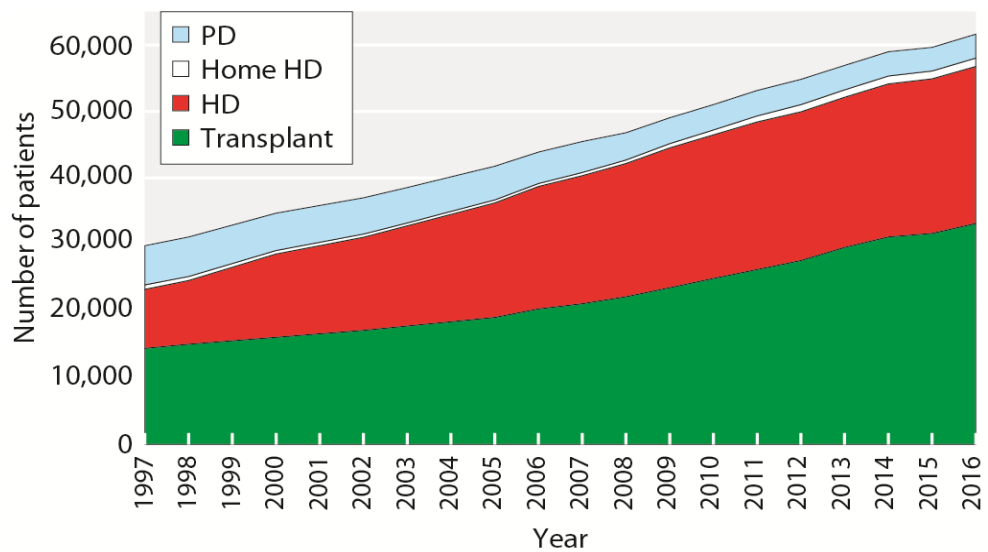
Although the focus of this thesis is on patient reported outcomes in advanced CKD an understanding of the physical health problems and burden of treatment and disease is important in order to understand these outcomes in context.

### Disease Burden

The prevalence of advanced CKD is increasing worldwide, **Figure 1** shows the increasing prevalence in RRT patients in the UK.

Accurate figures for the financial cost of CKD in the UK are challenging to find, but in 2002 the cost of treating people with end stage renal disease (ESRD) was estimated to account for around 2% of the NHS budget despite only affecting 0.05% of the population<sup>10</sup>

**Figure 1** Growth in prevalent UK patients by treatment modality at the end of each year 1997–2016<sup>1</sup>

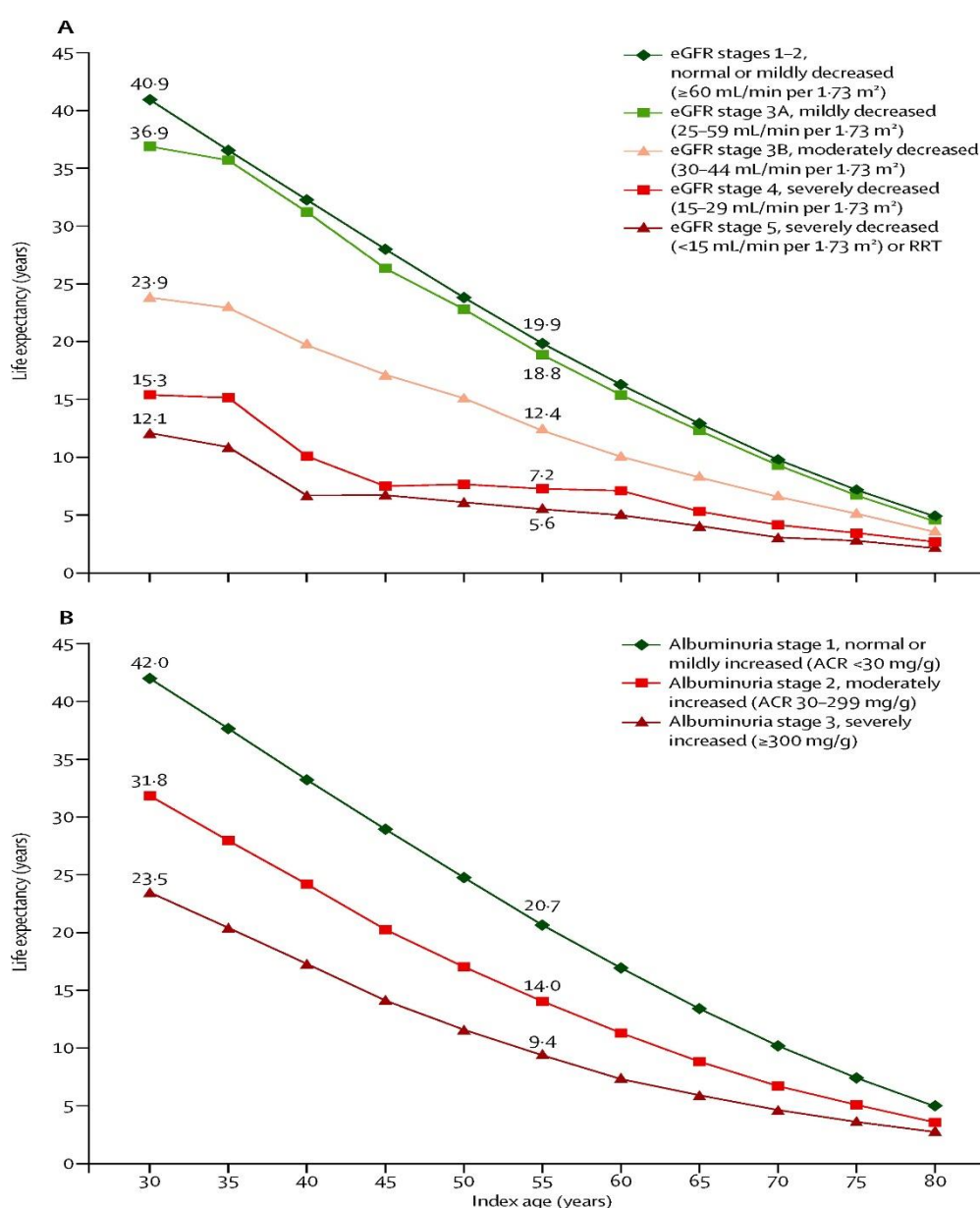


More recently an attempt has been made to model the cost of CKD to the NHS which suggested a figure of approximately £1.44 to £1.45 billion for 2009-2010. This represented ~1.3% of all NHS spending , with half spent on renal replacement therapy (RRT) which accounted for just 2% of the CKD population <sup>11</sup>. Subsequent modelling of the cost of excess strokes and MIs attributable to CKD produced an estimate of an additional £174–£178 million <sup>11</sup>.

There is an increased risk of progression of CKD with increasing albuminuria and with decreasing GFR, thus it is important that those at risk of progression are followed up and monitored appropriately. However, the main risk associated with the presence of early stage CKD is not progression of CKD to ESRD but increased morbidity and mortality **Figure 2**. demonstrates the decreasing life expectancy with both falling GFR and

increasing albuminuria, the majority of this increased risk is markedly increased rates of cardiovascular (CV) death<sup>12</sup>.

**Figure 2** Life expectancy, according to chronic kidney disease stages  
(Canadian Patient data)

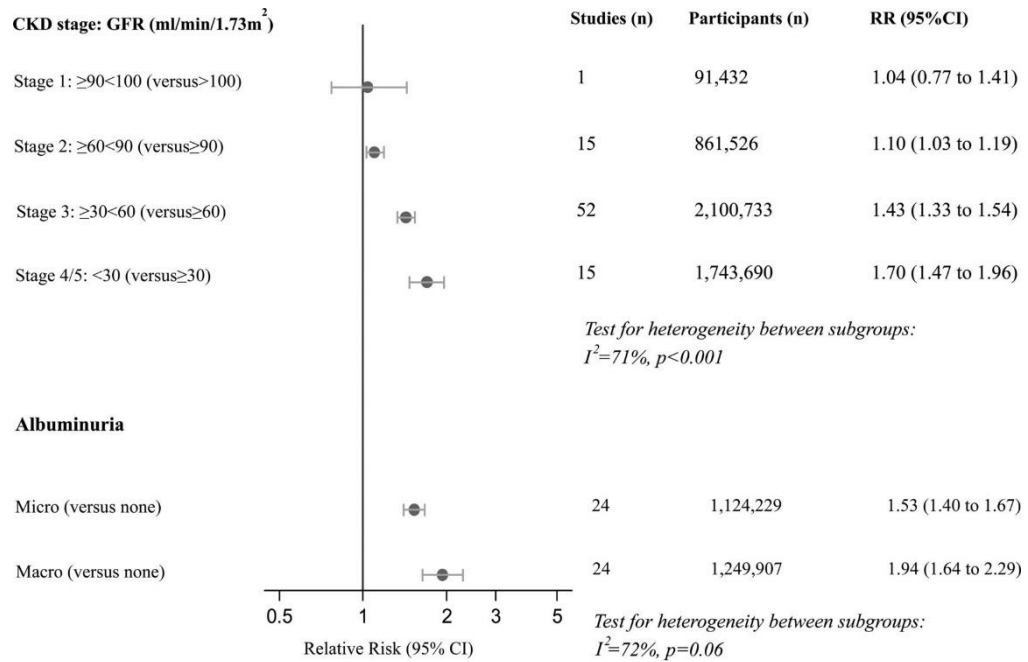


(A) eGFR stages and (B) albuminuria stages. Data are adjusted per eGFR and albuminuria stage for sex to the WHO world average in 2000–05. eGFR = estimated glomerular filtration rate. RRT=renal replacement therapy.<sup>12</sup>

Many studies over the past twenty years have confirmed the link between the presence of CKD and CV events including death. Increased incidence of events as diverse as arrhythmia, sudden cardiac death, heart failure, stroke, atherosclerosis (including myocardial infarction) and venous thromboembolism have all been reported to be independently associated with the presence of CKD <sup>13-18</sup>. In addition, the risk of death or further complications associated with interventions (such as coronary angioplasty and or coronary artery bypass grafting, insertion of implantable cardiac defibrillators) for these conditions is also increased <sup>19-22</sup>. It was shown in a meta-analysis of 2,253,741 participants examining stroke risk in CKD vs non CKD populations, that decreasing GFR or increasing albuminuria was associated with an increasing risk of all cause stroke Figure 3 <sup>23</sup>.

Similar patterns are seen with all the other CV events above. People diagnosed with CKD 3 are more likely to die from a CV event than to progress to ESRD, but those that do progress are likely to have amassed a significant CV risk profile <sup>24-26</sup>

**Figure 3** Relative Risk of stroke with decreasing eGFR and rising proteinuria <sup>23</sup>

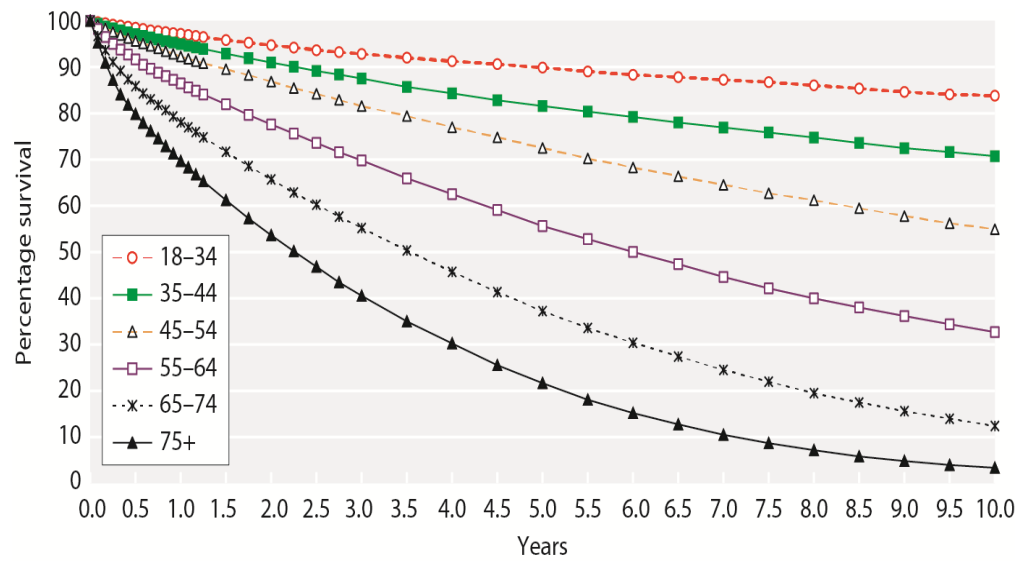


RR: Relative risk; GFR: glomerular filtration rate; CI: confidence interval

Advanced CKD is associated with increased all-cause mortality, **Figure 4** shows the survival data for incident renal replacement therapy (RRT) patients in the UK broken down by age <sup>1</sup>. This mortality is notable for markedly elevated CV deaths <sup>14, 27</sup>.

There is also a large increase in CV and all cause morbidity. Although many of the risk factors are the same across treatment stage and modality there are important differences.

**Figure 4** Survival of UK incident RRT patients (unadjusted), 1997–2015 cohort (from day 0) <sup>1</sup>



Individuals with advanced CKD have already potentially accumulated a number of classical CV risk factors such as hyperlipidaemia, hypertension, smoking, obesity, diabetes and increasing age. Indeed, some individuals will already have had one or more CV events prior to developing CKD 4/5. Attempts to mitigate this increased risk in dialysis populations, via the application of conventional therapies for CV disease prevention (smoking cessation, statins, weight loss, antiplatelet agents), have been largely ineffective as the pathogenesis appears quite different to the general population who develop conventional atherosclerotic ischemic heart disease

28.

In addition to these CV risk factors they are likely to have accumulated a number of other non-classical risk factors via one or more of the following.

### *Structural Cardiovascular Disease*

There are several structural and functional changes to the arterial tree that are observed in CKD. Although many patients may have “classical” atherosclerotic disease, patients with CKD also demonstrate a number of morphologically distinct changes. CKD stage is associated with the presence and degree of arterial wall thickening, vascular calcification, arterial stiffening and endothelial dysfunction<sup>29-33</sup>. These factors predispose to the development of hypertension and a failure of autonomic regulation of blood pressure.

Historically, echocardiography studies during the 1990s showed the high prevalence of structural cardiac abnormalities in patients starting dialysis and this has been confirmed in further multiple studies<sup>34, 35</sup>. There is a high incidence of heart failure in advanced CKD with both systolic and diastolic dysfunction seen; in addition there is a higher incidence of valvular dysfunction and conduction defects<sup>36, 37</sup>.

The two biggest causes of CV death in HD patients are cardiac arrhythmias and cardiac failure, with evidence suggesting that HD-driven cardiac injury is critical in the pathogenesis of both<sup>38-40</sup>. The exact mechanisms behind the increased CV deaths are still to be elucidated, however new approaches to dialytic therapies may go some way to improving survival but potentially at the price of increased treatment burden<sup>41</sup>.

In addition to these direct CV effects there is growing evidence of other organ involvement such as cognitive impairments and psychological morbidity<sup>42-44</sup>.

### *Haematological*

Many patients develop anaemia with advancing CKD and there are now a variety of medications available to help mitigate this. However initial optimism was dampened when clinical trials showed that returning haemoglobin levels to “normal” physiological values was associated with increased mortality in some studies and increased risk of stroke in others<sup>45-47</sup>. Alongside anaemia, patients with advanced CKD often have both an increased risk of thromboembolic events but also an increased bleeding tendency. This is due in part to uraemia interfering with normal platelet functioning.

### *Endocrine and Mineral Bone Disease*

As CKD progresses there is increasing dysregulation of the system that regulates bone metabolism and homeostasis. This results in abnormal serum levels of Calcium (Ca), Phosphate ( $\text{PO}^4$ ) parathyroid hormone (PTH) and vitamin D. These result in altered bone mineralisation, with ectopic mineralisation especially in the vasculature. As a consequence it is often necessary to both regulate dietary intake and take medications aimed at controlling these levels with the aim of reducing long term complications. Sexual dysfunction is common in advanced CKD in both sexes. It is

multifactorial but related in part to dysfunction of the hypothalamic-pituitary-gonadal axis. There is also an increased prevalence of hypothyroidism and other hormonal imbalances.

### *Malnutrition and inflammation*

Malnutrition is common in advanced CKD and is a consequence of several interrelated factors. As CKD progresses appetite is often reduced at the same time as tablet burden is increasing and a variety of dietary and fluid restrictions are introduced. In addition alterations in bowel flora, hormonal dysregulation and metabolic acidosis impact on nutrient utilisation and energy requirements predominantly via activation of inflammatory pathways and an imbalance in hormonal response in favour of a catabolic state<sup>48-50</sup>.

### *Treatment effects (including immunosuppressant's) \_*

There are many different diseases that lead to the development of CKD and many of these have specific treatments and treatment side effects. Specifically, diseases due to alterations in the immune system will often be treated by immunosuppressant drugs. The desired outcome in this situation is to halt progression of CKD but these drugs can have long lasting effects on health. Depending on the specifics of the underlying disease and the exact drug and formulation used, they can lead to weight gain and/or the development of diabetes; they can increase the incidence of certain cancers (especially skin but also bladder) and increase the risk of serious infection.

Also, some have an effect on fertility or can have unpleasant gastrointestinal side effects.

### *Existing co-morbidity*

People are living longer with other co-morbidities, thus more people are reaching ESRD with these other pre-existing co-morbidities. The commonest cause of ESRD in the UK is diabetes and this is often associated with multiple effects on other organ systems such as the eyes and peripheral nerves.

## **Treatment Burden**

### *Treatment approaches for advanced CKD – an overview*

There are a limited number of treatment options available for patients with advanced CKD. The aim of nephrology services, aside from preventing and/or slowing CKD progression, is to prepare patients approaching the potential need for RRT so that they are able to make a planned and managed start on their chosen modality. Patients are required to make choices at this time that potentially impact on every aspect of their future life, although by necessity the options are interchangeable.

### *Generic Approach*

All patients are offered medical management of the complications of advanced CKD relating to mineral metabolism, electrolyte disturbance, fluid balance and anaemia. These treatments often involve changes to lifestyle, and in particular dietary and fluid intake restriction, in addition to oral

medications and potentially injected therapies. Due to the nature of the treatments and disease many of these patients are required to attend frequent outpatient appointments. Many patients also have multiple other co morbidities, such as diabetes or underlying CV disease, which require additional specialist input. In addition, patients must also be prepared for appropriate RRT.

### *Haemodialysis*

Haemodialysis is a high cost but life-prolonging therapy which is unfortunately currently associated with a five year survival significantly worse than many common malignant conditions (breast, prostate and colorectal cancer) at about 40% <sup>51-54</sup>.

For the majority of patients starting RRT in the UK the initial and often only modality is HD. In order to have HD, patients require access to the vascular system, ideally via an arteriovenous fistula (AVF). This involves several steps over a period of months, including an operation, to make the AVF and time for it to mature ready for use. Unfortunately, for a large proportion of patients, more than one attempt or subsequent intervention is required to achieve a usable AVF. Once a patient has an AVF it also needs to be monitored and maintained to ensure ongoing patency, if subsequently lost further procedures will be required. In the absence of a viable definitive access (AVF or AV graft) there is an option for vascular access via a central venous catheter (CVC), however it is uncommon that this is a suitable long

term option as the use of a CVC is associated with increased risk of death, serious infection and CV events<sup>55</sup>.

The standard HD treatment currently requires patients to attend hospital three times a week for four hours each session. In addition to this there is travel and setup time. In reality for many especially older patients, an HD session can involve most of a day three times a week. During the session they are attached to the HD machine and a prescribed amount of fluid is removed along with the removal of “uremic toxins”. Common symptoms on HD include feeling dizzy (often attributed to low blood pressure), leg cramps, nausea and general discomfort from sitting still. Some will recover very rapidly after an HD session, while for others recovery (“back to normal”) can be measured in many hours.

The majority of conventional HD sessions are delivered in dedicated HD units but there are an increasing number of patients who are able to deliver the treatment themselves at home, which gives much more flexibility and independence. One approach to mitigating some of the problems associated with conventional HD and the way it is delivered has been to look at varying the intensity and or timing of HD sessions, either more frequent but shorter sessions (5\*3 hours per week) or longer sessions such as overnight at various frequencies. For some patients this can be achieved in unit but the majority of patients on these modified regimes in the UK are home HD patients.

### *Peritoneal dialysis*

Peritoneal dialysis requires the placement of a tube through the abdominal wall into the abdominal cavity. This is usually undertaken as a day-case procedure, either performed by physicians or surgeons. Once healed this is then used for the exchange of dialysis fluid as per the hospital prescription. Typically this is a treatment that patients and/or their carers are taught to do independently at home and involves four exchanges of fluid per day each taking about half an hour (continuous ambulatory peritoneal dialysis (CAPD)). Patients need to be scrupulous in their hygiene in order to reduce the risk of infection. An alternative regime involves being connected to a machine that will automatically perform around 10 exchanges throughout the night (automated peritoneal dialysis (APD)). Such connections may be made by the patient, their carers or by a visiting specialist nurse.

Individuals on PD will often report a number of symptoms related to their treatment regime, ranging from abdominal pain and or bloating to bowel disturbance and the worsening or development of hernias.

Patients on PD also have an elevated CV death rate but there is also an increased risk of death due to infection<sup>56</sup>. Traditionally PD has been offered to a younger (and fitter) cohort of patients but in recent years it has been offered as a supported therapy for patients for whom conventional PD would not be possible.

## *Transplant*

For those who are suitable, on a population level renal transplantation gives the best outcome in terms of long-term survival and lower comorbidity. In order to be considered for renal transplantation there are a set of criteria that need to be met including CV assessments, absence of cancer, fitness for anaesthetic, surgical and anatomical suitability and psychological suitability. Patients either then require an available living matched donor (often a relative) or must wait on a list for a deceased donor. For those on the deceased donor list in the UK there is a points system in operation, this system takes many donor and recipient factors into account when allocating kidneys in an attempt to optimise benefit. Due to the need for genetic compatibility and differences in attitudes to organ donation, patients from ethnic minorities will often wait longer for a suitable donor

Patients listed for transplantation are by definition “fitter” than those not listed, however there is still a persisting elevation in CV risk. Patients are required to take lifelong medication to prevent rejection of the transplanted kidney. There is an increased risk of malignancy, especially skin cancers which are associated with immunosuppressant therapy. Immunosuppression also leads to an increased susceptibility to some types of infection and a proportion of patients will develop diabetes after renal transplantation.

### *Conservative Care*

There are a cohort of patients who actively choose not to receive RRT, often this is influenced by age and existing comorbidity and frailty alongside patient choice. They will still be offered medical therapy as outlined above and can in some instances live for many months or more with extremely diminished kidney function<sup>57-60</sup>.

### *Financial costs of CKD*

In addition to the costs of treatment bourn by the state there are significant financial and social costs to the individual and their wider family when someone develops advanced CKD. Many find it difficult to work due to a number of factors including poor overall health and the burdens of treatment.

## **Burden**

The factors discussed above all contribute to a high disease and treatment burden in advanced CKD. Patients on dialysis, or with advanced (but not receiving RRT) CKD, face a significant number of restrictions in daily life, alongside the physical and time requirements of any dialysis treatments (for example 4 hours plus travelling time, three days a week for HD; or fluid exchanges 4 times every day for PD). They are also required to adhere to strict fluid and dietary restrictions. ESRD and its management are associated with a wide variety of symptoms such as lethargy, itching, pain<sup>61</sup> and treatment-related adverse effects, including dizziness on HD and bloating or

gastrointestinal disturbance on PD. In addition, dialysis patients are expected to take a median of 19 tablets a day<sup>62</sup>, which can militate strongly against nutrition and challenge fluid restrictions. The above factors combine to sap patients' confidence and interfere with activity, exercise and social engagement. The remainder of this thesis will seek to discuss and explore these effects.

### **Patient reported outcome Measures**

Many of the tools used to explore the concepts discussed in the remainder of this thesis will broadly fall into the category of patient reported outcome measures (PROMs), these offer a means of measuring outcomes that can only be assessed by the patients themselves. There are many PROMs available to the clinician, measuring a range of outcomes with reference to the individual's perceptions of their functional status, wellbeing and/or experience. The defining feature that all PROMs share is that they are intended for completion by the patient; most comprise of one or more questions where response is obtained either using the Likert or Visual Analogue (VAS) scales. A Likert scale consists of a series of statements with fixed point responses (typically 5 or 7) around a centrally sometimes neutral option. The VAS is a line with descriptive phrases "anchors" at each end describing the extremes of response, typically the line is 100mm long and can be either horizontal or vertical. The respondent then places a mark

along the line corresponding to their current state between these two anchors<sup>51, 63</sup>.

PROM's have been developed and utilised in a variety of different clinical and research contexts<sup>64</sup>. PROMs can be generic or disease specific and measure a variety of constructs such as health-related quality of life (HRQOL), functional status, health utilities, or disease specific symptoms. PROMs have been used in clinical trials as either the primary or secondary endpoint for many years and are now increasingly used as a measure of effectiveness<sup>65</sup>. Recently, national bodies have mandated collection of PROMs in several settings to assess the quality of care provided at facility level. In 2008 the Centres for Medicare and Medicaid Services adopted a set of clinical performance measures to assess the quality of dialysis care in the United States, including a requirement for regular measurement of HRQOL<sup>66</sup>. Since 2009 it has been mandatory within the UK to collect PROMs data pre- and post- elective hip and knee replacements, inguinal hernia repair and varicose vein surgery<sup>67</sup>.

Many of these psychosocial factors and their assessments overlap and their division into separate categories is somewhat artificial, however these categories serve as useful headings from which to start an exploration.

## Validation

Many PROMS have been validated in both general and or specific populations. This is a complex and often time consuming process that aims to ensure that the PROM is measuring what it is intended to measure and that there is internal consistency and test retest reliability. If a PROM is translated into another language and or used in a different condition, then it should undergo another round of validation in that new population. The PROMS described in this chapter have all undergone a validation process in relevant English speaking populations.

## Health Related Quality of Life

Health-related quality of life (HRQOL) is a concept used to describe a comprehensive picture of how a person's health affects their overall well-being. There is no universally accepted definition although formal measurement of HRQOL can be traced back to about 45 years ago and it has been an expanding field ever since. Since its very inception there have been two parallel purposes to recording HRQOL. The first was as a measure of outcome for an individual patient and the second, and more commonly reported, to document and record outcomes at a service level either for the purposes of research or audit.

Regardless of the specific method or design of the HRQOL assessment tool the individual responses to the items in each questionnaire are usually returned using either the Likert scale (or a variation of) or on a visual

analogue scale. In addition, there may be some questions in a HRQOL assessment that require true/false or yes/no answers.

Many groups have compared the use of individual VAS and Likert scales in a variety of different conditions (symptoms). Davey et al. compared the VAS and Likert scales to a more robust assessment of anxiety and found comparable results from both, although there were significant numbers of individuals that didn't complete the VAS correctly in this study <sup>68</sup>. The responses however may be different depending on the scale used as found by Brunier and Graydon when comparing fatigue in HD patients using both scales <sup>69</sup>. Guyatt et al. compared the methods for assessing change in function over time and again found them to have comparable sensitivity. Although the VAS had greater variability in improvement, the overall differences were not dissimilar between methods <sup>70</sup>. This is perhaps not surprising as the VAS is inherently more variable (100 possible outcomes compared to 20-30 for a typical Likert).

By convention all HRQOL instruments are reported such that a higher score signifies better QOL. There are many different questionnaires that can be used to assess HRQOL but broadly speaking there are two different methodologies for reporting the outputs, either preference based or health profiles (generic or disease specific). These are based on two very different approaches to measuring health. Preference based methods yield a single aggregate score (typically between 0 – 1) for health status known as a

health utility. They are particularly useful in the field of health economics and have the advantage that they are often quick to complete. Health profile methods combine a number of health concepts and are intended to be applicable across populations, disease specific methods are designed for specific populations (often although not always defined by a disease entity). Health profile methods are often focused on areas that are likely to be amenable to treatment or that change with the natural history of the disease, they are therefore more useful at the individual patient level. They return individual values for each component of HRQOL covered within the questionnaire, with some questionnaires these can then be combined into composite scores covering broader areas (such as physical or mental health). However they require a little more time to complete and analyse.

Preference based methods are derived from decision and utility theories and aim to derive a single measure of health utility (typically 0 = dead to 1 = perfect health). One of the precursors of preference based tools was the health status index (HSI) <sup>71</sup>. This was an attempt to mathematically model the impact of disease on activities of daily living based around the concept of function/dysfunction. There are a variety of methods of assigning a preference weight to a specific disease state. Techniques such as standard gamble (SG) and time trade off (TTO) require a patient to compare survival in their current health state with decreasing survival times in a potential state of perfect health, and in the process assign a value to their current

health; however they can be difficult to administer and are not widely used outside specific research settings. The most commonly reported and used preference based HRQOL methods, utilise large population databases to assign a utility score to an individual's health status which has been derived from a multidimensional HRQOL questionnaire.

One of the main uses of preference-based methods is that health utilities can be used to produce Quality-Adjusted Life Years (QALY's). Probably the best known is the EQ 5D QALY's have become a standard measure of HRQOL in medical cost-effectiveness research over the past 30 years and are used by a variety of institutions including the national institute of health and care excellence (NICE) in the UK when making recommendations on new and existing treatments.

Health profile methods can be thought of as psychometric measures and are derived from classical measurement theory with a focus on validity, reliability and sensitivity to change of each health dimension, the most widely used of these is probably the Short Form 36 (SF 36). They comprise multi-item scales for each domain which are then combined to give a health profile.

The development of Generic health profile instruments can be traced back to the late 1960s when a group in California were working in the human population laboratory (HPL) and over a number of years published a number

of papers using the HPL to demonstrate the relationships between self-reported health and outcomes such as depression and mortality<sup>72, 73</sup>. The use of disease specific methods can be traced back further to the 1940 – 50s when tools for arthritis and stroke were being developed<sup>74</sup>.

The first tools developed were often very long and cumbersome and there was therefore a drive in the mid-1980s to develop short form versions in order to facilitate data collection and analysis (and reduce costs). This led to the development of many of the tools that are still in use today.

In 2017 Aiyegbusi et al published a systematic reviews of the measurement properties of HRQOL instruments in nephrology<sup>75</sup>. This gives a detailed summary of the instruments currently being used in Nephrology research. There have also been a number of systematic reviews of the literature with regards to specific PROM outputs such as HRQOL and where relevant these have been referenced in the remainder of this chapter.

### *Available Generic instruments*

There have been a very large number of generic health profile and preference based HRQOL tools developed or trialled over the years. The main ones in use today are the SF 36, SF 20, SF 12, Quality of Wellbeing (QWB-SA) and the Sickness impact profile (SIP) which are all health profile measures and the EQ 5D, Health utilities index (HUI) and SF 6D which are commonly used preference based measures.

## Short Form

In the mid 1980-90s the Medical Outcomes Study group developed a family of short form (SF) QOL measures.

### *SF 36*

Probably the most widely used of the short form versions is the SF 36, it was originally developed in the late 1980s and a revised version 2 was released in 1996 which remains in use <sup>76-79</sup>. It is reported to take around 10 minutes to complete and comprises 36 questions across 8 concepts of functional health and wellbeing (Physical functioning; Physical role i.e. role limitations caused by physical problems; Pain; General Health; Vitality; Social Functioning; Emotional Role i.e. role limitations caused by emotional problems; mental health). In addition, it has two overarching summary measures of physical and mental health (Physical component scale (PCS) and the Mental component scale (MCS)). The PCS and MCS can be reported independently and in many published papers are the only HRQOL outcomes reported from the SF 36.

There are two versions with differing recall periods of either 4 weeks or one week and it has been translated into and validated in over 170 languages <sup>80</sup>. There are large databases of general population norms against which a study population can be assessed and the MCS and PCS are standardised so that 50 represents the population norm with a standard deviation (SD) of 10.

### *Other Short Form Versions*

Despite the popularity of the SF 36 and its relative ease of application there was still a need for a QOL measure that could be delivered more quickly, thus the SF 20 and SF 12 were developed<sup>81</sup>. They are based around the same constructs and questions as the SF 36 but with fewer questions. They trade depth of information provided for speed and ease of application, however for large population studies they are felt to provide good resolution and detect change over time. The SF 12 was developed directly from the SF 36 by regression analysis to select those questions that accounted for 90% of the variability in key components and returns both the PCS and MCS as per the SF 36. The SF 20 used the same original data set from which the SF 36 was derived but contains 6 overall health concepts instead of the 8 of SF 36; it does not return summary scores.

In addition to the above SF versions that all produce a health profile, the SF 6D is derived from answers to either the SF 36 or the SF 12 and will transform the health profile into a preference-based health utility measure that can be used for calculating QALY's. This is not a stand-alone tool but a method for gaining additional useful outputs from the original SF 36 or SF 12 data<sup>82, 83</sup>.

The SF 36 and SF 12 have also been used as the basis of kidney disease specific measures, the KDQOL-SF and the KDQOL-36 respectively (see page 32 for further discussion).

The SF 36 is probably the most widely used and reported generic health profile QOL instrument in any field and also in renal disease. A simple database search returns over 1300 articles relating to “renal” and SF 36 since 1992. It therefore has the advantage that there is a large volume of data that can be accessed to compare against different groups, not just the “normal” population results but other disease states that might be considered to have similar disease burden. It has the disadvantage of not covering a large number of factors that impact specifically on patients with advanced CKD and so may not be as sensitive to small changes in QOL in this group<sup>84</sup>.

#### Quality of Wellbeing self-assessment (QWB-SA)

This was developed before the SF 6D in response to a perceived need for a QOL measure that could be used to calculate QALY's. It was derived from the much longer quality of wellbeing questionnaire (QWB) in order that it could be used for self-completion<sup>85</sup>. It contains 81 items and reports a single health utility outcome value of between 0= dead and 1= perfect health.

#### EUROQOL EQ 5D

In May 1987 a group that later became known as the EUROQOL group met for the first time to try and develop a “standardised non disease specific instrument for describing and valuing health related quality of life ..... should facilitate the collection of a common data set for reference

purposes”<sup>86</sup>. The team subsequently developed the EQ 5D, this consists of 5 questions from which the respondent is required to pick the most appropriate statement of three possible answers, there is an additional question recording self-rated health on a VAS. The responses are combined to give an overall health utility (0= dead and 1= perfect health).

This is probably the most widely used preference based HRQOL instrument and has the advantage that it is very quick to complete and score. It has been validated in many languages and is readily available.

#### Health Utilities Index (HUI)

The HUI is another preference-based method; the original HUI was developed to look at HRQOL following premature birth. Subsequent iterations HUI 2 and HUI 3 were developed with the general population in mind. They contain different domains with HUI 2 having a domain relating to fertility, self-care and emotions; in general the developers recommend that HUI 3 is used first line with HUI 2 giving additional information<sup>87, 88</sup>. They take about 10 minutes to complete but need additional processing to get the health utility score.

#### Sickness Impact Profile (SIP)

This contains 136 questions in 12 areas of activity and takes about 30 minutes to complete<sup>89</sup>. The focus of the SIP is on activities of daily living and the impact of disease on the ability to perform these.

## Others

There are many other generic instruments in circulation that may have specific applications. The choice of instrument depends on many factors including the need to compare the results to a general or specific population and the use to which the data is to be put.

The World Health Organisation quality of life project began in 1991 with the stated aim of developing an international cross-culturally comparable QOL questionnaire. Like many QOL instruments it has been revised and a shortened instrument comprising 26 items across four domains (physical health, social relationships, psychological health and environment) is now available called the WHOQOL-BREF<sup>90</sup>.

The 15D is not widely used but was designed to be used either as a health profile or preference based questionnaire. It comprises 15 items and is therefore relatively quick to complete<sup>91</sup>.

## *Available CKD Disease Specific Instruments*

There are several renal specific HRQOL tools that have been developed. These include the KDQOL series of questionnaires discussed above that are based around the SF series (KDQOL-LF, KDQOL-SF and the KDQOL 36). Others include the Quality of life index Dialysis, Kidney disease Questionnaire, Renal quality of life profile, the CHOICE Health experience

Questionnaire and IPOS Renal. The majority of these are actually treatment specific rather than kidney disease specific.

#### KDQOL series

The KDQOL series of questionnaires was developed by the RAND Corporation in collaboration with the Kidney Disease Quality of Life working group beginning in 1994. The original version was the KDQOL-LF which contained 134 items based around the SF 36 with specific items added to address issues of concern relevant to patients with kidney disease <sup>92</sup>.

Subsequent to this there was a desire for a shorter version, thus the KDQOL-SF was developed which still has the SF 36 as its core but with a reduced number of additional items to a total of 80 questions <sup>93, 94</sup>. The 12 kidney disease domains are Symptoms; effects of kidney disease; burden of kidney disease; work status; cognitive function; social interaction; sexual function; sleep; social support; dialysis staff encouragement; overall health and Patient satisfaction.

The KDQOL was further refined in 2002 to produce the 36 item KDQOL-36 which has the SF 12 as its core and a pared down set of items from the older versions but still covering the same broad themes <sup>93</sup>.

Of note is that all the KDQOL series were initially designed and validated for use in patients receiving dialysis, the KDQOL-SF has subsequently been used and validated in patients who have a renal Tx <sup>95</sup>. The KDQOL-SF has been

mandated by the Centre for Medicare services for annual assessment of QOL in RRT patients in the USA since 2008.

The results of all the KDQOL series are reported as per either the SF 36 or SF 12 along with the additional Kidney Disease Component Summary (KDCS). It is also possible to report the 12 individual kidney disease components separately. Scores range from 0 to 100 for each dimension and a higher score indicates better HRQOL.

#### Quality of life index Dialysis (QLI D)

The QLI D is based around a common core (the QLI) with added questions of relevance to dialysis patients; it measures a combination of satisfaction and importance relating to various aspects of life. The importance ratings are used to weight the satisfaction responses, so that the scores reflect satisfaction with aspects of life that are valued by the individual. It contains 34 items across four domains (health and functioning, psychological/spiritual domain, social and economic domain, and family) and produces a score for each and an overall value<sup>96</sup>.

#### Kidney disease Questionnaire

Developed in the early 1990s in Canada by Andreas Laupacis and the Canadian Erythropoietin Study Group, this was a HD specific assessment of HRQOL that contains 26 questions divided across five dimensions (fatigue, physical symptoms, relationships with others, depression, and frustration).

Importantly for this questionnaire the physical symptoms section is specific to the patient and is then reused in subsequent applications of the questionnaire to that individual, thus it is specifically designed for longitudinal use<sup>97,98</sup>.

#### Kidney transplant Questionnaire

This was also developed by Andreas Laupacis along similar methods and contains 25 items across 5 domains<sup>99</sup>.

#### Renal quality of life profile

This was developed for use in all patients with ESRD and contains 43 items across 5 domains<sup>100</sup>. It takes about 10 minutes to complete and gives an overall score for HRQOL but no individual breakdown.

#### CHOICE Health experience Questionnaire

This was developed as part of the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease ([ESRD] CHOICE) study and was designed to evaluate the effectiveness of alternative dialysis prescriptions and used changes in HRQOL as an outcome. At its core is the SF 36 with additional dialysis specific domains and the final version of this questionnaire contained 83 items over 21 domains<sup>101</sup>.

#### IPOS Renal

Developed from the palliative care outcomes scale, this short scale contains 11 questions, it covers symptoms, information needs, practical issues and

family anxiety. It is intended for repeated use over time although can be used as a measure at a single time point.

### *Selecting an Instrument*

The selection of a HRQOL instrument will depend on many factors. In some instances the decision is made at a policy level to use a specific instrument such as in the USA with dialysis units being mandated to use the KDQOL 36 annually <sup>66</sup>. Centres participating in The Dialysis Outcomes and Practice Patterns Study DOPPS all administer the KDQOL-SF <sup>102</sup>.

Table 1 lists the various QOL instruments discussed above summarising some of the features that might be factors in choosing a specific instrument for an individual purpose.

The balance in choosing an instrument is between time (for both the patients and clinicians) and cost versus depth of information as well as considering the availability of local expertise. The EQ 5D is a good measure if the requirement is for a health utility outcome for use in calculating QALY's with no other data required. The HUI will also give the same results but takes a little longer to complete and analyse.

**Table 1 Summary of HRQOL instruments discussed**

| Instrument name                        | Target group | Number of questions/<br>time to complete | Health profile (HP) or Preference based (PB) | Other comments                                                                                                                                                       |
|----------------------------------------|--------------|------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Choice health experience questionnaire | Dialysis     | 83                                       | HP                                           | Core is the SF 36 with additional dialysis specific domains. Dialysis specific measure, however not widely used and time consuming                                   |
| EQ 5D                                  | Generic      | 5 (+1)                                   | PB                                           | Very common in clinical practice and research. Suffers from floor and ceiling effects in chronic disease. Widely available and quick. In many languages              |
| Health Utilities Index (HUI)           | Generic      | 10 minutes                               | PB                                           | Initially developed for use in fertility and premature birth. Different versions depending on area of interest. Requires additional processing to get the hui output |
| IPOS Renal                             | Renal        | 11                                       | HP                                           | Free to use and short recall period so suitable for frequent administration. Focused mostly on symptoms and social and information needs                             |
| KDQOL 36                               | Renal        | 36                                       | HP                                           | Based on SF 12, widely used in the renal community over the last 10 years. Outputs of PCS and MCS can be compared to other health groups.                            |
| KDQOL I-LF                             | Renal        | 134                                      | HP                                           | Time consuming to administer and rarely used now                                                                                                                     |
| KDQOL -SF                              | Renal        | 80                                       | HP                                           | Based on SF 36, commonly used in advanced CKD and RRT.                                                                                                               |
| Kidney Disease Questionnaire           | Renal        | 26                                       | HP                                           | Developed for use in a specific study but has the advantage that was designed to be used repeatedly in the same individual.                                          |
| Kidney Transplant Questionnaire        | Transplant   | 25                                       | HP                                           | Similar to kidney disease questionnaire but for Tx recipients.                                                                                                       |
| Quality of Life Index Dialysis         | Dialysis     | 34                                       | HP                                           | Uses the respondent's importance ratings to weight satisfaction responses                                                                                            |
| Quality of Wellbeing (QWB-SA)          | Generic      | 81                                       | PB                                           | Although long this reports a single health utility so can be used to calculate QALY's                                                                                |
| Renal Quality of Life Profile          | Renal        | 43                                       | HP                                           | Single score but no breakdown of individual domains                                                                                                                  |
| SF 12                                  | Generic      | 12                                       | HP                                           | Short and easy to perform, reports summary scores for PCS and MCS                                                                                                    |
| SF 20                                  | Generic      | 20                                       | HP                                           | Returns 6 domains but no summary scores                                                                                                                              |
| SF 36                                  | Generic      | 36                                       | HP                                           | The most commonly reported across the world with many translations. Can be costly and time-consuming analyses.                                                       |
| SF 6D                                  | Generic      | N/A                                      | PB                                           | This is a post hoc analysis of SF 36 or SF 12 to give a health utility output.                                                                                       |
| Sickness Impact Profile (SIP)          | Generic      | 136                                      | HP                                           | Focus on activities of daily living and ability to perform.                                                                                                          |

In some instances i.e. when more interested in the impact of disease on activities, the SIP may be more appropriate as this gives much more detailed information within this narrower definition.

The SF 36 has the advantage of there being a large volume of existing data and relatively well understood outputs, but it has a cost implication both in the initial availability and in the time taken to both administer and analyse the data. However, in the setting of ESRD it is probably preferable to opt for the KDQOL-SF or KDQOL 36 over the SF 36 depending on the depth of information required. The KDQOL versions are freely available but will still have the time costs associated. If an additional Health utility is required there is the option of converting the output via the SF 6D.

Since 2015 the SONG (Standardising outcomes in Nephrology) initiative has been working on compiling and developing a set of standardised outcomes to be used in Nephrology research across the globe. This work is ongoing but includes the use and or development of a number of PROMs and is likely to lead to greater standardisation over time.

### *Defining Clinical significance*

In medical and scientific literature in general we are accustomed to seeing results presented as a function of statistical significance, commonly defined

as a p-value of  $< 0.05$  (or less than a one in twenty chance of the observed result happening by chance). With large samples it is possible to get highly significant p-values with very minimal changes in the outcome. This model of presentation and analysis does not necessarily lend itself so well to concepts such as HRQOL. It is entirely feasible to have a statistically significant difference or change in HRQOL but for this to be of no clinical significance to the individual or population. While many studies do continue to present the results of HRQOL studies with conventional statistical analysis, another layer of analysis is often helpful if we are to assess whether the observed difference has any clinical significance. As such there has been much discussion and work around defining these clinically important differences (CIDs). Despite this there is very little consensus regarding the optimal method to report changes in HRQOL research.

For the purposes of understanding it has been argued that CIDs might be more usefully defined as the minimal CID (mCIDs):

“the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patients management”<sup>103</sup>.

There are two overarching approaches to defining mCIDs, either distribution based or anchor based.

## Distribution Based

Distribution based methods generally expand on the analysis and statistical interpretation of the data beyond the simple assessment of difference between the means. They use the statistical distribution of the results to calculate the differences with broadly three approaches.

The first is the statistical significance as calculated using the paired t-test or growth curve analysis. These tests are widely used, and the outputs understood, however the disadvantage of these methods is that the results are highly influenced by sample size and as stated above may not reflect what is clinically significant for an individual or population.

The second evaluates the changes in relation to the sample variation as defined by the effect size. Effect size can be defined as the difference between two means divided by a standard deviation however there are at least three methods for determining effect size depending on the denominator used. The standardised effect size as described by Cohen is probably the most common and uses the SD of the study population HRQOL metric at baseline. The standardised response mean uses the SD of difference scores of the population and the responsiveness statistic uses the SD for stable individuals<sup>104-106</sup>. Cohen provided benchmarks as a guide to interpretation of the resultant effect sizes for the standardised effect size, these are “small” effect .20, “moderate” effects .50 and “large” effects .80<sup>104</sup>. These descriptors have also been used for the other methods of

calculating effect size. These methods have the advantage of being independent of sample size however the degree of heterogeneity in the study population can have significant impacts on the effect size calculation, the bigger the baseline SD the smaller the effect size.

The third distribution-based method is to calculate the standard response mean, which is the ratio of the individual change to the SD of change in the population (or for the responsiveness statistic to the SD of change in a stable population). There are published effect size estimates for a number of chronic conditions calculated for the SF 36 and a large systematic review in 2003 by Norman et al. concluded that in most circumstances the threshold for discriminating change in HRQOL in chronic disease was around half an SD

107 .

### Anchor Based

Anchor based approaches compare HRQOL changes to other measures that have clinical relevance. Within this definition there are potentially three approaches.

The first is the cross-sectional approach to defining anchor based mCIDs. This takes a cohort of patients that are defined by a specific clinical or psychosocial difference. The mean difference in HRQOL of these groups is then used to define the mCIDs with respect to that attribute (may be level of disease activity, bereavement, employment status). One of the

considerations when using cross sectional groups to define mCIDs is that these groups are likely to differ in many other relevant and overlapping variables aside for HRQOL. Another cross-sectional approach would be to present a subset of your target population with several pairs of different theoretical health states (or current compared to either a defined state in the past or a theoretical state). They then complete the HRQOL instrument with regards to both and are asked to indicate directly if they prefer the first or second health state or are indifferent. Over a number of iterations the mCIDs for this population and instrument can then be derived. This direct approach is time consuming and rather artificial and may not reflect the actual HRQOL reported for a given scenario.

Longitudinal approaches use individuals as their own controls and so avoid some of the issues around differences and as they use actual clinical states reflect HRQOL at the time of that disease state. However they are probably easiest to define when there is a specific intervention such as a hip replacement or other operation, HRQOL can then be compared to objective outcomes such as mobility or to self-reported patient satisfaction.

Another anchor might be measured variables such as weight, or other defined disease specific clinical assessments. As HRQOL is impacted by so many variables it might be the observed changes are due to other factors than the observed change in the anchor variable. It is also possible for a

mCID as defined by these methods to be within the natural variability of the instrument and as such caution is required<sup>106, 108</sup>.

In all these situations the mCID is anchored to a specific outcome and as such might not be generalizable, however there have been studies that have shown remarkable convergence of these mCIDs between different disease states and as such they are sometimes used more generally<sup>103, 109, 110</sup>.

### In Practice

In some situations it has been shown that distribution based and anchor based methods are roughly comparable, however neither adequately answer the question of clinical significance on their own and it has been argued that a combination of both is required to get a fuller picture<sup>105</sup>. Unfortunately many studies still only report the mean and SD when discussing the results of HRQOL studies with the minority defining the mCID or how this was derived. There remains no consensus on reporting mCID in HRQOL research although several groups have tried to reach consensus for individual disease states and HRQOL instruments. In 2004 an expert consensus panel report defined standards for mCID in patients with coronary artery disease and congestive heart failure when using the SF 36 and the chronic heart failure questionnaire<sup>111</sup>.

For the most widely used instruments like the SF 36 and its derivatives there are large databases of population norms. The individual domains and the

summary outputs of the SF 36 (and other SF instruments) are calibrated on a scale of 1-100 so that the population norm (mean) gives a score of 50 (with an SD of 10 for the summary scores). This would seem to make interpretation much easier than with unadjusted scores but still leaves the clinician with the issue of defining what is clinically significant change as opposed to statistically significant. If we apply the half SD rule to the SF 36 we get a change of  $\pm 5$  as being considered a mCID in the absence of other data. This might work for the summary scores but is more complicated for the individual domains that before transformation might only contain 20 or less possible health states (as a result a change of  $\pm 5$  could result from an individual level change of one point in only one part of one domain). There has been no work to define mCID using the SF 36 specifically in CKD but in heart disease it has been suggested that mCIDs for the individual domains range from 15 to 25 (representing on average three individual level changes) <sup>111, 112</sup>.

Preference based methods of assessing HRQOL are by convention calibrated so that perfect health is 1 and death 0; again a statistically significant change may not be clinically significant, however the same methods have been used in estimating mCID's.

Whichever method of defining mCID is used it should be remembered that for both the individual and group the actual mCID may well depend on the clinical context in which it is being used and the decisions that are reliant

upon it. It may also be dependent on the direction of change and the baseline from which an individual is starting.

In a study undertaken in the UK involving elderly CKD 5 non dialysis patients the mCID for the MCS and PCS derived from the SF 36 has been determined to be in the region of 5.7 for PCS and 9.9 for MCS <sup>113</sup>.

### *Factors that influence HRQOL in the general population*

HRQOL is impacted by many factors in the general population, generally it decreases with advancing age and is lower in females. Many social factors impact on HRQOL such as education, social support, employment and income, HRQOL also varies between ethnic groups and countries. The number and nature of comorbidities also has an effect with lower HRQOL in those with mental health issues and with increasing numbers of comorbidity <sup>114-116</sup>.

### *Factors that influence HRQOL in people with CKD*

Studies in renal patients have used a variety of health profile and preference based QOL tools, both generic and disease specific <sup>117-120</sup>. Regardless of the instrument used and the way that they are reported, studies have consistently shown that patients with advanced CKD have lower QOL scores than the age matched general population <sup>62, 119, 121</sup>.

In 2005 Perlman et al. reported a study using the SF 36 looking at QOL in 634 individuals with CKD (eGFR <50) under follow up in nephrology clinics.

Most of these patients had CKD 4. The results were compared to both healthy controls and to a previous cohort of HD patients. They reported that there was no significant correlation between eGFR and QOL but that individuals with CKD did have lower overall QOL than the control population, although this was confined mostly to the PCS, the scores for the mental health domains (aside from vitality) were the same as the population controls. There was a tendency for patients with CKD 4 to have lower scores than CKD 5 but this was not statistically significant <sup>122</sup>. Between 2003 and 2006 Mujais et al. recruited patients with CKD stage 3-5 to a prospective observational cohort study in the US and Canada. They recruited 1186 patients who completed the KDQOL at baseline. They reported that HRQOL declined by CKD stage, this was most marked for the PCS with only CKD 5 having a notable effect on MCS scores <sup>123</sup>.

In 2000 Lamping, et al. in their study of 174 elderly (mean age 76.3 years) patients starting dialysis reported that the MCS (as measured using the SF 36) were similar to age matched controls, however the mean PCS scores and overall QOL were significantly lower than in age matched controls <sup>117</sup>. In 2009 Abdel-Kader et al. also reported on a total of 177 patients with either ESRD on dialysis or CKD 4/5 who completed the SF 36 as part of a larger study. Patients with ESRD had lower scores for the physical function domain but overall PCS and MCS scores were comparable, no comparison was made to population norms in this study <sup>124</sup>.

Merkus et al. looked at HRQOL in 226 patients from 13 Dutch dialysis centres three months after starting chronic dialysis and showed that QOL was reduced across all domains of the SF 36. Mean scores for role functioning and general health perceptions corresponded to around the lowest scoring 10% of the general population <sup>125</sup>.

This reduced QOL has been shown to be a predictor of mortality and morbidity (especially in the form of hospital admissions). In 2003 Knight et al. reported on the results of 14,815 patients newly initiated on HD, between 1996 and 1998, in facilities operated by Fresenius medical care in North America who completed a SF 36 between 1 and 3 months after initiation. This confirmed that the overall MCS and PCS scores were lower than the general population norms. It showed that in age adjusted multivariable analysis both MCS and PCS scores were independently associated with one-year mortality. They also examined changes in MCS and PCS at 6 months and reported that a 10 point (1 SD) decline in either was significantly associated with additional increased mortality risk <sup>126</sup>. Osthus et al. reported in 2012 on mortality in prevalent dialysis patients in Norway by quartile of QOL as measured by the SF 36 and the SF 12. This showed, independent of which tool was used, that there was a correlation between mortality and PCS with the highest mortality rate in patients in the lowest quartile of PCS, there was no association with MCS <sup>127</sup>. This group also reported separately on a cohort of dialysis patients with diabetes compared

to patients with either diabetes or dialysis alone. HRQOL was assessed using the KDQOL-SF and demonstrated a significant difference in MCS scores between dialysis patients with and without diabetes, there was a tendency to lower PCS scores in the diabetic patients but this did not reach statistical significance. In this cohort of diabetic patients PCS scores were not an independent predictor of mortality however patients without diabetes and a PCS above the median did have higher rates of survival compared to those with lower PCS scores <sup>128</sup>.

Another large US cohort of dialysis patients reported by Lowrie et al. in 2003 reported on data from 13,952 prevalent HD patients who completed the SF 36 questionnaire, they then reported on hospitalisations in the six months after completion and overall mortality. This study again confirmed lower than population norms for both the summary MCS and PCS components. Both MCS and PCS were associated with risk of hospitalisation in the 6 months after completion and both were also associated with mortality rate <sup>129</sup>. Also in 2003 DOPPS group published a paper showing very similar results in 10,030 patients from the US Europe and Japan using the KDQOL-SF. The original sample was 17,236 but a large proportion did not complete or only partially completed the KDQOL-SF, these patients were older with greater co morbidity and lower body mass index (BMI) and lower pre dialysis systolic blood pressure. The non-completers had a higher risk of both death and hospitalisation compared to those that completed all questions even after

adjustment for comorbidities, sociodemographic variables, treatment factors time on dialysis and country. For those that did complete the questionnaire all components were shown to be independently associated with both hospitalisation and death, however the greatest effect was for the PCS; patients in the lowest quintile of PCS had a 56% higher risk of hospitalisation and a 93% greater adjusted risk of death than those in the top quintile<sup>130</sup>.

#### Demographic and biochemical factors that influence HRQOL

Several large cohort studies have examined HRQOL as a function of demographic and biochemical factors. In 1997 the Modification of Diet in Renal Disease Study reported on the QOL of their participants; this study comprised of 1284 patients with CKD who completed assessment of HRQOL (using the QWB) alongside assessments of symptoms, renal function, blood pressure (BP) and serum albumin. Patients with insulin dependent diabetes were excluded from the study, thus only 3% had diabetes. Most participants had either glomerular disease or polycystic kidney disease. The QWB utility score was higher in univariate analysis in younger males with higher GFR, higher income and education levels and in those that had polycystic kidney disease as the cause of their CKD. There were no differences based on race or smoking status. On multivariable analysis there was a significant positive correlation between QWB and income, education

and GFR and a significant negative correlation with age and female gender

131.

The study by Mujais et al. referred to above went on to look at categorical correlates with HRQOL at baseline in patients with CKD 3-5. PCS scores were lower in older patients while the MCS scores were higher; sleep was better in older patients. Women had lower PCS and MCS scores. Specific comorbidities (diabetes, history of congestive heart failure, or a history of myocardial infarction) were associated with lower PCS scores. In addition the degree of anaemia had an effect on the PCS and to a lesser degree on the MCS. Low albumin had a negative effect on PCS. These effects were still present and significant in the multivariable regression analysis <sup>123</sup>.

The Haemodialysis Study (HEMO study) was a randomised clinical trial of the effects of HD dose and membrane flux on mortality and morbidity in chronic HD patients. Analysis of data from this cohort stratifying by age demonstrated that as age increased (18-54, 55-69, or  $\geq 70$  years) overall HRQOL as measured by the KDQOL decreased. However over the three years follow up, the rate of decline in HRQOL was greatest in the 55-69 year age bracket, although the overall changes in HRQOL over this time period were only small and seen only in the PCS scores and therefore of doubtful clinical significance. However it should be noted that there were high rates of dropout (including death) over the three years so that interpretation of these results is complicated. An attempt was made to account for this by

the study authors which again found differences in rate of change but these remained small in magnitude<sup>132</sup>.

Another subgroup analysis, this time of the DOPPS cohort, reported in 2007 on 9526 patients who had completed the KDQOL and a medical questionnaire. They found that increasing age and female gender were associated with lower PCS but that there was no association with MCS. The estimated unadjusted reduction in PCS per 5 years of age was 1.05. After adjustment for covariates and multiple comparisons they reported associations in PCS scores with a large number of other factors such as employment status (being employed is protective for PCS and MCS), level of education (more is protective), overall income (less is detrimental to both PCS and MCS), living in a nursing home (detrimental), serum albumin (low serum albumin detrimental), and the presence of comorbidities (cerebrovascular/neurologic, cardiac disease, peripheral vascular disease, diabetes, lung disease and psychiatric disease). Lung disease and the presence of cerebrovascular or psychiatric disease also had a negative impact on the MCS scores. However when examining the kidney disease related scales of the KDQOL increasing age was beneficial, although female gender was still associated with lower scores for symptoms/problems but better scores for social interaction and sexual function. Unemployment was associated with lower scores in several of the kidney disease related scales as was not having attended college, lower income, living alone or living in a

nursing home. While not having an effect on the summary scores, factors such as haemoglobin levels and type of vascular access did have statistically significant impacts on the physical role subscale<sup>133</sup>.

Another study to look at correlates of biomarkers with HRQOL in CKD and ESRD was described by Pagels et al. They recruited 535 patients with CKD 2-5 and 55 controls who completed the SF 36 and had biomarkers assessed (Blood Pressure, weight, Body mass index (BMI) and blood tests for haemoglobin (Hb), albumin, C reactive Protein (CRP), phosphate and renal function (creatinine). In addition patients with CKD 2-3 and the controls had GFR measures by iohexol clearance and patients with CKD 4-5 had estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula<sup>134</sup>. As with many studies there was a progressive decline in all HRQOL dimensions with declining GFR and patients with CKD 2-3 had significantly lower HRQOL than the normal controls. On multivariable linear regression analysis with PCS as the response variable, five factors entered the model: CRP, cardiovascular disease, GFR, diabetes and age in that order. In this cohort they did not see an effect of gender, the effect of BMI was only seen for BMI >30 for whom the PCS scores were lower on univariate analysis<sup>135</sup>.

In addition to these cohort studies looking at overall associations, there have been a number of studies that have looked at potentially modifiable factors such as anaemia. Many of these were part of large drug trials of erythropoietin stimulating agents (ESAs) for correcting anaemia. None of

these trials had HRQOL as a primary endpoint but many did include its assessment within the protocol.

In the early 1990s the national cooperative recombinant human erythropoietin (Epo) study (a phase IV open label study) assessed the effects of starting ESAs on HRQOL as assessed with the SF 36. They compared the responses of 484 dialysis patients new to ESAs with 520 dialysis patients, who were already established on the therapy, at baseline and after an average follow up of 99 days. For those patients that were new to ESAs there was a mean increase in haematocrit of 4.6 with significant improvements in physical functioning, social functioning, mental health, and vitality with overall improvements in the MCS but no statistically significant difference in the PCS. The greatest improvement was in vitality which increased by 9.3 (on a scale of 1 – 100). As a secondary endpoint they also assessed the associations between HRQOL and haematocrit.<sup>136</sup>

Three large studies followed in 2006-2009 looking at effects of ESAs in patients with CKD and anaemia. The cardiovascular risk reduction by early anaemia treatment with epoetin beta (CREATE) trial published in November 2006 recruited 603 patients with CKD 3-4 (mean eGFR 24.9) and mild to moderate anaemia (defined as Hb 11.0 – 12.5 g/dl). They were randomly assigned to receive epoetin beta with a target Hb of 11.0 – 12.5 g/dl, or 13.0 – 15.0 g/dl. QOL was a pre-determined secondary endpoint and was assessed by the SF 36. The study did not show any difference in the primary

endpoint of first cardiovascular event. At one year the median difference in Hb was 1.9 g/dl and QOL was significantly better in the higher target group in several domains (general health, mental health, physical function, physical role, social function and vitality). However by year 2 the median Hb difference was 1.7 g/dl and difference in HRQOL was maintained for general health and vitality only. There was no overall increase in adverse events in the higher target group however there was an increase in headaches and hypertensive episodes <sup>46</sup>.

In the same issue of the New England Journal of Medicine the correction of haemoglobin and outcomes in renal insufficiency (CHOIR) was published. This trial using epoetin alfa had two target Hb levels of 13.5g/dl and 11.3 g/dl and recruited 1432 patients with CKD 3-4 (eGFR 15-50 ml/min/1.73m<sup>2</sup>). Baseline Hb in both groups was 10.1 ± 0.9 g/dl with good separation between the groups in follow up. The study was stopped early as more patients in the higher target group had at least one serious adverse event. There was no statistically significant difference in the HRQOL between groups <sup>137</sup>.

Finally in 2009 the results from the Trial to reduce cardiovascular events with Aranesp therapy (TREAT) were published. This recruited 4038 patients with type 2 diabetes, CKD 3-4 and anaemia. Half were assigned to a target Hb of 13g/dl and the others to placebo (with rescue ESA if Hb < 9 g/dl). There was no difference in HRQOL as assessed by the SF 36 however there

was an improvement in FACT-Fatigue score at 25 weeks in treatment group with a change that was considered clinically relevant in 55% of the treatment group and 50% of the placebo group. The higher target group did not have any reduction in deaths or cardiovascular events however there was a statistically significant increase in the risk of stroke in the treatment group <sup>47</sup>. Since these trials were published there have been very clear guidelines drawn up by the nephrology community on the treatment of anaemia with specific target Hb levels and advice against full correction of anaemia. However there has been ongoing debate about the role of anaemia and anaemia correction in HRQOL.

Another factor that has been looked at specifically is sleep; several studies have looked at this aspect including in the DOPPS cohort. In their study they reported a correlation between sleep and HRQOL and overall MCS and PCS scores on the SF 36. There was also an independent association between poor sleep and mortality. However in this study poor sleep was very common and reported by nearly half of all HD patients <sup>138</sup>. Subsequently similar results have been shown by Kumar et al. in CKD 3 -5 patients, who completed the KDQOL and there was significant correlation between sleep quality and PCS and MCS <sup>139</sup>.

In addition to these physical traits there has been interest in psychosocial factors that might influence HRQOL. In 2011 Chen et al performed a systematic review and meta-analysis looking at the psychosocial correlates

to HRQOL specifically in dialysis patients. They identified 81 studies for inclusion; in this analysis the psychosocial constructs with the strongest associations were stress, affect and cognitive appraisal (how the patients understood the world) <sup>140</sup>.

### Treatment Factors

Generally studies have shown that there is a difference in HRQOL dependant on RRT modality although these findings are not universal <sup>141-143</sup>.

Certainly in most studies better QOL is reported in patients with a functioning renal Tx as compared to those receiving dialysis. A group in Turkey reported results from a cross sectional study of Tx recipients (302), HD (64) and PD (207) patients as well as normal controls (278). They used the SF 36 as the HRQOL assessment method and reported that QOL was better in Tx recipients compared to HD or PD, however the Tx patients were around 10 years younger and more likely to be male. The Tx population still had lower reported QOL when compared to a healthy control group <sup>144</sup>. Another study of 40 patients who had received a living donor Tx reported by Hossain et al. in Bangladesh showed good QOL scores when compared to healthy controls and kidney donors at a mean duration of 28 months from Tx <sup>145</sup>. A separate study of 120 patients receiving RRT, either 3 months post renal Tx or undergoing HD (40 patients) or PD (20 patients) was reported in 2014. The Tx patients were assessed at 3 and 12 months post-Tx. All patients completed the SF 36 and the KDQOL; they reported a significant

difference in PCS post transplantation as compared to stable HD or PD patients. There were no differences in MCS and no change in PCS for Tx patients between 3 and 12 months<sup>146</sup>.

A number of longitudinal studies have mostly shown that this difference in HRQOL is real and not related to differences in the cohorts studied such as age, comorbidity or time on RRT, however the magnitude of the change was dependant on many of these factors.

In 2012 Painter et al. described a longitudinal study that included 20 patients who subsequently received a living donor kidney Tx. They completed the KDQOL-SF two weeks before and six months after transplantation. Only 5 of the 20 were already undergoing HD at baseline with the others receiving a pre-emptive Tx. At baseline these patients had similar scores to the rest of the HD patients in the study and at six months their PCS scores had improved significantly and were similar to healthy controls. There was no comment made in the paper regarding MCS scores but from the data presented the baseline scores in this small cohort were not statistically different to controls<sup>147</sup>.

A group from Helsinki reported on a follow up study of patients who started on dialysis between 2004 and 2006 and who at 31<sup>st</sup> October 2012 had a functioning renal Tx. 49 patients completed a 15D HRQOL questionnaire initially when starting dialysis and at follow-up in 2012. The patients' scores

were classified as either better (57.4%), unchanged (21.3%) or worse (21.3%). However for those patients who had previously been on home HD only 47.6% were better, 28.6% unchanged and 23.8% worse whereas for those previously on PD 78.6% were better<sup>148</sup>.

In 2014 a group from Norway reported on 110 patients who had undergone renal Tx in the preceding three to four years. They had each completed the KDQOL-SF at baseline and were then invited to complete it again sometime after the initial study. Of the original 301 patients in the study 142 had died in the intervening period, 31 were excluded and 110 had a functioning Tx. There were significant changes (improvements) in the kidney specific elements of the KDQOL. In the SF 36 general domains there were improvements in the general health, vitality, social function and role physical domains but the authors did not feel that these were clinically relevant changes (as defined by greater than half a SD from baseline)<sup>149</sup>.

Many studies have compared HRQOL in different dialysis modalities with some showing a difference in individual components of HRQOL between HD and PD but there is no consensus on the overall effect. There have been several smaller studies that have tried to look at this question.

In 2004 a group in Switzerland published a study using the EQ 5D in a large group of dialysis patients. 455 HD and 64 PD patients completed the EQ 5D with a response rate of around 80%. They reported that the groups had

similar age, gender and duration of dialysis and found no differences in QOL between modalities <sup>150</sup>. A single centre group in Turkey assessed QOL using the SF 36 in 75 HD , 41 PD and 20 Tx patients without finding any statistically significant differences between modality <sup>151</sup>. However another group in Turkey more recently reported on a group of 154 patients (90 HD, 64 PD) and found higher MCS and PCS scores in HD patients as compared to PD <sup>152</sup>. Ginieri-Coccossis et al. in Athens reported on a cross sectional cohort of patients on dialysis divided by both modality and time on dialysis (< or > 4 years). HRQOL was assessed by WHOQOL-BREF. They report that overall QOL was lowest in those on HD for > 4 years but did not find any other differences in QOL between the groups. They noted that the HD group > 4 years had a mean time on RRT of  $12.65 \pm 6.64$  compared to  $5.82 \pm 1.13$  for PD. When the HD and PD cohorts were matched for variables such as age, co morbidity and time on RRT (all now < 4 years) there remained a difference only in the domain of environment on the WHOQOL-BREF <sup>153</sup>.

A study conducted in Brazil looking at change in QOL in prevalent dialysis patients over 12 months had 189 HD and 161 PD patients who completed follow-up. HRQOL was assessed with the KDQOL-SF (but with the SF 12 substituted for the SF 36). In this cohort patients on PD were likely to be older and diabetic but had been on dialysis for less time. At baseline there were no differences in the MCS and PCS scores but PD patients had better scores in several of the kidney specific domains (burden of kidney disease,

patient satisfaction and staff encouragement) and this persisted throughout the study period. However a greater percentage of patients on HD had clinically significant increases in QOL over this time<sup>154</sup>.

There have though been some larger cross-sectional studies in the USA. Diaz-Buxo and colleagues reported that in a large cross-sectional population they demonstrated differences in some specific domains of the SF 36 between dialysis modalities. A total of 16,755 HD patients and 1260 PD patients (CAPD = 728, APD = 532) completed the SF 36 during 1996, the results again show that it is the PCS scores that are lower in dialysis with relatively preserved MCS scores. Initial unadjusted analysis did not show any difference between HD and PD but when this was split by PD prescription a difference in the physical functioning scores was apparent with the highest in CAPD then HD then APD. When adjusted for age, sex, race and diabetes there was no difference between CAPD and HD but the significantly lower scores for APD persisted. When the same analysis was repeated for MCS scores APD patients had higher scores with no difference between HD and CAPD<sup>155</sup>. In 2004 Wu et al. reported on HRQOL by RRT modality in a large cohort of US patients. The PD population was oversampled to allow statistical comparisons and comprised 26% of the cohort, home HD (HHD) patients were excluded from this study. A total of 928 incident patients completed the CHOICE Health Experience Questionnaire when starting dialysis and of these 585 also completed it at one year. 101 of the non-

completers had died during the study period. QOL was statistically better in several domains in those that completed the baseline and one year follow up. The PD patients at baseline had higher QOL scores, they also tended to be younger, white, college educated, employed, married and living further from the treatment centre. When examining change over one year, patients on HD tended to show a greater improvement in QOL, particularly in physical functioning, general health, and sleep and overall QOL however PD patients showed greater improvement in the financial domain <sup>156</sup>.

There is a lack of longitudinal study of HRQOL according to modality, however there is one study from the Netherlands. As part of the Netherlands Cooperative Study on the Adequacy of Dialysis, Merkus et al. reported on the changes in HRQOL over time and with changing dialysis modality. They recruited 230 patients at initiation of RRT who were asked to complete the SF 36 at 3, 6, 12 and 18 months. Of those that entered the study 139 did not change modality, 26 switched to another form of dialysis, 35 were transplanted and 28 died. At baseline the QOL was similar for those patients that went on to receive a Tx as those that stayed on PD; this was higher than for those that stayed on HD or subsequently switched modality. The lowest QOL at baseline was reported in those that died during the follow up period. Analysis of those patients that stayed on PD as opposed to stayed on HD showed that PCS scores fell for both over time but that

although initial QOL was better in the PD group this fell more rapidly than for those on HD. There were no differences in the MCS scores over time <sup>157</sup>.

A large study of PD patients ADEMEX (Adequacy of peritoneal dialysis in Mexico) began in 1998 and recruited 965 patients who either continued with their conventional prescription or an intervention group with a modified prescription aimed at achieving higher creatinine clearance. Patients completed the KDQOL and were followed up for 24 months. There was no difference in HRQOL between the groups in any of the composite outputs of the KDQOL <sup>158</sup>.

In 2010 Brown et al. published the results of a QOL study in older (over 65) prevalent dialysis patients and compared QOL between HD and PD. They reported that QOL was similar, if not better, in those on PD <sup>159</sup>

Several studies have sought to explore the relationship between different HD prescriptions and settings with regards to HRQOL. There are various ways that the dialysis prescription and delivery can be modified, in particular the length of individual treatments, frequency of treatments, time of day and setting (HD centre or home). A conventional HD prescription is 4 hours three times a week in a HD centre during the day or evening. In addition, by changing settings on the HD machine it is potentially possible to alter the side-effect profile, for example with temperature or sodium control or changing from standard HD to hemodiafiltration (HDF). Changing

the duration and or frequency of the dialysis will also have the effect of changing the prescribed and delivered dose of dialysis. Interest in this area is increasing as studies have suggested that alterations in HD prescription might have additional health benefits. Alongside this several studies have looked at the impact on HRQOL of modifying the HD prescription in this way. There is some evidence that for those patients established on extended hours HD (for example 5\*3 hours a week (short daily)) that their HRQOL may be improved as compared to conventional HD although this has not been confirmed for frequent nocturnal HD<sup>160, 161</sup>.

The HEMO study was set up to look at modifying the dose of dialysis and looked at changes in KDQOL scores at three years as a secondary endpoint. Patients were allocated to either standard dose or high dose HD. After three years PCS had deteriorated in both groups. However, there was a difference in pain and physical component scores with both being statistically better in the high dose HD group but the overall effect was very small when compared to the natural variability of these scores and likely of no clinical significance<sup>162</sup>.

Williams et al. reported on a small study of 21 patients in a crossover trial of conventional versus short daily HD for 4 weeks each. They assessed QOL using the Alberta quality of life instrument at baseline and after each 4 weeks on treatment protocol. They reported that over this short time period

there was an improvement in overall QOL at the end of the frequent HD course<sup>163</sup>.

In 2003 Ting et al. reported on their cohort of 42 patients with high levels of comorbidity who switched to short daily HD while maintaining the same overall dialysis time. 20 of these patients completed 12 months of short daily HD and completed KDQOL at pre-defined time points. All patients had significant improvements within three months in energy/fatigue, symptoms/problem list, effects of kidney disease, cognitive function, quality of social interaction and symptoms during HD. There were also significant improvements in physical functioning, physical role, sleep, emotional role and general health. These improvements were maintained over one year on frequent HD<sup>164</sup>.

The New England Journal of Medicine published a paper in 2010 by the Frequent Hemodialysis Network (FHN) Trial Group. 245 patients were randomly assigned to either continue with conventional (2.5 – 4 hours 3 \* per week) HD or to change to frequent HD (1.5 – 2.75 hours 6 \* per week) for the study period of 12 months. Patients completed the SF 36 at baseline and 12 months. The study reported a significant improvement in the composite co-primary endpoint of death or change in PCS score in the frequent HD group but frequent HD did result in the need for more frequent intervention to maintain vascular access<sup>165</sup>. Further analysis from the FHN group collected data from both the above trial and another trial of nocturnal

HD conducted by the same group. They found significant improvements in PCS and physical functioning at 12 months in the frequent HD group but no difference in the nocturnal group. However objective assessment of physical activity (tested by the short physical performance battery) did not find any differences in actual physical performance <sup>166</sup>.

Painter et al. in the USA presented data relating to 43 HD patients who either stayed on conventional (4 hours 3\* per week) HD (n = 13), converted to daily (3 hours 5 or 6 \* per week) HHD (n = 10) or had a living related renal Tx (n=20?). They were assessed at baseline and 6 months after the change using the KDQOL. The patients that stayed on conventional HD had no change in their physical functioning or PCS scores while those who converted to daily HHD had a positive change in scores for both, however these were not statistically significant, perhaps because of small numbers <sup>147</sup>.

The FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study published an interim report in 2012 on the effects of frequent home HD on QOL as assessed by the SF 36. In total 154 (out of a total cohort of 291) patients completed 12 months follow up with SF 36 at baseline and 12 months. 90 % of the patients had transitioned to home HD and all were on 6\* per week HD. Both MCS and PCS increased over one year as did all of the 8 individual domain scores <sup>161</sup>.

A number of studies have looked at the effects of nocturnal HD on QOL. 52 patients in Canada were randomised to either continue with conventional 3\* per week HD or transition to nocturnal home HD. They completed the EQ 5D and the KDQOL-SF and the study demonstrated improvement in effects of kidney disease and burden of kidney disease domains but no change in overall EQ 5D or PCS or MCS scores <sup>167</sup>. An observational cohort study in Australia of 63 patients converted from their current home HD regime to nocturnal home HD did find improvements in some of the individual domains of the KDQOL but no improvements in the PCS or MCS. However prior to entering the study some patients were already doing either frequent and/or extended hours HD at home <sup>168</sup>. As mentioned above, the FHN nocturnal trial did not find a difference in QOL when conventional HD was compared to frequent nocturnal <sup>160</sup>.

Fong et al. in Toronto reported on 69 patients who were either on PD or nocturnal HHD (8 - 10 hours during sleep 5 – 7 nights per week). They all completed the KDQOL-SF, basic demographics were well matched aside from HHD patients were younger and more likely to have had a previous kidney Tx. They found no differences in PCS, MCS or the KDCS, however the patients on HHD did have lower levels of perceived social support <sup>169</sup>. There is a body of evidence regarding patient satisfaction with care in dialysis patients and relating this to different modality choices, with patients who

opt for PD having greater levels of satisfaction than conventional HD irrespective of patient and disease specific factors <sup>170</sup>.

### *HRQOL Summary*

As discussed there are many different factors that influence HRQOL both in the general population and specifically in people with CKD. Some of these are not modifiable such as gender and age, some might be amenable to interventions outside of the medical model such as education, social support, income and employment (although treatment decisions can impact on this). Other factors such as eGFR, sleep, anaemia, CRP (inflammation), and albumin levels might be amenable to medical interventions. The level of comorbidity is another area where medical interventions may have an impact, especially in addressing some of the risks of developing CV disease that are specific to this population.

Poor HRQOL in ESRD and advanced CKD is associated with an increase in both morbidity and mortality. There is reasonably solid evidence for improved HRQOL in patients who receive a renal Tx however many of our patients are not eligible for this treatment, and even those that are may have to wait many months or years until a suitable organ is available. The demographic of patients with ESRD is also not amenable to intervention at this late stage although public health measures aimed at reducing obesity and type 2 diabetes have a role to play. As discussed many of the other factors that impact on HRQOL are also not directly amenable to intervention

by medical teams but might be impacted by such services as social work and youth workers who can access specialist services and support for areas including training, employment and social support.

Although several strategies, based around modifications in dialysis type and delivery, or interventions aimed at addressing nutrition, anaemia or inflammation, in our patients have been proposed to improve HRQOL there is still a need for further research in this area <sup>121</sup>. There is insufficient evidence currently for proposing a specific dialysis modality or modification on the grounds of improving HRQOL. A better understanding of the factors that underpin the variations in HRQOL results might lead to the development of further strategies for intervention.

### Symptom tracking

The assessment of symptoms is another area that is dominated by the use of PROMs. In some medical conditions there is also a long tradition of symptom tracking using clinician completed instruments but these will not be discussed here. Many different instruments have been developed to quantify and measure symptoms in both the general and CKD specific populations. Some of these are embedded within the HRQOL instruments already discussed but others stand alone.

### *Available CKD Specific Instruments*

Patients with advanced CKD have a high symptom burden and so this is an area of intense interest which has led to the development of a number of different and highly specific instruments for assessing symptoms in this patient group.

#### **KDQOL**

The KDQOL is probably the most widely used instrument for symptom tracking in RRT, it can be reported independently although is often used only as a component of the overall KDCS. It contains a list of 12 symptoms/problems associated with ESRD rated by degree of “bother” giving a score of 0 (no symptoms) to 48 (extremely bothered by all 12 symptoms). The KDQOL also contains questions relating to depression/mood, sleep and sexual functioning<sup>92, 93</sup>.

#### **Dialysis symptom index (DSI)**

The DSI was developed specifically for use in haemodialysis patients, it contains a list of 30 common symptoms in ESRD. Patients are asked to complete as yes/no and if yes to rate severity 1 – 5<sup>124, 171, 172</sup>. It has subsequently been used in all RRT modalities and in CKD 4/5 patients not on RRT.

### Dialysis Recovery Time (DRT)

This is a single question posed to patients on HD <sup>173</sup>. “How long does it take you to recover from a dialysis session?”

### Thirst Distress Scale (TDS)

Developed for use in HD patients this is a 6 item questionnaire specifically focused on symptoms of thirst <sup>174</sup>.

### Dialysis Thirst Inventory (DTI)

This is another instrument for assessing thirst, this contains 7 items <sup>175</sup>.

### Modified transplant symptom occurrence and symptom distress scale (MTSOSD)

The MTSOSD was developed to look specifically at symptoms associated with different immunosuppressive regimes; the original version had 45 items and the subsequently revised (due to newer immunosuppressant regimes) has 59 items <sup>176</sup>.

### *Screening for Depression*

Depression is a common diagnosis in the population at large and very common in patients with advanced CKD. There are a variety of instruments that have been developed to help screen for depression and depressive symptoms. These are not diagnostic tools and are designed to be used as a guide as to who to investigate further with a structured interview.

### The Hospital Anxiety and Depression Scale (HADS)

The HADS was developed from a study conducted in a hospital outpatient clinic. HADS is comprised of 14 questions (7 which assess levels of depression and 7 which assess anxiety). Each half has a maximal score of 21 and reportedly takes around 2-4 minutes to complete<sup>177</sup>. It is often used within the hospital setting by allied health professionals as a screening tool for depression and anxiety. In the general population a cut-off of 11 on either scale is considered abnormal. It has been validated for use in ESRD where a cut off value of  $\geq 12$  is proposed<sup>178</sup>.

### Patient health questionnaire (PHQ 9)

The PHQ 9 is another screening tool for depression that has been widely used. Specifically in the UK National Health Service (NHS) it was used within General Practice (GP) surgeries for several years as part of a government programme. It is comprised of 9 questions with a maximum score of 27 and it can be completed in one to two minutes<sup>179</sup>. It has been validated for use in dialysis patients in whom a score of 10 or greater is proposed as a positive screen (this is the same value as for the general population). At this cut off value there is a positive predictive value of 79% and negative predictive value of 98% in ESRD patients<sup>180</sup>.

### Beck Depression inventory (BDI)

The BDI is a 21-item questionnaire that measures characteristic attitudes and symptoms of depression. It was originally developed in the 1960s since

when a shorter version has been developed<sup>181, 182</sup>. The original version of the BDI has a maximal score of 63 and has been validated in patients with ESRD with a suggested cut off of between 13 and 16 depending on the reference used<sup>178, 180</sup>, the corresponding value for the general population and those with CKD but not on dialysis is 11<sup>183</sup>.

### *Sleep*

Sleep quality is assessed as part of the KDQOL and some other HRQOL instruments. It can also be assessed using standalone instruments. Often it is not sleep quality that is being assessed but a measure of fatigue or sleepiness. Fatigue is defined as physical and mental tiredness that does not get better after resting.

#### *Pittsburgh Sleep Quality Index (PSQI)*

The PSQI is used to quantify the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven domains, (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month)<sup>184</sup>.

#### *Epworth Sleepiness Scale (ESS)*

The ESS is not an assessment of sleep but sleepiness and is widely used in assessment of specific sleep disorders such as obstructive sleep apnoea. It

comprises 8 questions and has a maximum score of 24, scores for the normal population are reported to be between 1 – 10<sup>185</sup>.

#### Fatigue Severity Scale (FSS)

The FSS is an assessment fatigue. It comprises 9 items relating to sleepiness that are scored 1 -7. The total scores are added together and divided by 9 to get the result, a normal score is around 2.8<sup>186</sup>.

#### *Generic symptom assessment instruments*

A variety of instruments contain lists of symptoms as part of their overall construction. The Illness perceptions questionnaire revised (IPQ-r) has a section on symptom prevalence and severity. 12 of the 14 symptoms listed in the IPQ-r are the same as in the KDQOL. See page 87, Illness perceptions questionnaire revised (IPQ-r) for further discussion.

In 2017 Basch et al reported on a study that had randomised individuals receiving chemotherapy for cancer treatment to either standard care or a symptom reporting PROM with inbuilt feedback to the treating clinician<sup>187</sup>. Although not a pre specified analysis of the data the team performed a survival analysis which demonstrated increased survival by up to 5 months in the symptom reporting group. The team speculated that this could be due to a variety of mechanisms either related to early intervention preventing later consequences or an effect on the individual's ability to undergo and or

tolerate chemotherapy for longer. Further work will be needed to look at the potential for implementing this system in advanced CKD.

### *Selecting an Instrument*

Often the interest in symptoms is as part of a bigger picture relating to HRQOL in which case the KDQOL may continue to be the best instrument. However if there are specific areas of enquiry then any of the above instruments may be suitable.

Unfortunately they all have one important drawback in ESRD patients and in HD patients in particular. The recall period for each of the instruments described above is typically 4 weeks although some are up to three months and none are less than a week. This is relevant in patients who may well have fluctuating symptoms relating to their intermittent treatment. Currently the IPOS Renal is the only instrument in use that is capable of recording clinically relevant symptoms on a frequent basis. The wider availability and uptake of directed symptom assessment on a frequent basis has the potential to improve patient care via a process of early warning and integration into patient care pathways.

### *Summary of Evidence*

KDQOL has been used repeatedly to look at both specific symptoms and symptom burden. Patients with advanced CKD have repeatedly been shown to have a high symptom burden and a wide range of symptoms regardless of

treatment stage or modality. A 2007 review of studies looking at symptoms in ESRD found that the most prevalent symptoms in ESRD were fatigue/tiredness, pruritus, constipation, anorexia, pain, sleep anxiety, dyspnoea, nausea, restless legs and depression all of which were reported in at least 25% of the population, with fatigue reported by over 70% <sup>188</sup>. When symptom prevalence was assessed using the DSI the median number of symptoms reported by patients on HD was 9 with inter quartile range (IQR) of 6 – 13. The number and severity of symptoms directly correlated with HRQOL <sup>171</sup>. The DSI has subsequently been used in other CKD cohorts and shown a similar symptom burden with advanced CKD and on PD. Patients with ESRD had a mean number of symptoms of  $11.2 \pm 6.4$  versus  $10.2 \pm 5.6$  for CKD 4-5 <sup>124</sup>.

A cohort of 436 Dutch pre dialysis patients were assessed for HRQOL (SF 36) and symptoms (IPQ-r). With progression of CKD the number of symptoms increased and was associated with a greater likelihood of starting dialysis, renal transplantation or death. At the start of pre-dialysis care patients had a mean of 4.8 symptoms increasing to 6.7 during the study period. At the start of the study each of the 12 symptoms (as per KDQOL) were experienced by at least 20% of the cohort and fatigue was experienced by 82.5% <sup>189</sup>. Assessment of symptoms in Tx patients usually focuses on those that are attributable to immunosuppressant therapy, however there are data to show that fatigue persists in many patients post transplantation <sup>190</sup>,

<sup>191</sup>. Symptoms related to therapy are common and vary depending on the individual immunosuppressant regime. Fatigue remains the most prevalent, however other symptoms include increased appetite, trembling hands, eyesight problems, sleeplessness, joint pain and brittle skin <sup>192</sup>.

With regards to HD recovery times, longer recovery times are correlated with poorer HRQOL and higher risk of hospitalisation and mortality in a large international cohort study <sup>193</sup>. It has been suggested that dialysis recovery time it might be a useful screening question, as a way of identifying patients at risk of poor outcomes including poor HRQOL. Assessment of thirst is not often reported in the CKD/ESRD literature. Thirst is however a common symptom in patients on HD who are fluid restricted due to reduced or absent urine output <sup>175</sup>.

In the general non-comorbid UK population the prevalence of depression is around 2.6%. Diagnosing depression requires more than the use of the screening tools outlined above, however all these screening tools have been used in CKD and ESRD patients alongside clinical judgement and structured interview to suggest or confirm a diagnosis of depression. When assessing HRQOL we have already discussed that the MCS scores are relatively preserved, however there is a large body of evidence that shows that both depression and depressive symptoms have a high prevalence in ESRD and advanced CKD. Studies have repeatedly demonstrated dialysis and CKD to be associated with high rates of depression, currently approaching 25% of

HD patients<sup>124, 188</sup>. In addition depression and depressive symptoms have been shown to be an independent predictor of all-cause mortality in ESRD. However most large-scale studies have focused on HD patients. In 2000 Kimmel et al. published a longitudinal study of African American HD patients screened every 6 months using the BDI. The mean baseline BDI score was  $11.4 \pm 8.1$ . There was no association between baseline BDI and mortality, however worsening BDI over time was associated significantly with higher mortality<sup>194</sup>.

In 2002 as part of the DOPPS study group Lopes et al. published data on depression and mortality in HD patients in the US and Europe. They used a combination of diagnosed depression from the medical notes and the answers to two specific questions relating to mood (in the KDQOL-SF). In this study the prevalence of physician diagnosed depression was 17.7% (16.2% in European centres and 19% in the US). Using the self-reported questions 26.8% were positive for at least one question and 13.7% positive for both. The percentages were higher in the European population than for the US. After adjustment for demographic and social factors as well as a number of co-morbidities the presence of depression, however defined, was associated with an increased risk of mortality and hospitalisation<sup>44</sup>. In 2010 a UK study by Chilcot et al. reported that the presence and severity of depression (as assessed using the BDI) was associated with mortality, with a BDI  $\geq 16$  having a hazard ratio of 2.7<sup>195</sup>. A subsequent study involving 6415

patients and reported by Lacson et al. also showed an association in incident HD patients between the presence of depression (on the SF 36 subscale) and one year mortality<sup>196</sup>.

Several studies have reported a higher incidence of depression in those patients starting on PD as opposed to HD. In 2016 Chen et al. presented data on a large cohort of patients in Taiwan and concluded that there was a higher prevalence of depression in the patients on PD. However the PD cohort was relatively small and there may well be societal and structural health care factors specific to Taiwan that make it difficult to generalise these results<sup>197</sup>. Another cohort in Turkey also reported that PD patients were much more likely to be depressed (by BDI criteria) than patients treated with HD, however far more of the HD patients were in employment (unemployment is a strong risk factor for depression) and it is again unclear if there are other factors within the healthcare system that may influence the choice of modality and also affect depression<sup>152</sup>. Overall it is difficult to draw specific conclusions about dialysis modality and depression. There are no longitudinal studies of depression on dialysis by modality. However, further examination of the study by Merkus et al. in the Netherlands looking specifically at the mental health (MH) component of the SF 36 over 18 months found no difference in the scores between those who started and stayed on HD and those who started and stayed on PD<sup>157</sup>. In fact, the initial

cohort reported that at 3 months after starting RRT, mental health domain scores on the SF 36 were higher for those patients starting on PD <sup>125</sup>.

A meta-analysis in 2013 by Palmer et al. included 249 studies with a combined total of 55,982 patients. They reported a prevalence of depression based on questionnaire of 39% in dialysis patients (22.8% with interview-based assessment). Prevalence for transplanted patients was 26.6% (21.4% direct interview) and for CKD 26.5% (21.4% direct interview); there was no breakdown by CKD stage <sup>198</sup>. A study in the US by Hedayati et al. used structured interview in 272 consecutive CKD 2-5 (but not on dialysis) patients to diagnose depression. They reported a prevalence of 21% for a major depressive episode with no variation between CKD stages. There was an association with the presence of diabetes, comorbid psychiatric condition or a history of drug or alcohol abuse <sup>199</sup>.

These figures for the presence of depressive symptoms or major depression are broadly comparable to the prevalence in other chronic medical conditions such as type II diabetes (17.6%) <sup>200</sup>, hypertension (21.3% by interview, 29.8% self-rating) <sup>201</sup>, coronary artery disease (18.7 % of women and 12.0% of men) <sup>202</sup> and congestive heart failure (33.6% by questionnaire and 19.3% direct interview) <sup>203</sup>. These data suggest that depression is common in chronic health conditions but that there is a tendency to over diagnose depression with the use of questionnaires in populations with a

high level of co-existent somatic symptoms such as CKD <sup>204</sup>. Efforts should be made to confirm the diagnosis by use of structured interview.

Sleep and specifically poor sleep quality is another area that has been shown in some studies to be associated both with lower HRQOL and higher mortality in patients on dialysis. Data from DOPPS suggests that poor sleep quality (from KDQOL-SF data) is associated with significantly lower MCS and PCS scores with a relative risk of mortality 16% higher for patients with poor sleep quality <sup>138</sup>. Separately in 2010 Kumar et al. looked at sleep quality in people with CKD not on dialysis using the same measure and reported that poor sleep was common (57%) and associated with worse MCS and PCS scores; higher self-reported daytime sleepiness was associated with a higher risk of mortality prior to ESRD <sup>139</sup>. As part of the FHN trials group Unrua et al. reported on self-reported sleep in frequent HD patients as compared to convention HD or home nocturnal HD. They found no differences in self-reported sleep quality at 12 months between any groups <sup>205</sup>.

There are many plausible reasons why a patient with CKD and especially ESRD might have both poor sleep quality and fatigue, these include sleep interruption by treatments, symptoms such as pruritus, breathing difficulties and the presence of depression but more research is needed to understand these factors.

### *Symptom Summary*

Data relating to symptoms in CKD are numerous, but it can be difficult to draw meaningful conclusions aside from the fact that symptoms are common and associated with other morbidity and mortality. There are little or no data looking at interventions aimed at specific symptoms (with the notable exception of anaemia treatment and effects on overall HRQOL and fatigue). However increasingly there is a focus both on overall HRQOL and on specific symptoms and the effects that specific treatments may have on these. There is a need for more longitudinal and interventional trials with change in symptoms as an outcome to begin to fully understand the complex interplay of factors influencing overall outcomes for our patients.

### **Social impacts**

No illness exists in isolation. Disruptions to lifestyles, activities, and interests as a result of disease and treatment may have an important impact on QOL. Some attempts have been made to specifically look at these social effects of illness.

### *Available instruments*

Many HRQOL instruments contain elements of assessment of social impact. The SF 36 has 2 questions on social functioning. This is the most commonly reported method of assessing social impacts of disease states. Additional questions on social support and sexual functioning and employment were

added to the KDQOL to look at these aspects in more detail. Other instruments have been developed to look specifically at this aspect.

#### Illness Intrusiveness Ratings Scale (IIRS)

The IIRS is a 13- item, self-reported instrument. It can be scored to generate a total score (13 – 91) or three subscale scores (relationships and personal development, intimacy, and instrumental). It was originally developed for use in ESRD but has been used in many different chronic disease states since

<sup>206</sup>.

#### Sickness Impact Profile (SIP)

The SIP was discussed on page 30 Sickness Impact Profile (SIP) as a HRQOL instrument but might also be thought of under the heading of social aspects as it focuses on the ability to complete activities of daily living.

#### Medical Outcomes Study (MOS) Social Support Survey

This is a 19-item instrument developed for patients with chronic disease. It is focused on the availability of support in four dimensions: emotional/informational, tangible, affectionate, and positive social interaction <sup>207</sup>.

#### Social Support List (SSL)

This is a 75 item self-reported instrument originally developed in the Netherlands and subsequently translated into English. It has a number of subscales under the headings of interactions and discrepancies (Everyday

emotional support, Emotional support with problems, Esteem support, Instrumental support, Social companionship and Informative support)<sup>208</sup>.

### *Summary of Evidence*

Although each of these instruments has been used in research involving people with CKD the approach is far from consistent and the data limited. A review in 2013 by Purnell et al. identified 46 studies comparing “life participation activities” in dialysis or Tx patients. The review did not find any differences between HD and PD for work, travel, recreation or freedom. Freedom and work were improved for those with a renal Tx compared to dialysis<sup>209</sup>.

In 1990 Devins et al. reported on a study of 100 patients on dialysis or with a functioning renal Tx. They found that (using the IIRS) patients with a Tx had better social functioning (less illness intrusiveness) and there was no difference between the other treatment modalities (PD, unit or home HD)<sup>210</sup>. A separate study by the same group went on to look at IIRS scores in ESRD as compared to multiple sclerosis and rheumatoid arthritis. They reported that the patients with multiple sclerosis had the highest illness intrusiveness ratings with no statistical difference between ESRD and rheumatoid arthritis. However there was a difference in which areas were affected with more intrusiveness experienced in the area of diet and sexual functioning in ESRD<sup>211</sup>. A survey in Toronto compared illness intrusiveness of PD and nocturnal home HD using the IIRS in prevalent patients. There was

no significant difference in total (or subcategory) IIRS between the two groups<sup>169</sup>. Brown et al. subsequently also used the IIRS to look at potential differences between HD and PD in 120 elderly patients in the UK. After adjustments for age, time on dialysis, comorbidity scores, symptom count, social network score, gender, nutritional status and cognitive function they reported that patients on HD had higher IIRs<sup>159</sup>.

Plantinga et al. published a study involving 1041 dialysis patients that assessed social support (MOS Social Support Survey) and looked at outcomes by quartile of social support. Having social support in the highest quartile decreased the risk of hospitalisation by 15% as compared to the bottom quartile, there was no effect on mortality<sup>212</sup>. A different approach was made by Goedendorp et al. when they wanted to examine factors relating to fatigue in renal Tx recipients. They asked patients to complete the SIP and BDI as well as the SF 36 and another specific questionnaire looking at satisfaction with social support. They reported that increasing fatigue was associated with a number of factors including social support however this significance disappeared when logistic regression analysis was undertaken<sup>190</sup>.

A paper using the SSI in the Netherlands reported on 528 incident dialysis patients, who completed the SSI at 3 months alongside multiple other assessments of HRQOL and health status. They reported an association between social support discrepancies (the degree to which support met

expectations) and mortality. There was no association with levels of social support as recorded by interactions <sup>213</sup>. The same instrument was used to look at predictors of perceived health status (from SF 36) in 136 patients with a functioning renal Tx in Slovakia. Better social support was associated with better MCS and PCS but only in those under the age of 40. Other factors such as drug side effects and serum creatinine levels were also associated with PCS and MCS scores <sup>214</sup>.

### *Social Impacts Summary*

When looking at social factors there is no agreed consensus on what is measured. Some focus on the impact of disease on ability to undertake specific social roles, while others look at activities or the availability of support. As with symptoms and general HRQOL there is a large degree of overlap both in what is being “measured” and the factors that influence the “outcomes”.

However it can be seen that ESRD has a large social impact on patients and that the degree of social support has an impact on outcomes in terms of both hospitalisations and mortality. Much more work now needs to be done to explore these relationships with a view to designing and testing possible interventions aimed at improving overall outcomes.

## Other Patient reported measures

### Perception and decision making

We have discussed several factors that contribute to the overall “outcome” in our patients. Some of these are fixed such as age, gender, ethnicity, some are socially modifiable (education, employment, social support, income) and some are modifiable with either disease treatment or modification to disease treatment regimes. There are however another set of factors that impact on “outcome”. These are the underlying psychological functioning and personality of the patient and more specifically how these relate to illness and treatment behaviours. There is mounting evidence, across many chronic conditions, that an individual’s illness and treatment beliefs can predict a range of outcomes including QOL, return to work, help-seeking behaviour and adherence to treatment.

Recent research has suggested that the most robust method for identifying the factors which influence patients’ decisions regarding their treatment, such as treatment adherence, involves an assessment not just of treatment beliefs, but also beliefs of the associated illness <sup>215, 216</sup>. Two of the most dominant theoretical models in this area are self-regulation theory <sup>217</sup> and the necessity and concerns framework <sup>218</sup>.

Self-regulation theory specifies that individuals are motivated to ‘make sense’ of their illness and this informs whether and how they attain their

goals for their illness (e.g., full recovery, minimise pain, maximise quality of life etc.). The beliefs that patients hold to 'make sense' of their illness have been found to reliably cluster around 5 key areas:

- Identity; labels given to the disease and its symptoms (e.g., diabetes, weight gain).
- Cause; what caused the disease (e.g., genes, stress).
- Timeline; beliefs regarding how long the disease will last (e.g., acute, cyclical, chronic).
- Consequences; beliefs regarding how the disease will affect the person (i.e., physical, psychological and social consequences)
- Control/cure; the extent to which the disease can be controlled or cured.

The necessity and concerns framework extend the aforementioned self-regulation theory by specifically focusing on individuals' beliefs regarding their treatment. The framework proposes that individuals hold beliefs regarding both the necessity of their treatment (i.e., the personal need for the treatment) and also beliefs regarding their concerns about the treatment (i.e., concerns about negative effects such as unpleasant symptoms and long-term consequences); and these, in turn, affect decisions regarding treatment adherence.

### *Available Instruments*

Assessment of these factors has traditionally centred on face to face interview. However there have also been specific instruments developed to look at questions around belief and perception. By necessity these are slightly less rigid than the instruments described before and are designed to be modified, in specific ways, for the disease state or treatment of interest.

#### *Illness perceptions questionnaire revised (IPQ-r)*

This comprises a series of questions in line with self-regulation theory exploring beliefs about cause, duration, consequences, personal and treatment control, how understandable the illness is, and emotional response. It also has a section on symptom prevalence<sup>219, 220</sup>. The subscales are scored separately, and higher scores represent stronger beliefs.

#### *Beliefs about medicines (BMQ)*

This is a series of questions in line with the necessity and concerns framework exploring beliefs about medications (treatments), both those that are prescribed to the individual and general medication beliefs<sup>221</sup>.

#### *Multidimensional health locus of control (MHLC)*

This questionnaire is designed to explore an individual's beliefs surrounding their control over a specific situation (medical condition). It returns results relating to the balance of internal control and the elements of external control comprising chance and powerful others<sup>222</sup>.

## Adherence

Historically many words have been used almost interchangeably when referring to the relationship between the prescribed and received treatment. The term compliance can be defined as; “The extent to which the patient’s behaviour matches the prescriber’s recommendations” but has fallen out of favour as it implies a lack of patient involvement. The term adherence emphasises the need for agreement and is now much more commonly used. Adherence can be defined as “The extent to which the patient’s behaviour matches agreed recommendations from the prescriber”

<sup>223</sup>.

Assessment of adherence varies depending on the treatment of interest. It is however either essentially a counting exercise or in some instances investigators have used surrogate (measured) variables such as laboratory results. There is also no accepted definition of non-adherence. In addition adherence is a time dependant variable and is not a binary concept as adherence is often partial. In 2012 a European consensus group (ABC - Ascertaining Barriers to Compliance) published a new taxonomy for describing and defining adherence to medications, this may go some way to standardising reports in the future **Figure 5** <sup>224</sup>.

**Figure 5 Summary of taxonomy and definitions of Adherence**

| <i>Taxonomy</i>                   | <i>Definition</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Adherence to medications</i>   | The process by which patients take their medications as prescribed, composed of <i>initiation</i> , <i>implementation</i> and <i>discontinuation</i> .<br><i>Initiation</i> occurs when the patient takes the first dose of a prescribed medication.<br><i>Discontinuation</i> occurs when the patient stops taking the prescribed medication, for whatever reason(s).<br><i>Implementation</i> is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose.<br><i>Persistence</i> is the length of time between initiation and the last dose, which immediately precedes discontinuation. |
| <i>Management of adherence</i>    | The process of monitoring and supporting patients' adherence to medications by health care systems, providers, patients, and their social networks.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Adherence-related sciences</i> | The disciplines that seek understanding of the causes or consequences of differences between prescribed (i.e. intended) and actual exposures to medicines.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

### *Summary of Evidence*

In the general chronic disease literature there is a wide body of evidence that illness beliefs and perceptions interact with behaviours and outcomes. There is a limited body of existing research that has suggested a relationship between beliefs and QOL, adherence to treatment and mortality specifically in CKD patients. In 2013 Jansen et al. described a study of 266 patients including 105 who were pre-dialysis. They completed the IPQ-r and half of the dialysis patients completed it again after 8 months. They reported that dialysis (HD and PD) patients believed more strongly that treatment controls the illness and perceived more illness consequences as compared to pre-dialysis patients. Patients on dialysis for longer had more negative perceptions of treatment consequences. Analysis over time showed that illness perceptions changed especially those related to control <sup>225</sup>.

In 2004 Covic et al. conducted a study of 82 stable HD patients who completed the SF 36 and the IPQ-r. They reported an association between both PCS and MCS scores with illness perceptions specifically around course

of disease, personal control and emotional response, with these accounting for between 15 and 31% of the variance in PCS and MCS <sup>226</sup>. In 2012 a group in France published a paper looking at clinical, sociodemographic and psychological correlates with HRQOL in prevalent HD patients. They surveyed 300 patients including the HLOC and SF 36. They reported that internal locus of control and external (influence of powerful others) positively correlated with MCS and especially the mental health score of the SF 36 on regression analysis <sup>227</sup>. In 2016 a study of Tx patients concluded that using the brief IPQ, poor (negative) illness perceptions were associated with reduced QOL, however the response rate for this study was only 27% making generalisations difficult <sup>228</sup>.

In 2009 van Dijk et al. published work looking at the relationship with illness perceptions and mortality. 182 incident dialysis patients completed the IPQ-r at baseline. Mortality data was collected after an average follow up of 3.5 years. Mortality rates were higher in those patients that perceived their treatment to be less effective <sup>229</sup>. In 2011 Chilcot et al. reported on a study of 223 HD patients with IPQ-r results and mortality follow up. They also reported that perception of treatment control (the ability of the treatment to control the illness) was associated with mortality after adjusting for covariates such as age, albumin, comorbidity and depression <sup>230</sup>. Another study in Romania also examined the relationship between illness perceptions and mortality in HD patients. They showed that over a period of

6 years IPQ-r responses varied in three of the five domains (treatment control (more likely to control the disease), consequences (less significant) and emotional response (less intense)). However they also showed an association between perceptions of treatment control and mortality<sup>231</sup>.

A recent study of illness beliefs in kidney Tx recipients reported on a survey of 52 patients in a single unit and the associations of illness perceptions, QOL and psychological distress. They reported that negative illness perceptions were associated with poorer QOL and that they also predicted anxiety but not depression<sup>228</sup>.

In pre-dialysis patient's illness perceptions have also been described in relation to the time to starting HD. Patients with stronger negative perceptions of illness progressed faster to dialysis. Specifically kidney function declined faster in patients who perceived that their kidney disease could not be personally controlled and in those who perceived that they did not fully understand their kidney disease. Faster progression was also associated with perception of kidney disease as being cyclical in nature, having many negative consequences and causing negative feelings<sup>232</sup>.

Studies in other chronic diseases (such as asthma, diabetes and heart disease) have aimed to assess perceptions and/or beliefs, with the aim of designing intervention trials designed to change outcomes and behaviour. These studies show that illness perceptions and beliefs are modifiable and

suggest the potential to alter behaviours and outcomes via this route<sup>215, 216, 233-237</sup>.

Studies that look at beliefs and perceptions often have adherence as part of the outcome measure as a marker of behaviour. One area of interest is the adherence to phosphate medication and dietary restrictions. A review of the literature in 2008 found 34 studies looking at adherence to phosphate binders and determinants thereof. The reported rate of non-adherence varied between studies from 22 – 74%, this is partially explained by the differences in definition and measurement. Only 9 of the studies assessed beliefs and 6 of these showed a correlation with adherence however several different methodologies were used<sup>238</sup>. A study published in 2015 also found that in 112 patients enrolled in a trial to evaluate adherence interventions, that necessity beliefs (from BMQ) were associated with non-adherence to phosphate binders at baseline<sup>239, 240</sup>. Other studies have also looked at medicines beliefs with regards to phosphate control. In 2014 a study of 221 haemodialysis patients on phosphate binders completed a modified version of the BMQ that included additional questions regarding phosphate binders. The authors found that medicines beliefs specific to phosphate binders and phosphate control were associated with adherence to phosphate binders<sup>241</sup>. In addition a recent study in Norway has looked at a structured education session trying to modify beliefs, completing the BMQ pre and post intervention. The intervention led to a change in the BMQ responses 3-

4 weeks after the intervention but no statistical change in serum phosphate (although levels were already at target in a large proportion of participants<sup>242</sup> .

Another area of particular interest with regards adherence is fluid restriction in HD patients, a study in 2010 looked at illness perceptions in this context. They found that perceptions around timeline and consequence predicted adherence (defined as patients in the upper quartile of Inter dialytic weight gain (IDWG))<sup>243</sup>. In 2011 a group in Ireland conducted a study of health beliefs and fluid restriction again in HD patients, they found that there were greater levels of adherence to dietary sodium restrictions when this behaviour was associated with greater “perceived benefits” and fewer “perceived barriers”<sup>244</sup>.

In 2005 there was a small study in the UK that aimed to improve compliance with fluid restriction through the use of a structured 4-week intervention plan of education, cognitive and behavioural strategies to enhance self-management of fluid intake. They reported that there was an improvement in mean IDWG 10 weeks after completion of the program<sup>245</sup>. Multiple other studies have looked at similar interventions with varying degrees of success and/or methodological rigor, however none of these studies has assessed beliefs or perceptions prior to the intervention<sup>246, 247</sup>. To my knowledge to date there are no published papers looking at other adherence measures in advanced CKD using the BMQ.

Previous studies have demonstrated patient demographic features that predict adherence with treatment. In 1998 Leggat et al. published results of a study of 6,215 US patients on dialysis. Non-compliance was defined in multiple ways (skipping one or more HD sessions per month, shortening by 10 or more minutes one or more HD sessions per month, an inter dialytic weight gain (IDWG) of more than 5.7% of dry weight or an elevated serum phosphorus (7.5mg/dl)). Using these definitions socio-demographic predictors of non-compliance were black ethnicity (aside from on the measure of phosphate), age 20 – 39 years, and smokers. Mortality was increased in those who regularly missed or shortened HD sessions and in those with high IDWGs<sup>248</sup>.

Subsequently another group reported similar results as part of the CHOICE study. Assessment was made of adherence to HD prescriptions and patients were classified as non-adherers if they missed more than 3% of appointments. Patients who were black, current smokers and those with a history of illicit drug use were more likely to be classified as non-adherers. Non-adherence was associated with an increased risk of death (hazard ratio [HR] 1.69)<sup>249</sup>. A literature review in 2007 concluded that although definitions make firm conclusions difficult, non-adherence to HD is both common and is associated with increased mortality and morbidity<sup>250</sup>.

### *Perception and Decision making Summary*

There is plenty of evidence that however we define it, adherence to treatments in ESRD is variable and in some cases very limited, be that HD time, fluid or dietary restrictions or medications.

There is some evidence that beliefs and understanding in this patient group influence adherence behaviours and there is evidence that these beliefs change over time. In addition there is evidence that lower levels of belief in the ability of treatment to control disease are associated with increased mortality. There is evidence in other patient groups that the beliefs are directly modifiable via tailored interventions. Studies looking to further understand the interaction of belief and behaviour in advanced CKD with a view to informing further interventional studies are desirable in order to ensure that we continue to make the best use of available resources and the potential that evolving technologies offer.

### **Outcome preferences**

As discussed in the preceding sections ESRD and its treatment impose many restrictions and burdens on an individual patient's life. Every day patients make decisions about their management (fluid restriction, medication, dietary restriction and HD session length) that may influence symptom control and in the longer-term, survival. However these may be competing interests as what is necessary to achieve one goal is in many instances different to that which is required to achieve the other.

There is emphasis in the pre-dialysis phase on tailoring a patient's treatment choices to best reflect the individual's preferences and many patients (especially the elderly) opt for conservative care at this stage. This is a conscious process of balancing the potential for prolonged survival against the burdens and tolerability of treatment and any real or perceived symptomatology.

However there is very little research into the factors which drive these choices in an individual and no focus on how these factors may continue to be balanced once an individual has started dialysis. As discussed, there is now an increasing focus on HRQOL as a separate and valued outcome but historically the medical approach is to make treatment recommendations aimed at prolonging survival based on the best evidence available. Very little work has been done exploring the balance of patient's desired outcomes or preferences.

### *Methods*

This is a newly emerging field of enquiry. Conjoint analysis has been successfully used in a variety of chronic conditions to determine patient preferences for outcomes associated with hypothetical therapies. This technique has been adapted from market research where it has been used for many years. Conjoint analysis allows for the simultaneous measurement of the joint effects of two or more independent variables (attributes) on the ordering of a dependant variable (preference). It is a statistical technique

used to determine how people value different attributes. There are a number of different methodological approaches to conjoint analysis. Whatever the collection method the output is a series of preference weights for each attribute indicating how important each is to an individual (or population).

#### Full profile

A subset of profiles are generated by the conjoint software containing all the attributes of interest varying across the prescribed levels. Participants are presented with this series of profiles and asked to rate each one individually. The more attributes of interest, the more profiles need to be generated and the more difficult it becomes for the individual to make an assessment. For this reason normally only 3 – 8 attributes might be chosen for such an analysis.

#### Discrete choice experiment

Profiles are presented in pairs and the most preferable is chosen from each pair. With this technique it is possible to present many more attributes by only presenting a partial profile at each pair. The more attributes of interest the more pairs need to be presented.

#### Adaptive Conjoint analysis

This is computer aided and the presented profiles are generated based on previous answers. Hence each participant is presented with a different set

of profiles. It has the advantage of reducing the number of profiles that need to be presented to each individual.

### *Summary of Evidence*

#### General

One of the earliest reports using this technique in the field of health care looked at the factors relating to a smoking cessation program and what modifications would be acceptable to participants <sup>251</sup>. Another early use was in the redesign of children's services and what parents/carers' and children's priorities were for the new service <sup>252</sup>. In many ways these studies and many related ones can still be considered "market research" however over time the questions being asked have become more complex and more "medical".

In 2005 Lloyd et al. produced a study looking at patients with epilepsy and the relative importance of seizure control as compared to adverse drug effects and cost <sup>253</sup>. Another study in 2012 also focused on epilepsy and showed that seizure reduction was the priority but that this was closely followed by long term confusion and weight change as concerns. Concern about dosing frequency and short-term side effects was much less <sup>254</sup>. Other studies have looked at treatment preferences/priorities in other areas including depression, osteoporosis, heart failure and oncology <sup>255-258</sup>.

A small number of studies have taken this interest in treatment priorities to the level of assessing survival as one of the attributes. Many of these have

been in the field of oncology where the balance is between chemotherapy side effects and symptom free survival. A study by Bridges et al. looked at patients with non-small cell lung cancer examining the relative importance of progression free survival, symptoms and mode of treatment administration. They found that improvements in progression-free survival and symptom severity were most important, but the relative importance of survival decreased with the severity of symptoms. Fatigue was the most important symptom and oral administration was preferred to infusion but this had the lowest overall importance weight <sup>259</sup>. Another study in advanced or recurrent ovarian cancer again had progression free survival as an attribute; in this study women were predominantly choosing chemotherapy regimens based on progression free survival but they were willing to trade a significant reduction in survival for reductions in treatment related toxicity <sup>260</sup>.

A study published in 2016 looked at the differences in preferences between patients, physicians and the general population in the treatment of refractory chronic lymphocytic leukaemia. They found that physicians placed the most weight on overall survival, patients on treatment administration and the general public put more weight on avoidance of serious infections <sup>261</sup>.

In 2010 Stanek et al. examined symptoms versus survival in patients with congestive heart failure. This is perhaps more relevant to patients with

advanced CKD as they have similar symptom clusters and poor overall survival prospects. They discovered that in symptomatic patients there was a clustering into either a preference for survival or a preference for symptom control with the majority falling into the latter group. There were no predictors of which group an individual patient would be in (age, gender, ethnicity, severity of heart failure, cause, QOL or objective measure of heart function)<sup>262</sup>.

### CKD

There are few papers published using conjoint analysis in patients with CKD. The majority of these are focused on areas other than direct treatment choices. There is one paper using the technique to explore the attitudes to service development in the general public <sup>263</sup> and one that looks at treatment options in Lupus Nephritis <sup>264</sup>. There are two studies that focus on the preferences of physicians when considering transfusion in CKD and when faced with an elderly patient approaching ESRD and modality choice <sup>265, 266</sup>. There are three examining attitudes to Tx allocation and risk <sup>267-269</sup>.

One group in Australia has published two papers relating to the same cohort of patients exploring patients' and caregivers' attitudes to RRT modality choice in the pre dialysis setting. They found that patients were willing to trade life expectancy to reduce the number of visits to hospital and to increase their ability to travel. Caregivers were less willing to trade life expectancy. 65% of patients preferred home based therapy as opposed to

72% of care givers. However it is worth noting that the life expectancy levels were set at 2,5,10 and 15 years and this is not realistic in the setting of ESRD<sup>59, 270</sup>. One further study has looked specifically at treatment preferences in ESRD, this time at factors related to the choice of conventional or daily HD. They found that 44% (of 126) patients would not choose daily HD regardless of health benefits. Willingness to switch increased in the remainder as QOL, health benefits, weekly transportation time and hospitalisations decreased<sup>271</sup>. A further study underway in New Zealand is exploring patient and caregiver preferences on factors related to modality and setting choice<sup>272</sup>.

### *Outcome preferences Summary*

As outlined above there is very little in the literature in regard to structured assessment of outcome preferences and decision making in advanced CKD. This is an area that if developed could help in the difficult decisions that individual patients are required to make in the time before commencing RRT.

## **Conclusion**

Advanced CKD is known to be associated with a number of harms and impacts on physical health and quality of life. A better understanding of how different aspects of patient reported outcomes interact with the more traditional medical outcomes and how individuals understanding and treatment beliefs may impact on choices and behaviours could lead to a more personalised discussion and improve the ability of healthcare

professionals to facilitate shared decision making and improve concordance with therapy. This in turn might be hoped to lead to improvements in quality of life and potentially physical health.

## Aims

- To define the QOL profile of a prevalent population with advanced CKD and the relationship with symptoms
- To investigate the relationship treatment beliefs and illness perception and the interaction with biochemical and demographic factors
- To develop and test a way of measuring and recording the outcome preference phenotype in advanced CKD
- To explore how perception of treatment burden impacts on outcome preference
- To explore the utility of frequent symptom tracking in a prevalent RRT population

## Chapter 2. Methods

Outline methods are described here with more detailed methods given in the relevant results chapters as required. This thesis comprises results from two different studies that are outlined below.

### **Influence of illness beliefs and treatment outcome preferences in patients with end stage renal disease (INTUITIVE)**

This questionnaire-based study was designed to explore illness beliefs and preferences in advanced CKD in the wider context of psychosocial and physical factors.

The study and protocol were approved by the relevant local research ethics committee and the NHS Trust's medical research department.

#### **Patient Recruitment**

All patients were recruited from within Derby Hospitals NHS Foundation Trust's renal department.

#### ***Inclusion Criteria***

- Age  $\geq 18$  at study entry
- Any patient requiring RRT and under regular follow up or any patient attending renal pre dialysis clinic and predicted to start RRT within one year

### *Exclusion Criteria*

- Significant cognitive impairment such that patients are unable to understand the study questions

### *Recruitment and Screening*

#### *All Patients:*

All potential participants were given contact details for the renal unit to request further information or decline participation. After at least 24 hours patients were then contacted by me and asked if they required any further information. For those that were interested in participating in the study a face to face meeting was then arranged. During this meeting the patient completed the consent paperwork and either completed the first study visit or arranged another convenient time for a study visit. Patients unable to understand verbal or written information in English were provided with a suitable interpreter from Derby Hospitals NHS Foundation Trust.

Patient participation was recorded in patients' notes as per Trust protocol and the patient's general practitioner was informed. Patients' were allocated a unique participant identification number for all subsequent study documentation and a separate list was maintained in the participant recruitment log within the trial master file (TMF). The original Consent Form was filed in the TMF, and copy's given to the patient and filed in patient's medical records.

### *Withdrawal of Participants*

Participants had the right to withdraw at any time without giving any reason.

Participants would be withdrawn if they withdraw consent for the study or if they suffered new, significant and permanent cognitive impairment such that they were unable to understand the study questions. They would also be withdrawn if they moved out of area.

### **Study Procedures**

Study participants were asked to complete a series of questionnaires at each study visit. Each visit took approximately 90 minutes. Where possible all questionnaires were completed in the presence of a research team member and at one sitting. For patients unable to understand English a suitable interpreter was provided for the completion of the questionnaires.

### **Visit schedule**

All participants undertook a baseline visit with a subset (10%) undertaking a second study visit after around 1 year. This second visit was to look at stability of the PROM outputs over time.

### **Questionnaires**

#### **A copy of all questionnaires is attached in the appendix (see Appendix**

Copy Questionnaires) at the end of this thesis. Below is a brief summary and rationale of each.

### *Quality of life*

The KDQOL 36 was chosen as a generic measure of HRQOL. This instrument utilizes the SF-12 supplemented with 24 additional questions directly related to domains of burden of kidney disease. The output is reported in 16 standardized cells. We used the previously validated UK version. The burden of kidney disease domains and the summary PCS and MCS scores are widely reported in the literature making comparison meaningful.

### *Symptoms*

#### *The Dialysis symptom index (DSI)*

The DSI was chosen to collect data on symptom prevalence and burden. Within the questionnaire patients are asked to answer a series of 30 questions relating to the presence of a specific symptom with a yes/no and if yes to rate severity 1 – 5.

#### *Screen for depression*

As a screen for depression we opted for the Patient Health Questionnaire-9 (PHQ-9). A cut off score of 10 was used to identify patients for further assessment (around 90% specificity and sensitivity for diagnosing clinical depression in the dialysis population)<sup>180</sup>.

### *Disease Burden*

This was assessed with four instruments:

### Illness intrusiveness

The Illness intrusiveness ratings scale (IIRS) was used to quantify some of the social impacts.

### Treatment burden and tolerability

We wanted an estimation, of each individual patient's perceived treatment burden (TB) and treatment tolerability (TT). These were assessed by asking patients to mark on a 100 point scale.

### Dialysis treatment recovery time

For patients on HD, dialysis treatment recovery time (DRT) was recorded. This is a very simply collected key metric of overall wellbeing, and particularly sensitive to HD treatment related factors. Treatment recovery time varies between minutes and days and allows direct measurement of the temporal burden of therapy above and beyond time spent actually on the dialysis machine.

## *Understanding and decision making*

### Illness perceptions

Illness perceptions questionnaire revised (IPQ-r), a series of questions exploring beliefs about cause, duration and impact of disease, I adapted this to be kidney disease specific. This has been previously validated in other disease situations and is designed to be altered in this way.

### Beliefs about medicines

Beliefs about medicines questionnaire (BMQ), a series of questions exploring belief about medications. This has been previously validated in other disease situations and is designed to be altered to be disease and treatment specific. Thus there were four versions looking at beliefs in relation to dialysis, fluid and dietary restriction in addition to prescribed medications specifically for kidney disease and in general.

### Outcome preferences questionnaire (OPQ)

I used full-profile conjoint analysis techniques to develop a question set designed to elicit patient preferences with regards to treatment outcomes. The resultant OPQ consisted of 25 treatment profiles that patients were asked to rate on a scale of 1-10. Each profile represented a potential outcome of a new treatment. Attributes were chosen to reflect a specific aspect of ESRD or its management and specifically included survival and treatment burden as we were interested in the impact of these on the decision process. The other 4 attributes were tiredness, shortness of breath, depression and physical discomfort. Each attribute varied across 4 severity levels. Severity levels for symptoms and treatment burden were assessed relative to current status and were presented as a little more, a lot more, a little less or a lot less, survival was presented as plus/minus 6 or 12 months.

### **Additional information**

Additional information was collected and recorded in the case report form (CRF).

This included social and demographic factors, diagnosis, timing of initial referral to nephrology, co-morbidity, medication and CV risk factors. For patients on dialysis initial choice of RRT, initial modality and interventions or complications relating to treatment (infection, access loss/intervention, admissions) during the study period were also recorded. In addition during the study period, data was collected from the medical records at three-month intervals, on fluid balance, nutrition, calcium and phosphate balance, delivered dose of dialysis, anaemia, new co-morbidity. After the initial study period patients continued to be followed up for the purpose of collecting mortality data.

### ***Laboratory Assays***

There were no blood samples taken as a part of this study. The results of laboratory investigations, performed as part of routine clinical care, were however collected, specifically renal profile and full blood count data. Typically this was monthly for dialysis and 3 monthly for transplant recipients. The pre dialysis patients had bloods every 4 -6 weeks.

## Statistical Plan

### *Sample Size Determination*

Due to the observational nature of this study and lack of published data, it was not possible to perform formal sample size determinations. Of more significance however is the current inability to select the most 'clinically' significant measure to utilise in these assumptions. The data generated by this pilot study will be valuable to informing sample size estimates for future studies.

### *Statistical Methods*

Demographic data are presented as mean  $\pm$  SD, all PRO data are reported as mean  $\pm$  SD unless otherwise stated in which case they will be median and inter quartile range (IQR). ANOVA was used to look for variation across groups. Correlations were assessed using Pearson's correlation for variables with normal distribution and for non-parametric variables Spearman's correlations were used to determine association between PROs and demographic or clinical data. The independent samples T test and Mann-Whitney U test were used to compare groups, depending on the distribution of data. Statistical significance was set at 5% and all data were analysed using SPSS, Version 24 (IBM Corp, Armonk, NY).

Missing values were dealt with for IIRS missing values coded as 1 (not applicable) and PHQ9 missing values assumed to be 0. All other missing values were recorded as null.

## Derby Evaluation of Illness

### Study Design

A custom website (<http://www.kidneypatientsurvey.com>) was built to capture daily PROMs utilising visual analogue scales (VAS). The use of VAS allowed free selection of status along a line from worst (0) to best (100). The specific outcomes of interest were determined by literature review of published data on symptom burden in CKD and information on patient priorities from our own unpublished patient survey<sup>124, 188, 273</sup>. This process resulted in the selection of 6 separate domains: general wellbeing (GWB), pain, sleep, breathing, energy and appetite.

### Patient recruitment

Use of the website was initially offered to all patients undergoing unit-based haemodialysis (HD) within our unit who reported having regular access to the internet. The project was subsequently rolled out to include patients attending our pre dialysis clinics and to peritoneal dialysis (PD) patients. Each participant was given a set of simple written instructions and a unique username and password with which to register on the site. Once registered, the website issued them with a PIN to use with their username for all subsequent data submission. A news section of the website was updated at intervals to keep patients informed about the project. A copy of the master key table linking each username with a specific individual patient identity remained on a separate secure internal hospital computer system,

inaccessible from the internet. Supplementary information on HD day, hospital admissions, additional treatments and routine laboratory investigations was collected from the electronic patient record. For the purpose of this initial evaluation recurrent efforts to reinforce repeated engagement with this PROM were not made.

### Statistical Plan

After seeking appropriate advice from the Trust research and development department this work was considered not to require formal ethical approval as it was regarded as an extension to current patient care processes. The data were downloaded from the website server after 11 months and combined with the supplemental clinical data. Demographic data are presented as mean  $\pm$  SD; all PRO data are reported as median and inter quartile range (IQR) unless otherwise specified. Spearman's correlations were used to determine association between PROs and demographic and clinical data, the Mann-Whitney U test was used when comparing variables between groups. Statistical significance was set at 5% and all data were analysed using SPSS, Version 19.0.0.1 (Armonk, NY: IBM Cor).

### **Chapter 3. An exploration of HRQOL in individuals with advanced CKD; relation to other PROMs and biochemical metrics. Is it all about symptoms?**

#### **Abstract**

##### ***Introduction***

Available data show that Health Related Quality of Life (HRQOL) is poor in advanced CKD. I set out to explore the HRQOL in a population with advanced CKD and look at the relationships with other patient reported outcome measures (PROMs) and with demographic, treatment related and laboratory data. In the general population HRQOL correlates with age, gender and a number of sociodemographic factors. A better understanding of the factors that underpin the variations in HRQOL in advanced CKD might lead to the development of further strategies for intervention.

##### ***Methods***

Prevalent haemodialysis (HD; n= 26), peritoneal dialysis (PD; n= 9), transplant (Tx; n= 14) and CKD 5 patients (n= 5) were recruited and completed the KDQOL-SF along with a number of additional questionnaires including the illness intrusiveness ratings scale (IIRS), PHQ-9 (cut point PHQ  $\geq 10$  for depression screening in dialysis), dialysis recovery time (DRT) and measures of treatment tolerability (TT) and burden (TB) and the dialysis

symptom index (DSI). Additional demographic and routine biochemical and treatment related data were collected from the patient record.

### *Results*

54 individuals (26 Haemodialysis (HD), 9 Peritoneal dialysis (PD), 14 Transplant (Tx) and 5 Pre dialysis) completed the KDQOL SF with outputs in the composite domains of Physical Component Score (PCS), Mental Component Score (MCS) and Kidney Disease Component Score (KDCS). Overall scores for PCS were below the general population norm whilst MCS scores were near to the general population norm. PCS was greater in Tx ( $43.28 \pm 11.81$ ) when compared to HD ( $33.01 \pm 10.96$ ) and met the previously published threshold for minimal Clinically Important Difference (mCID) ( $> 5.7$ ). There was no difference in the outputs of PHQ9, DSI (total symptom count or symptom burden), TT, TB or IIRS between the groups and no significant demographic or biochemical correlations with HRQOL. There were significant inverse correlations for MCS with symptom count ( $r = -0.570$ ,  $p < 0.0005$ ) symptom burden ( $r = -0.564$ ,  $p < 0.0005$ ) and PHQ9 ( $r = -0.619$ ,  $p < 0.0005$ ) and with PCS for symptom count ( $r = -0.463$ ,  $p < 0.0005$ ) and symptom burden ( $r = -0.447$ ,  $p = 0.001$ ). The specific symptoms that correlated inversely with MCS in the dialysis population were tiredness ( $r = -0.615$ ,  $p < 0.0005$ ), dry mouth ( $r = -0.615$ ,  $p < 0.0005$ ), dry skin ( $r = -0.623$ ,  $p < 0.0005$ ) and Itching ( $r = -0.595$ ,  $p < 0.0005$ ).

## Discussion

We have confirmed that HRQOL is poor in advanced CKD, this however does not seem to correlate with age or other demographic factors as would be expected in the general population. The correlation of worsening MCS and PCS with increasing symptom count and symptom burden as well as depression is not surprising but lends weight to the argument for tackling symptoms. In the dialysis population MCS correlates inversely with the burden of specific symptoms and this relationship gives a potential focus to these efforts. The presence or degree of specific symptoms appeared to have less of an effect on PCS and further work is needed in this area. Interventions that focus on managing/minimising these symptoms might lead to the desired improvements in HRQOL.

## Introduction

Further information is required to understand the interrelation of factors that lead to poor HRQOL in advanced CKD with the aim of designing intervention trials in the future aimed at improving outcomes. We set out to look at the relationships between HRQOL as captured by the KDQOL SF, with other PROM outputs and clinical and demographic factors in a population with advanced CKD.

There is a wealth of data demonstrating that HRQOL is poor in patients with advanced CKD with or without dialysis and a developing understanding that poor QOL is associated with increased mortality<sup>274</sup>. In addition there is a

very high prevalence of reported depression in advanced CKD and dialysis populations<sup>124, 195</sup>. Data also suggest that the presence of depression is associated with the rate of progression to ESRD and with overall mortality<sup>44, 195, 275</sup>. There are also data showing that individuals with advanced CKD have a high symptom burden irrespective of treatment and that QOL is related closely to symptom burden in ESRD<sup>276</sup>.

While there is a growing understanding of the prevalence of poor QOL and depression coupled with high symptom burden in advanced CKD, there is little guidance on what can be done to alleviate this at the individual patient level. A number of projects are under development to allow collection of HRQOL data at the individual level in a systematic way with the ability to feed this information back to both the individual and the clinician. However much more needs to be understood about how these various patient reported outcomes interact and interrelate both with each other and with patient and treatment related factors. An improved understanding of the factors that underpin the variations in HRQOL results might lead to the development of further strategies for intervention.

## Methods

Participants were recruited from the prevalent RRT and pre dialysis programme. There was no formal sample size calculation for this study due to lack of data on which to base any calculation however the aim was to recruit as many individuals as would consent, and I had capacity to study

within the timeframe. In reality, recruitment was slow especially in those not on haemodialysis as individuals were not prepared to accept the time commitment required for the study. In total 167 individuals were approached and 61 consented however 3 did not have a first study visit due to problems with scheduling, one was called for transplant prior to completing the visit and the other two were unavailable.

Participants completed a series of questionnaires as part of the INTUITIVE study. All patients were studied at baseline and 10% had a further study visit after around 12 months. For the purposes of exploring HRQOL the questionnaires included KDQOL SF, UK version 1.3<sup>94</sup>. In addition assessment of depression was by Patient health questionnaire (PHQ9)<sup>179, 180</sup>, symptoms were assessed by Dialysis Symptom Index (DSI) and impacts of disease and treatment were explored using the Illness Intrusiveness Ratings Scale (IIRS), Treatment Tolerability (TT) and Treatment Burden (TB) recorded on a 100 point visual analogue scale and dialysis recover time (DRT). Additional information was obtained from medical records with regards to comorbidity, treatments and routine monitoring.

KDQOL SF questionnaires were analysed using an Excel spreadsheet as described by Hayes in the manual for use and scoring<sup>277, 278</sup>, resulting in individual component scores. The individual component scores were then transferred to SPSS version 24 for further analysis. KDQOL outputs are standardised so that maximum QOL on any subscale is 100, MCS and PCS

are standardised so that 50 represents the general population norm with a standard deviation (SD) of 10. When undertaking multiple comparisons the level of statistical significance was adjusted using the Bonferroni correction

277.

## Results

For the INTUITIVE study 58 individuals were recruited and completed at least part of the study protocol. Overall completion rates for each questionnaire were high ranging from 98% completing the IPQr down to 88% of individuals completing the outcome preference questioner. The questionnaires tended to be completed in the same order and the outcome preference questionnaire was the last to be presented. **Table 2** shows the basic characteristics of the 58 individuals at recruitment. 54 individuals (26 HD, 9 PD, 14 Tx and 5 Pre dialysis) completed the KDQOL SF with sufficient answers to give valid outputs in the composite domains of Physical Component Score (PCS), Mental Component Score (MCS) and Kidney Disease Component Score (KDCS).

Baseline demographic and biochemical data for these 54 are shown in **Table 3**, the demographics were similar across all treatment status groups although there was a higher proportion of smokers in the pre dialysis cohort. Biochemical parameters differed in line with the treatment status.

**Table 2** Demographics for all patients recruited into Influence of illness beliefs and treatment outcome preferences in patients with end stage renal disease study

|                                                             |                             | N %       | Mean $\pm$ SD       |
|-------------------------------------------------------------|-----------------------------|-----------|---------------------|
| Age (years)                                                 |                             |           | 61 $\pm$ 13         |
| Gender                                                      | Male                        | 36 (62.1) |                     |
| RRT Vintage (years)                                         |                             |           | 5.55 $\pm$ 7.25     |
| RRT Status                                                  | Haemodialysis (HD)          | 29 (50.0) |                     |
|                                                             | Peritoneal Dialysis         | 10 (17.2) |                     |
|                                                             | Transplant                  | 14 (24.1) |                     |
|                                                             | Pre Dialysis                | 5 (8.6)   |                     |
| Smoker                                                      | Yes                         | 4 (7.4)   |                     |
|                                                             | Ex                          | 14 (25.9) |                     |
| Diabetes                                                    | Yes                         | 22 (37.9) |                     |
| Heart Failure                                               | Yes                         | 5 (8.6)   |                     |
| Comorbidity count                                           |                             |           | 1.72 $\pm$ 1.36     |
| Number in the Household                                     | 1                           | 19 (32.8) |                     |
|                                                             | 2                           | 22 (37.9) |                     |
|                                                             | 3 or more                   | 17 (29.3) |                     |
| Religious                                                   | Religious Belief            | 42 (72.4) |                     |
| Highest Education                                           | Pre 16                      | 12 (21.4) |                     |
|                                                             | Post 16                     | 14 (25.0) |                     |
|                                                             | Degree                      | 6 (10.7)  |                     |
|                                                             | Professional Qualifications | 7 (12.5)  |                     |
|                                                             | No Formal Qualifications    | 17 (30.4) |                     |
| Employment Status                                           | In work                     | 13 (22.8) |                     |
|                                                             | Retired                     | 31 (54.4) |                     |
|                                                             | Unemployed                  | 13 (22.8) |                     |
| Total Number Tablets / day                                  |                             |           | 8.85 $\pm$ 4.56     |
| Phosphate Binder tablets / day                              |                             |           | 1.56 $\pm$ 1.97     |
| Prescribed antidepressants                                  | Yes                         | 5 (8.8)   |                     |
| Mean IDWG (HD patients only) (kg)                           |                             |           | 1.32 $\pm$ .57      |
| Albumin (g/L)                                               |                             |           | 32.27 $\pm$ 4.40    |
| Adjusted Calcium (mmol/L)                                   |                             |           | 2.45 $\pm$ .14      |
| Bicarbonate (mmol/L)                                        |                             |           | 22.45 $\pm$ 2.37    |
| HbA <sub>1c</sub> (%)                                       |                             |           | 6.93 $\pm$ 1.37     |
| Potassium (mmol/L)                                          |                             |           | 4.59 $\pm$ .65      |
| Phosphate (mmol/L)                                          |                             |           | 1.47 $\pm$ .41      |
| Parathyroid Hormone (ng/L)                                  |                             |           | 256.92 $\pm$ 198.31 |
| eGFR (mL/min/1.73m <sup>2</sup> ) (Transplant and CKD only) |                             |           | 13.61 $\pm$ 14.29   |
| Haemoglobin (g/L)                                           |                             |           | 113.66 $\pm$ 16.81  |

RRT = Renal Replacement therapy, IDWG = Intradialytic weight gain, eGFR =estimated glomerular filtration rate

Overall scores for PCS were ( $36.46 \pm 11.72$ ), and this is  $> 1$  SD below the general population norm ( $50 \pm 10$ ) whilst MCS scores ( $50.78 \pm 10.99$ ) were near to the general population norm. There were only minimal differences between the treatment status groups for any of the KDQOL subscales and they only reached statistical significance for burden of kidney disease and physical functioning **Table 4**. With regards to the summary scores of PCS, MCS and KDCS, PCS was greater in Tx when compared to HD and this would meet the previously published threshold for mCID ( $> 5.7$ )<sup>113</sup>. There was no difference in MCS between the treatment groups. KDCS was statistically better for Tx when compared to any of the other groups. There was no difference in the outputs of PHQ9, DSI (total symptom score or symptom burden), TT, TB or IIRS between the groups **Table 5**.

**Table 3** Summary demographics for those completing KDQOL and breakdown by renal replacement therapy status.

|                                   |                             | Treatment Status |           |                            |           |                           |          |                             |           |                    |        |
|-----------------------------------|-----------------------------|------------------|-----------|----------------------------|-----------|---------------------------|----------|-----------------------------|-----------|--------------------|--------|
|                                   |                             | Total (54)       |           | Haemodialysis (n=26)       |           | Peritoneal Dialysis (n=9) |          | Transplant (n=14)           |           | Pre Dialysis (n=5) |        |
|                                   |                             |                  |           | (A)                        |           | (B)                       |          | (C)                         |           | (D)                |        |
|                                   |                             | Mean ± SD        | N %       | Mean ± SD                  | N %       | Mean ± SD                 | N %      | Mean ± SD                   | N %       | Mean ± SD          | N %    |
| Age (years)                       |                             | 61 ± 13          |           | 63 ± 14                    |           | 62 ± 10                   |          | 59 ± 10                     |           | 53 ± 16            |        |
| Gender                            | Male                        |                  | 35 (64.8) |                            | 18 (69.2) |                           | 5 (55.6) |                             | 9 (64.3)  |                    | 3 (60) |
| RRT Vintage (years)               |                             | 5.55 ± 7.25      |           | 4.86 ± 5.05                |           | 0.80 ± 0.79               |          | 10.36 ± 10.57               |           |                    |        |
| Smoker                            | Yes                         |                  | 4 (8.0)   |                            | 1 (4.2)   |                           | 0        |                             | 0         |                    | 3 (60) |
|                                   | Ex                          |                  | 14 (28.0) |                            | 2 (8.3)   |                           | 4 (44.4) |                             | 8 (66.7)  |                    | 0      |
| DM                                | Yes                         |                  | 19 (37.9) |                            | 11 (44.8) |                           | 5 (60.0) |                             | 3 (21.4)  |                    | 0      |
| Heart Failure                     | Yes                         |                  | 4 (8.6)   |                            | 3 (13.8)  |                           | 1 (10.0) |                             | 0         |                    | 0      |
| Comorbidity Count                 |                             | 1.6 ± 1.3        |           | 1.9 ± 1.6                  |           | 2.0 ± 1.1                 |          | 1.2 ± 0.9                   |           | 1.2 ± 1.1          |        |
| Number in the Household           | 1                           |                  | 19 (35.2) |                            | 10 (38.5) |                           | 2 (22.2) |                             | 6 (42.9)  |                    | 1 (20) |
|                                   | 2                           |                  | 20 (37.0) |                            | 8 (30.8)  |                           | 4 (44.4) |                             | 5 (35.7)  |                    | 3 (60) |
|                                   | 3 or more                   |                  | 15 (27.8) |                            | 8 (30.8)  |                           | 3 (33.3) |                             | 3 (21.4)  |                    | 1 (20) |
| Religious                         | Religious Belief            |                  | 38 (70.4) |                            | 21 (80.8) |                           | 5 (55.6) |                             | 10 (71.4) |                    | 2 (40) |
| Highest Education                 | Pre 16                      |                  | 12 (23.1) |                            | 6 (24.0)  |                           | 3 (37.5) |                             | 3 (21.4)  |                    | 0      |
|                                   | Post 16                     |                  | 12 (23.1) |                            | 3 (12.0)  |                           | 4 (50.0) |                             | 1 (7.1)   |                    | 4 (80) |
|                                   | Degree                      |                  | 6 (11.5)  |                            | 3 (12.0)  |                           | 0        |                             | 2 (14.3)  |                    | 1 (20) |
|                                   | Professional Qualifications |                  | 7 (13.5)  |                            | 1 (4.0)   |                           | 1 (12.5) |                             | 5 (35.7)  |                    | 0      |
|                                   | No Formal Qualifications    |                  | 15 (30.4) |                            | 12 (48.0) |                           | 0        |                             | 3 (21.4)  |                    | 0      |
| Employment Status                 | In work                     |                  | 12 (22.6) |                            | 4 (15.4)  |                           | 3 (33.3) |                             | 5 (35.7)  |                    | 0.0    |
|                                   | Retired                     |                  | 29 (54.7) |                            | 15 (57.7) |                           | 4 (44.4) |                             | 8 (57.1)  |                    | 2 (50) |
|                                   | Unemployed                  |                  | 12 (28.8) |                            | 7 (26.9)  |                           | 2 (22.2) |                             | 1 (7.1)   |                    | 2 (50) |
| Total Number Tablets / day        |                             | 8.9 ± 0.6        |           | 9.0 ± 3.4 <sup>8,C,D</sup> |           | 8.2 ± 6.7                 |          | 10.2 ± 4.1                  |           | 5.9 ± 6.4          |        |
| Phosphate Binder tablets / day    |                             | 1.6 ± 2          |           | 2.8 ± 2                    |           | 0.8 ± 1.3                 |          |                             |           |                    |        |
| Prescribed antidepressant         |                             |                  | 5 (9.4)   |                            | 2 (7.7)   |                           | 2 (22.2) |                             | 0         |                    | 1 (20) |
| Mean IDWG (HD patients only) (kg) |                             | 1.32 ± 0.57      |           | 1.36 ± 0.56                |           |                           |          |                             |           |                    |        |
| Albumin (g/L)                     |                             | 32.3 ± 4.4       |           | 32.4 ± 4.0                 |           | 29.2 ± 5.1                |          | 35.6 ± 3.5 <sup>B</sup>     |           | 31.2 ± 2.8         |        |
| Adjusted Calcium (mmol/L)         |                             | 2.45 ± 0.14      |           | 2.47 ± 0.12                |           | 2.41 ± 0.20               |          | 2.49 ± 0.13                 |           | 2.36 ± 0.08        |        |
| Bicarbonate (mmol/L)              |                             | 22.45 ± 2.37     |           | 22.12 ± 1.85               |           | 22.78 ± 1.69 <sup>U</sup> |          | 25.00 ± 1.77 <sup>A,U</sup> |           | 19.65 ± 3.45       |        |
| HbA1C (%)                         |                             | 6.93 ± 1.37      |           | 7.28 ± 1.29                |           | 6.34 ± 1.21               |          |                             |           |                    |        |
| Potassium (mmol/L)                |                             | 4.59 ± 0.65      |           | 4.66 ± 0.66                |           | 4.34 ± 0.62               |          | 4.51 ± 0.65                 |           | 4.84 ± 0.68        |        |
| Phosphate (mmol/L)                |                             | 1.47 ± .41       |           | 1.58 ± 0.35 <sup>C</sup>   |           | 1.56 ± 0.47 <sup>C</sup>  |          | 0.98 ± 0.32                 |           | 1.54 ± 0.16        |        |
| Parathyroid Hormone (ng/L)        |                             | 256.9 ± 198.3    |           | 255.2 ± 153.6              |           | 297.8 ± 194.5             |          | 97.0 ± 68.7                 |           | 344.6 ± 408.9      |        |
| eGFR (mL/min/1.73m2)              |                             |                  |           |                            |           |                           |          | 39.6 ± 17.7 <sup>D</sup>    |           | 10.7 ± 2.0         |        |
| Haemoglobin (g/L)                 |                             | 113.7 ± 16.8     |           | 111.0 ± 17.5               |           | 114.5 ± 15.6              |          | 124.9 ± 15.1                |           | 104.9 ± 9.6        |        |

Results are based on two-sided tests assuming equal variances. For each significant pair, the key of the smaller category appears in the category with the larger mean. Significance level as indicated by <sup>superscript</sup> letters ≤0.05 <sup>1</sup>. RRT = Renal Replacement therapy, IDWG = Intradialytic weight gain, eGFR =estimated glomerular filtration rate <sup>1</sup>. Tests are adjusted for all pairwise comparisons within a row of each innermost sub table using the Bonferroni correction.

Table 4 Summary KDQOL outputs as total and by renal replacement therapy status

|                               | Treatment Status |       |                      |           |                            |           |                               |       |                    |       |
|-------------------------------|------------------|-------|----------------------|-----------|----------------------------|-----------|-------------------------------|-------|--------------------|-------|
|                               | Total (54)       |       | Haemodialysis (n=26) |           | Peritoneal Dialysis (n=9)  |           | Transplant (n=14)             |       | Pre Dialysis (n=5) |       |
|                               | Mean ± SD        |       | (A)                  | (B)       | (C)                        | (D)       |                               |       |                    |       |
|                               |                  |       | Mean ± SD            | Mean ± SD | Mean ± SD                  | Mean ± SD |                               |       |                    |       |
| Role; emotional               | 74.69 ±          | 40.40 | 73.08 ±              | 41.12     | 66.67 ±                    | 44.10     | 85.71 ±                       | 36.31 | 66.67 ±            | 47.14 |
| Energy/ fatigue               | 48.55 ±          | 26.56 | 41.79 ±              | 28.06     | 46.11 ±                    | 22.75     | 64.64 ±                       | 21.26 | 43.00 ±            | 25.88 |
| Social function               | 64.35 ±          | 31.51 | 54.81 ±              | 34.65     | 72.22 ±                    | 26.35     | 75.89 ±                       | 25.69 | 67.50 ±            | 30.10 |
| Emotional wellbeing           | 77.50 ±          | 19.79 | 74.15 ±              | 24.30     | 82.22 ±                    | 17.90     | 81.21 ±                       | 12.90 | 76.00 ±            | 12.00 |
| Role; physical                | 46.76 ±          | 43.45 | 45.19 ±              | 41.24     | 36.11 ±                    | 41.67     | 58.93 ±                       | 46.62 | 40.00 ±            | 54.77 |
| Pain                          | 64.73 ±          | 28.22 | 59.62 ±              | 29.17     | 63.33 ±                    | 23.88     | 76.46 ±                       | 26.89 | 61.00 ±            | 32.72 |
| General health                | 42.87 ±          | 23.08 | 36.73 ±              | 23.91     | 44.44 ±                    | 21.28     | 50.00 ±                       | 23.29 | 52.00 ±            | 16.81 |
| Overall health                | 64.15 ±          | 20.70 | 59.60 ±              | 21.31     | 62.22 ±                    | 16.41     | 75.71 ±                       | 22.09 | 58.00 ±            | 8.37  |
| Burden of kidney disease      | 57.52 ±          | 32.36 | 42.79 ±              | 26.79     | 72.92 ± 31.72 <sup>A</sup> |           | 82.57 ± 26.42 <sup>A,B</sup>  |       | 36.25 ±            | 19.96 |
| Cognitive function            | 84.82 ±          | 16.15 | 86.92 ±              | 14.54     | 85.93 ±                    | 13.52     | 81.45 ±                       | 20.29 | 81.33 ±            | 18.50 |
| Dialysis staff encouragement  | 87.78 ±          | 23.51 | 83.50 ±              | 24.40     | 96.88 ±                    | 5.79      | 86.54 ±                       | 30.58 | 100.00 ±           | .00   |
| Effects of kidney disease     | 74.86 ±          | 22.59 | 69.42 ±              | 24.75     | 73.96 ±                    | 21.88     | 88.63 ±                       | 17.19 | 66.16 ±            | 8.01  |
| Patient satisfaction          | 84.94 ±          | 14.10 | 81.33 ±              | 13.88     | 83.33 ±                    | 14.43     | 88.46 ±                       | 14.25 | 96.67 ±            | 7.45  |
| Physical functioning          | 50.82 ±          | 31.41 | 40.19 ±              | 28.37     | 44.44 ±                    | 35.57     | 72.82 ± 25.89 <sup>A</sup>    |       | 56.00 ±            | 27.93 |
| Quality of social interaction | 80.49 ±          | 17.17 | 82.31 ±              | 19.50     | 77.78 ±                    | 20.55     | 80.95 ±                       | 12.22 | 74.67 ±            | 10.95 |
| Sexual function               | 69 ± 39          |       | 64 ± 47              |           | 73 ± 27                    |           | 74 ± 33                       |       | 73 ± 34            |       |
| Sleep                         | 58.80 ±          | 23.10 | 56.53 ±              | 25.19     | 51.94 ±                    | 20.22     | 67.89 ±                       | 22.63 | 57.00 ±            | 14.73 |
| Social support                | 74.52 ±          | 30.06 | 68.00 ±              | 32.96     | 66.67 ±                    | 35.36     | 86.88 ±                       | 19.81 | 86.67 ±            | 18.26 |
| Symptoms                      | 78.52 ±          | 18.20 | 76.77 ±              | 19.90     | 78.10 ±                    | 13.87     | 84.91 ±                       | 17.35 | 70.91 ±            | 18.28 |
| SF12 MCS                      | 50.78 ±          | 10.99 | 49.35 ±              | 12.71     | 52.51 ±                    | 10.96     | 53.14 ±                       | 8.87  | 48.46 ± 6.84       |       |
| SF12 PCS                      | 36.46 ±          | 11.72 | 33.01 ±              | 10.96     | 33.70 ±                    | 10.14     | 43.28 ± 11.81 <sup>A</sup>    |       | 40.22 ±            | 11.63 |
| KDCS                          | 72.63 ±          | 13.49 | 68.50 ±              | 13.90     | 71.80 ±                    | 15.10     | 82.85 ± 7.97 <sup>A,B,D</sup> |       | 68.24 ±            | 6.30  |

Results are based on two-sided tests assuming equal variances. For each significant pair, the key of the smaller category appears in the category with the larger mean. Significance level versus other groups as indicated by superscript letters;  $p \leq 0.05$ <sup>1</sup>. PCS = SF12 Physical Component Scale, MCS = SF12 Mental Component Scale, KDCS = Kidney Disease Component Scale

<sup>1</sup>. Tests are adjusted for all pairwise comparisons within a row of each innermost sub table using the Bonferroni correction.

**Table 5** Summary PROM outputs as total and by renal replacement therapy status

|             |                     | Treatment Status |               |                      |               |                           |               |                   |               |                    |               |
|-------------|---------------------|------------------|---------------|----------------------|---------------|---------------------------|---------------|-------------------|---------------|--------------------|---------------|
|             |                     | Total (54)       |               | Haemodialysis (n=26) |               | Peritoneal Dialysis (n=9) |               | Transplant (n=14) |               | Pre Dialysis (n=5) |               |
|             |                     | N %              | Mean SD       | (A)                  |               | (B)                       |               | (C)               |               | (D)                |               |
|             |                     |                  |               | N %                  | Mean SD       | N %                       | Mean SD       | N %               | Mean SD       | N %                | Mean SD       |
| PH Q9       | Depression Unlikely | 44 (81.1)        |               | 21 (80.8)            |               | 7 (77.8)                  |               | 12 (84.6)         |               | 4 (80.0)           |               |
| TB          |                     |                  | 25 ± 30       |                      | 37 ± 35       |                           | 16 ± 21       |                   | 11 ± 16       |                    | 24 ± 34       |
| TT          |                     |                  | 21 ± 30       |                      | 30 ± 35       |                           | 19 ± 25       |                   | 11 ± 21       |                    | 11 ± 16       |
| DSI         |                     |                  | 11.34 ± 6.57  |                      | 11.38 ± 5.87  |                           | 12.00 ± 7.02  |                   | 9.85 ± 7.66   |                    | 13.80 ± 7.40  |
| DSI burden  |                     |                  | 34.17 ± 25.25 |                      | 32.38 ± 20.98 |                           | 36.11 ± 24.50 |                   | 32.93 ± 33.58 |                    | 43.40 ± 26.28 |
| IIRS        |                     |                  | 34.33 ± 14.96 |                      | 38.92 ± 13.56 |                           | 27.44 ± 16.77 |                   | 27.36 ± 12.57 |                    | 42.40 ± 15.57 |
| DRT Minutes |                     |                  |               |                      | 571 ± 880     |                           |               |                   |               |                    |               |

Results are based on two-sided tests assuming equal variances. For each significant pair, the key of the smaller category appears in the category with the larger mean. Significance level versus other groups as indicated by superscript letters;  $p \leq 0.05$ <sup>1</sup>.

PHQ9 = Patient health questionnaire, TB = Treatment Burden, TT = Treatment Tolerability, DSI = Dialysis Symptom Index, IIRS = Illness Intrusiveness Ratings Scale, DRT = dialysis recover time

<sup>1</sup>. Tests are adjusted for all pairwise comparisons within a row of each innermost sub table using the Bonferroni correction.

Determinants of HRQOL in the entire cohort were assessed and Table 6 shows the significant correlations after Bonferroni correction for multiple comparisons. There were no demographic or biochemical determinants of, or correlations with HRQOL.

**Table 6** Significant correlations of Demographic, biochemical and PROM outputs with KDQOL SF composite domains

| Variable            | Coloration Table     |                       |                      |
|---------------------|----------------------|-----------------------|----------------------|
|                     | MCS                  | PCS                   | KDCS                 |
| PHQ9                | r= - 0.619, p<0.0005 |                       |                      |
| TB                  | r= - 0.486, p<0.0005 |                       | r= - 0.569, p<0.0005 |
| DSI Total           | r= - 0.570, p<0.0005 | r= - 0.463, p<0.0005  | r= - 0.626, p<0.0005 |
| DSI Burden          | r= - 0.564, p<0.0005 | r= - 0.447, p = 0.001 | r= - 0.534, p<0.0005 |
| IIRS                | r= - 0.477, p<0.0005 | r= - 0.462, p<0.0005  | r= - 0.743, p<0.0005 |
| Muscle Cramp        | r= - 0.450, p=0.001  |                       |                      |
| Shortness of Breath |                      | r= - 0.450, p=0.001   |                      |
| Restless Legs       | r= - 0.499, p<0.0005 |                       |                      |
| Tiredness           | r= - 0.543, p<0.0005 | r= - 0.535, p<0.0005  | r= - 0.530, p<0.0005 |
| Dry Mouth           | r= - 0.578, p<0.0005 |                       |                      |
| Dry Skin            | r= - 0.470, p<0.0005 |                       | r= - 0.504, p<0.0005 |
| Itching             | r= - 0.558, p<0.0005 |                       |                      |
| Worrying            | r= - 0.611, p<0.0005 |                       | r= - 0.541, p<0.0005 |

PCS = SF12 Physical Component Scale, MCS = SF12 Mental Component Scale, KDCS = Kidney Disease Component Scale, PHQ9 = Patient health questionnaire, TB = Treatment Burden, DSI = Dialysis Symptom Index, IIRS = Illness Intrusiveness Ratings Scale

When analysed grouping all dialysis against Tx there was a statistical difference in PCS mean  $33.20 \pm 10.62$  vs  $43.28 \pm 11.81$  ( $p=0.005$ ), reaching the threshold for mCID of  $> 5.7$ , and the KDCS  $68.61 \pm 14.08$  vs  $82.85 \pm 7.97$  ( $p=0.002$ ); there was no statistical difference in MCS. There were also differences in Burden of kidney disease  $50.17 \pm 30.21$  vs  $82.57 \pm 24.42$  ( $p=0.001$ ), Effects of kidney disease  $70.74 \pm 23.51$  vs  $88.63 \pm 17.19$  ( $p=0.013$ ), Energy/Fatigue  $43.02 \pm 26.46$  vs  $64.64 \pm 21.26$  ( $p=0.009$ ) and physical functioning  $41.22 \pm 29.43$  vs  $72.81 \pm 25.89$  ( $p=0.001$ ).

The predictors of MCS, PCS and KDCS are broken down by dialysis or Tx on univariate analysis and listed in **Table 7** and **Table 8** respectively. There were

no correlations for PCS in the dialysis cohort and none for MCS in the transplant cohort.

**Table 7** Significant correlations of Demographic, biochemical and PROM outputs with KDQOL SF composite domains for individuals on dialysis.

| Variable         | Coloration Table    |     |                    |
|------------------|---------------------|-----|--------------------|
|                  | MCS                 | PCS | KDCS               |
| Serum Creatinine | r=-0.525, p=0.001   |     |                    |
| PHQ 9            | r= -0.703, p<0.0005 |     |                    |
| DSI total        | r= -0.689, p<0.0005 |     | r=-0.672, p<0.0005 |
| DSI Burden       |                     |     | r=-0.645, p<0.0005 |
| IIRS             |                     |     | r=-0.725, p<0.0005 |
| Tiredness        | r=- 0.615, p<0.0005 |     |                    |
| Dry mouth        | r=- 0.615, p<0.0005 |     |                    |
| Dry skin         | r=- 0.623, p<0.0005 |     |                    |
| Itching          | r=- 0.595, p<0.0005 |     |                    |
| Worrying         | r=- 0.733, p<0.0005 |     | r=-0.734, p<0.0005 |
| Nervous          | r=- 0.579, p<0.0005 |     | r=- 0.572, p=0.001 |

MCS = SF12 Mental Component Scale, PCS = SF12 Physical Component Scale, KDCS = Kidney Disease Component Scale, PHQ9 = Patient health questionnaire, DSI = Dialysis Symptom Index

**Table 8** Significant correlations of Demographic, biochemical and PROM outputs with KDQOL SF composite domains for individuals with a functioning Transplant

| Variable            | Correlation Table |                     |                     |
|---------------------|-------------------|---------------------|---------------------|
|                     | MCS               | PCS                 | KDCS                |
| Shortness of Breath |                   | r=- 0.831, p<0.0005 |                     |
| Dizziness           |                   |                     | r=- 0.831, p= 0.001 |
| Dry Mouth           |                   |                     | r=- 0.826, p= 0.001 |
| Dry Skin            |                   |                     | r=- 0.821, p= 0.001 |

MCS = SF12 Mental Component Scale, PCS = SF12 Physical Component Scale, KDCS = Kidney Disease Component Scale

9 participants went on to complete the KDQOL SF again at one year. There was no statistically different change between baseline and one-year summary component scores (paired samples T test).

## Discussion

This study has shown that the physical component of HRQOL is poor in advanced CKD. Worsening PCS correlated with total number of symptoms and to the overall symptom burden as well as the burden of the individual

symptoms of shortness of breath and tiredness. PCS was related to the treatment status such that individuals with a Tx had significantly better scores (statistically and reaching the minimal clinically important difference), however this is still below the general population norm. Separately the changes that are normally seen with age, gender, employment and education were not shown in these populations.

Conversely the MCS was close to the population norm; however again there was no relationship with age, gender, employment or education, contrary to the general population, nor was there any relationship with overall comorbidity count. MCS also correlated with total symptom count and with overall symptom burden as well as a number of specific symptoms, in particular restless legs, shortness of breath, tiredness, dry mouth and itching with increasing symptoms leading to worsening MCS. The Burden of kidney disease was lower in PD than in HD and lower in transplant than either HD or pre dialysis and the overall KDCS was better in the Tx population than all other groups.

When it came to other PROMs and the relationship to HRQOL the correlation of worsening MCS with high PHQ9 is not unexpected but given the high prevalence of depression in this patient group is important to recognise. IIRS also had an inverse correlation with all composite scores of the KDQOL SF suggesting that QOL is related to the degree of impact on

social factors, however in dialysis patients this relationship diminished and symptoms remained the predominant factor.

The figures obtained for this study for MCS and PCS are comparable to the DOPPS DPM data that reported that for Dec 2017 (most recent available) mean MCS for haemodialysis patients was 50.61 and mean PCS was 36.17. In addition previous DOPPS data comparing the QOL in Europe, the USA, and Japan also reported similar values for both MCS and PCS although there was significant variation between the different countries with PCS being higher in Japan <sup>279, 280</sup>. Although there was a higher PCS score in the Tx cohort this was not reflected in the MCS which is again consistent with published literature. The mean KDCS for Euro DOPPS in 2003 was 62.4, this compares to this cohort who for haemodialysis had a mean score of 68.5; in part this can be explained by the improved symptom scores in this cohort as measured by the KDQOL SF. The score in the Tx patients was higher for the KDCS which is attributable to better scores in burden of kidney disease, physical functioning and symptom scores which, although they did not reach significance, were higher in this group.

We know from groups like the standardised outcomes in nephrology (SONG) initiative that a number of specific symptoms are of high importance to individuals either on dialysis or with a functioning transplant <sup>281, 282</sup>. These include fatigue, depression, itching and restless legs and therefore align with a number of the symptoms associated with the HRQOL outputs in this study.

Since this study was conceived there has been a growing recognition of the contribution that frailty makes to HRQOL and outcomes in general in advanced CKD. Any future work should include a measure of frailty as part of the assessment in order to explore this in more detail. This study was limited by the data on biochemical and treatment factors being collected retrospectively and by the relatively low sample size especially in the pre dialysis cohort that meant that no firm conclusions could be drawn for this group.

This study has indicated some new areas for exploration in regard to HRQOL especially in the HD population. In addition more research is needed on the diagnosis and treatment of depression in advanced CKD and on the management of symptoms, especially those of tiredness, but also dry skin and mouth which are often overlooked but might be amenable to basic interventions.

## Chapter 4. Perception and beliefs: How are individuals with CKD making sense of their illness?

### Abstract

#### *Introduction*

Individuals' perception of their illness correlates with both mortality and quality of life in dialysis patients and the beliefs that individuals hold about treatments affect treatment adherence. Improved understanding of illness perceptions and beliefs and their relationship with outcomes will allow improved targeting of information and education. We aimed to examine these aspects of an individual's understanding of disease in both dialysis and non-dialysis dependant CKD patients. In particular we set out to explore perceptions surrounding causation of symptoms, the variation of different illness perceptions according to demographic and treatment factors and beliefs about treatments beyond medications.

#### *Methods*

The revised illness perceptions questionnaire (IPQ-r) offers a robust mechanism for examining individual's perception of illness. The Beliefs about Medicines Questionnaire (BMQ) explores individuals' beliefs about the necessity and concerns of treatments. It was adapted for beliefs about dialysis, fluid restriction, medicines and dietary restrictions. Individuals from

Haemodialysis (HD) (n=28), Peritoneal Dialysis (PD; n=10), CKD 4/5 (n=5) and transplant (n=14) clinics completed all relevant IPQ-r and or BMQ questionnaires. Illness perceptions are reported as increasing scores representing stronger beliefs regarding chronicity, the cyclical nature of the disease, negative consequences, negative emotional effects, personal ability to control the illness, treatments' ability to control the illness and level of understanding of their illness. BMQ outputs are reported as mean  $\pm$  SD, for necessity and concerns (Range 5 (not at all) to 25 (very), 15 = (neutral belief)) and necessity minus concerns score (N-C) (range  $\pm$ 20, 0 = balanced beliefs). Additional demographic and routine biochemical and treatment-related data were collected from the patient record.

### *Results*

54 individuals completed the IPQ-r. Symptoms were common in this cohort, total  $5.74 \pm 3.02$  with a range of 0 – 12 (max 14). More symptoms were attributed to kidney disease in the pre dialysis group ( $5.60 \pm 2.61$ ) than by HD ( $2.39 \pm 1.97$ ,  $p=0.010$ ), PD ( $2.30 \pm 2.50$ ,  $p=0.022$ ) or Tx groups ( $0.64 \pm 1.28$ ,  $p<0.0005$ ). Individuals on HD attributed a greater number of their symptoms to the dialysis ( $2.54 \pm 2.03$ ) vs PD ( $0.40 \pm 0.84$ ,  $p=0.002$ ). Illness perceptions in each of the remaining subscales for the cohort were (max); Chronicity (30)  $17.79 \pm 2.73$ , Cyclical (20)  $10.00 \pm 4.00$ , Consequences (30)  $19.16 \pm 3.57$ , Personal Control (30)  $17.97 \pm 3.79$ , Treatment Control (25),  $14.98 \pm 3.21$ , illness coherence (25)  $12.93 \pm 3.93$ , Emotional response (30)

15.56  $\pm$  4.94. Individuals on PD have higher beliefs around personal control compared to HD ( $p=0.042$ ) but there were no other statistical differences between modalities regarding illness perceptions. Age but not dialysis vintage correlated inversely with perception of negative consequences ( $r= -0.421$ ,  $p=0.001$ ) and emotional response ( $r= -0.307$ ,  $p=0.022$ ) and positively with treatment control ( $r=0.278$ ,  $p=0.042$ ).

The Tx participants had higher medication necessity beliefs 23.31  $\pm$  1.89 vs PD 18.90  $\pm$  5.07 ( $p=0.036$ ) and pre dialysis 15.60  $\pm$  4.16 ( $p=0.001$ ). Prescribed medication necessity correlated inversely with serum phosphate ( $r= -0.644$ ,  $p<0.0005$ ) in the dialysis group as did the N-C Prescribed medications ( $r= -0.691$ ,  $p<0.0005$ ). Almost half had necessity beliefs  $< 15$  for dietary restriction but all had beliefs  $> 15$  regarding dialysis necessity. 12 of 37 had a score of  $> 15$  with 2 having very high ( $> 20$ ) levels of concern about dialysis. Around 35 % of individuals in this study had concerns about fluid restriction and 20 % had concerns about dietary restriction.

### *Discussion*

We have shown that whilst individuals in pre dialysis attribute a greater proportion of their symptoms to kidney failure they have very low necessity beliefs with regards to prescribed medications. In contrast individuals with a renal transplant had very high medication necessity beliefs as would be desirable. Higher medication necessity beliefs correlated with improved phosphate control. However necessity beliefs regarding fluid and dietary

restriction were low for a substantial minority of individuals with corresponding high levels of concern.

With regards to illness perception there was little difference between groups although individuals on PD did have a greater perception of personal control than those on HD and increasing age resulted in a more positive perception of both physical and emotional consequence and of the ability of treatment to control kidney disease.

Although not captured in this study it is assumed that the improved phosphate seen with higher necessity beliefs is related to behaviours and concordance. Further work will look at exploring these findings in a bigger population and test this hypothesis with a view to constructing an approach aimed at increasing necessity beliefs and addressing concerns through targeted education ultimately with the aim of improving phosphate control.

## Introduction

Research has suggested that the most robust method for identifying the factors which influence patients' decisions regarding their treatment, such as treatment adherence, involves an assessment not just of beliefs and perceptions about their treatment, but also beliefs about the associated illness <sup>215, 216</sup>. Two of the dominant theoretical models in this area are self-regulation theory <sup>217</sup> and the necessity and concerns framework <sup>218</sup>. Both

seek to lay out a framework by which to structure our thinking and understanding of individual's response to disease.

Self-Regulation theory states that individuals are motivated to make sense of their illness in the five distinct areas of Identity (the label and what symptoms an individual attributes to their illness), Causation, Timeline, Consequences, and Cure/Control (this is further subdivided into personal and treatment control). This in turn informs if and how they attain their goals for their illness (e.g., recovery, maximise QOL etc.). The second model is the necessity and concerns framework which extends self-regulation theory to focus specifically on beliefs regarding treatment. It proposes that individuals hold beliefs both about the necessity and concerns regarding the effects of treatment and the balance of these effects decisions regarding treatment. The focus is not on how much or what an individual knows about their disease or treatment but how they feel about and react to it.

Historically both models were explored using qualitative interview, but this subsequently led to the development of structured questionnaires that allow a quantitative output. The IPQ-r is used to look at illness perception based on self-regulation theory and the BMQ is based on the necessity and concerns framework<sup>220, 221</sup>.

Both questionnaires have been used extensively to investigate perceptions and beliefs in a number of health conditions. The published literature

supports the link between illness perceptions and adherence to a variety of medical recommendations in other health conditions such as ischaemic heart disease or asthma<sup>215, 283-287</sup>. Peoples' beliefs derived from the IPQ-r have been shown to be associated with specific outcomes and behaviours in a wide range of health conditions, including myocardial infarction, asthma, smoking cessation and diabetes<sup>215, 233, 238, 283, 285, 288, 289</sup>.

The illness beliefs of haemodialysis patients have been explored as they relate to depression and HRQOL as well as mortality<sup>226, 229, 290</sup>. In addition there has been shown to be an association between illness perceptions in the pre dialysis setting and rate of progression to ESRD<sup>232</sup>.

Separately the BMQ was developed to explore individuals' beliefs about both the necessity of and concerns about medications, both those prescribed for their specific condition and more generally. The BMQ has shown relationships between beliefs and medication adherence in a number of health settings including depression, hypertension and asthma<sup>291-294</sup>. Work in ESRD and renal Tx populations has shown a relationship between medication beliefs and phosphate binder adherence and immunosuppression use respectively<sup>238, 295</sup>.

We set out to explore the relationships in individuals both on dialysis and in pre dialysis or with a renal transplant between illness beliefs and

conventional HRQOL measures as well as measurable outcomes such as potassium and phosphate control, and inter dialytic weight gain.

## Methods

Participants were recruited from the prevalent RRT and pre dialysis programme. They completed the IPQ-r and BMQ as part of the INTUITIVE study.

The IPQ-r has three distinct parts, two of which are reported in this study. The main section on illness perceptions has 38 questions on a 5 point Likert scale and was modified to replace the words “your disease” with the words “your kidney disease” (see appendix page xxxvii). The questionnaire also incorporates a symptom questionnaire (14 questions) and asks for symptoms to be attributed to different causations, the options presented were; kidney disease, dialysis, medication, fluid restriction, and other health problems, participants were asked to tick all that applied.

Results for IPQ-r are presented separately for each subscale;

1. Identity: derived from presence of symptoms related to the condition (range 0 -14)
2. Timeline acute/chronic: higher scores representing strongly held beliefs about chronicity (range 6-30)
3. Timeline cyclical: higher scores representing strongly held beliefs about the cyclical nature of the disease (range 4 -20)

4. Consequences: higher scores representing strongly held beliefs about negative consequences (6 -30)
5. Emotional representations: higher scores representing strongly held beliefs about the negative emotional effects of the illness (range 6 - 30)
6. Personal Control: higher scores representing strongly held beliefs about their ability to control the illness (6 -30)
7. Treatment control: higher scores representing strongly held beliefs about the treatments ability to control the illness (range 5 -25)
8. Illness coherence: higher scores representing strongly held beliefs regarding their understanding of the illness (range 5 -25)

The BMQ was modified to enquire separately about beliefs relating to; medications prescribed for kidney disease, the prescribed dialysis, the prescribed fluid restriction and the prescribed dietary restriction (each had 10 questions on a Likert scale), in addition participants also completed the BMQ general which looks at attitudes to medicines overall, (see appendix page xxxii). Participants were asked to complete all relevant sections such that only individuals on dialysis completed the BMQ dialysis. BMQ specific outputs are reported as mean  $\pm$  SD of the necessity and the concerns score (Range 5 (not at all) to 25(very), 15 = neutral belief in the necessity (or concern)). The Necessity minus Concerns score (N-C) (range  $\pm$ 20, 0 = balanced beliefs) is reported as an indicator of the balance of these

competing influences. BMQ general scores are reported as concerns overuse (4-20) and concerns harm (4-20). A score of 12 on these outputs would indicate a neutral position on the harms or overuse of medicines in general.

In addition information was obtained from the standard medical record with regards to comorbidity, treatments and routine monitoring. Ten Individual's repeated the questionnaires at one year to allow testing for stability.

## Results

57 individuals completed enough of the IPQ-r questionnaire to get at least one output. 54 completed the questionnaire in full. Demographic and clinical variables are presented in **Table 9**.

### *IPQ-r*

Symptoms were common in this cohort, of the 14 possible symptoms in IPQ-r the mean total number was  $5.74 \pm 3.02$  with a range of 0 - 12. There were higher symptom numbers reported in the pre dialysis group although this was not statistically different to either dialysis group it did reach significance against Tx  $7.80 \pm 1.92$  vs  $3.86 \pm 2.71$  ( $p=0.046$ ). More of these symptoms were attributed to kidney disease in the pre dialysis group than by HD ( $p=0.010$ ), PD ( $p=0.022$ ) or Tx ( $p<0.0005$ ). Individuals on HD attributed a greater number of their symptoms to the dialysis compared to PD ( $p=0.002$ ), see **Table 10** and **Figure 6**.

Table 9

Demographic, biochemical and PROM data for the cohort completing at least one section of IRQ-r and BMQ

|                                   |                      | Treatment Status |       |                      |       |                            |      |                   |           |                    |          |
|-----------------------------------|----------------------|------------------|-------|----------------------|-------|----------------------------|------|-------------------|-----------|--------------------|----------|
|                                   |                      | Total (n=57)     |       | Haemodialysis (n=28) |       | Peritoneal Dialysis (n=10) |      | Transplant (n=14) |           | Pre Dialysis (n=5) |          |
|                                   |                      | Mean ± SD        | (%)   | Mean SD              | (%)   | Mean SD                    | (%)  | Mean SD           | N (%)     | Mean SD            | N (%)    |
| Age (years)                       |                      | 61 ± 13          |       | 63 ± 14              |       | 62 ± 10                    |      | 59 ± 10           |           | 53 ± 16            |          |
| Gender                            |                      |                  | 63.2) |                      | 64.3) |                            | 0.0) |                   | 9 (64.3)  |                    | 3 (60.0) |
| RRT Vintage                       |                      | 5.65 ± 7.28      |       | 5.04 ± 5.05          |       | 0.80 ± 0.79                |      | 10.36 ± 10.57     |           |                    |          |
| Diabetes                          |                      |                  | 36.8) |                      | 42.9) |                            | 0.0) |                   | 3 (21.4)  |                    | 0.0      |
| Heart Failure                     |                      |                  | 8.8)  |                      | 4.3)  |                            | 0.0) |                   | 0.0       |                    | 0.0      |
| Religious                         | us Belief            |                  | 71.9) |                      | 82.1) |                            | 0.0) |                   | 10 (71.4) |                    | 2 (40.0) |
| Highest Education                 |                      |                  | 21.8) |                      | 2.2)  |                            | 30)  |                   | 3 (21.4)  |                    | 0.0      |
|                                   |                      |                  | 25.5) |                      | 4.8)  |                            | 50)  |                   | 1 (7.1)   |                    | 4 (80.0) |
|                                   |                      |                  | 0.9)  |                      | 1.1)  |                            | 0    |                   | 2 (14.3)  |                    | 1 (20.0) |
|                                   | ional Qualifications |                  | 2.7)  |                      | 3.7)  |                            | 10)  |                   | 5 (35.7)  |                    | 0.0      |
|                                   | mal Qualifications   |                  | 29.1) |                      | 48.1) |                            | 0    |                   | 3 (21.4)  |                    | 0.0      |
| Employment Status                 |                      |                  | 23.2) |                      | 4.3)  |                            | 0.0) |                   | 5 (35.7)  |                    | 0.0      |
|                                   |                      |                  | 53.6) |                      | 57.1) |                            | 0.0) |                   | 8 (57.1)  |                    | 2 (50.0) |
|                                   |                      |                  | 23.2) |                      | 8.6)  |                            | 0.0) |                   | 1 (7.1)   |                    | 2 (50.0) |
|                                   | loyed                |                  | 23.2) |                      | 8.6)  |                            | 0.0) |                   | 1 (7.1)   |                    | 2 (50.0) |
| Total Number Tablets / day        |                      | 8.9 ± 4.6        |       | 9.0 ± 3.5            |       | 8.2 ± 6.7                  |      | 10.2 ± 4.1        |           | 5.9 ± 6.4          |          |
| Phosphate Binder tablets / day    |                      | 1.5 ± 2.0        |       | 2.8 ± 2.0            |       | 0.8 ± 1.3                  |      |                   |           |                    |          |
| Mean IDWG (HD only) (kg)          |                      | 1.34 ± 0.56      |       | 1.39 ± 0.55          |       |                            |      |                   |           |                    |          |
| Albumin (g/L)                     |                      | 32.3 ± 4.4       |       | 32.4 ± 4.0           |       | 29.2 ± 5.1                 |      | 35.6 ± 3.5        |           | 31.2 ± 2.8         |          |
| Adjusted Calcium (mmol/L)         |                      | 2.45 ± 0.14      |       | 2.47 ± 0.12          |       | 2.41 ± 0.20                |      | 2.49 ± 0.13       |           | 2.36 ± 0.08        |          |
| Bicarbonate (mmol/L)              |                      | 22.5 ± 2.4       |       | 22.1 ± 1.9           |       | 22.8 ± 1.7                 |      | 25.0 ± 1.8        |           | 19.7 ± 0.5         |          |
| HbA <sub>1c</sub> (%)             |                      | 6.9 ± 1.4        |       | 7.2 ± 1.4            |       | 6.3 ± 1.2                  |      |                   |           |                    |          |
| Potassium (mmol/L)                |                      | 4.6 ± 0.7        |       | 4.7 ± 0.7            |       | 4.3 ± 0.6                  |      | 4.5 ± 0.7         |           | 4.8 ± 0.7          |          |
| Phosphate (mmol/L)                |                      | 1.47 ± 0.42      |       | 1.58 ± 0.35          |       | 1.56 ± 0.47                |      | 0.98 ± 0.32       |           | 1.54 ± 0.16        |          |
| Parathyroid Hormone (ng/L)        |                      | 52.8 ± 198.4     |       | 48.0 ± 151.6         |       | 97.8 ± 194.5               |      | 97.0 ± 68.7       |           | 344.6 ± 408.9      |          |
| eGFR (mL/min/1.73m <sup>2</sup> ) |                      |                  |       |                      |       |                            |      | 39.60 ± 17.73     |           | 10.66 ± 2.00       |          |
| Haemoglobin (g/L)                 |                      | 16.9             |       | 10.7 ± 17.7          |       | 14.5 ± 15.6                |      | 124.9 ± 15.1      |           | 104.9 ± 9.6        |          |

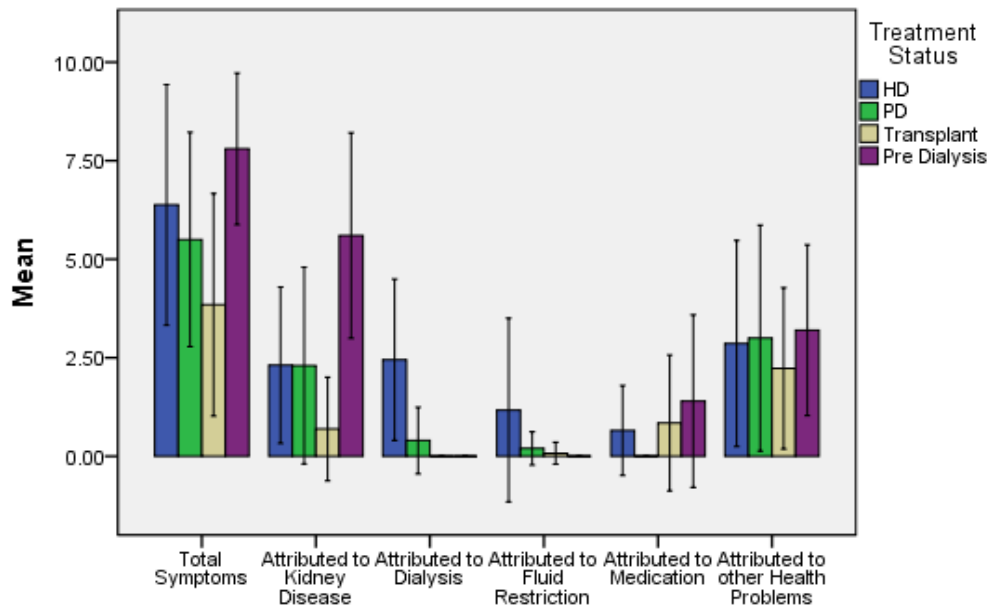
**Table 10 Symptom count and attribution by treatment status**

| Symptom Attribution  | Treatment Status |                          |                            |                   |                                |
|----------------------|------------------|--------------------------|----------------------------|-------------------|--------------------------------|
|                      | Total (n=57)     | Haemodialysis (n=28)     | Peritoneal Dialysis (n=10) | Transplant (n=14) | Pre Dialysis (n=5)             |
|                      |                  | (A)                      | (B)                        | (C)               | (D)                            |
|                      | Mean ±SD         | Mean ±SD                 | Mean ±SD                   | Mean ±SD          | Mean ±SD                       |
| Symptom (count)      | 5.84 ± 2.95      | 6.61 ± 2.85 <sup>C</sup> | 5.50 ± 2.72                | 3.86 ± 2.71       | 7.80 ± 1.92 <sup>C</sup>       |
| Kidney Disease       | 2.23 ± 2.32      | 2.39 ± 1.97              | 2.30 ± 2.50                | 0.64 ± 1.28       | 5.60 ± 2.61 <sup>A, B, C</sup> |
| Dialysis             | 1.32 ± 1.89      | 2.54 ± 2.03 <sup>B</sup> | 0.40 ± 0.84                |                   |                                |
| Fluid Restriction    | 0.65 ± 1.75      | 1.21 ± 2.36              | 0.20 ± 0.42                | 0.07 ± 0.27       |                                |
| Medication           | 0.65 ± 1.33      | 0.68 ± 1.16              |                            | .79 ± 1.67        | 1.40 ± 2.19                    |
| Other health problem | 2.84 ± 2.44      | 2.96 ± 2.60              | 3.00 ± 2.87                | 2.36 ± 2.02       | 3.20 ± 2.17                    |

Results are based on two-sided tests assuming equal variances. For each significant pair, the key of the smaller category appears in the category with the larger mean. Significance level versus other groups as indicated by superscript letters;  $p \leq 0.05$  <sup>1</sup>.

<sup>1</sup>. Tests are adjusted for all pairwise comparisons within a row of each innermost sub table using the Bonferroni correction

**Figure 6** Graph showing number and attribution of symptoms in IPQ Identity by Treatment status.



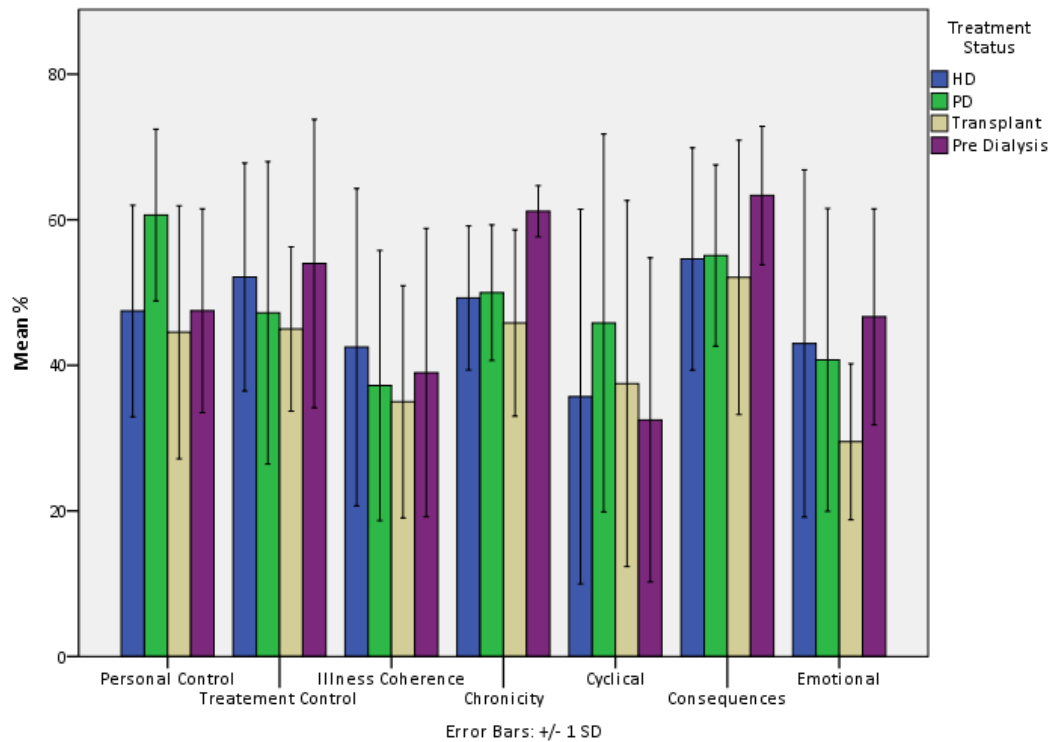
HD = Haemodialysis, PD= Peritoneal Dialysis.

Illness perceptions in each of the remaining subscales for the cohort were (max); Chronicity (30)  $17.79 \pm 2.73$ , Cyclical (20)  $10.00 \pm 4.00$ , Consequences (30)  $19.16 \pm 3.57$ , Personal Control (30)  $17.97 \pm 3.79$ , Treatment Control (25),  $14.98 \pm 3.21$ , illness coherence (25)  $12.93 \pm 3.93$ , Emotional response (30)  $15.56 \pm 4.94$ . As stated previously higher scores would be either expected or desirable for the elements of control, coherence and chronicity and lower scores expected or desirable for consequences, emotional response and cyclical disease.

Raw scores were converted to percentage of highest possible score to allow easier comparisons in further analysis by treatment status. There was variation in responses across the treatment modalities. Individuals on PD had higher beliefs around personal control ( $p=0.042$ ) compared to HD, they also appeared to have stronger beliefs relating to a cyclical nature of disease

although this did not reach statistical significance. Individuals with a Tx had a tendency towards a lower emotional response. Results broken down by modality and presented as % score are set out in Figure 7.

**Figure 7** IPQ outputs as % score by Treatment Status



HD = Haemodialysis, PD = Peritoneal Dialysis

Subscale analysis of the entire cohort did not show any effect from gender, education or dialysis vintage. Age correlated inversely with perception of negative consequences ( $r = -0.421$ ,  $p=0.001$ ) and emotional response ( $r = -0.307$ ,  $p=0.022$ ) and positively with treatment control ( $r=0.278$ ,  $p=0.042$ ). Individuals who were retired had significantly lower perception of negative consequence  $47.64 \pm 12.36$  than those either in work  $61.22 \pm 10.26$  ( $p=0.001$ ) or unemployed  $65.06 \pm 16.54$  ( $p<0.0005$ ). In addition being

unemployed as compared to retired, resulted in a significantly more negative emotional response  $58.85 \pm 22.21$  vs  $32.18 \pm 16.85$  ( $p=0.001$ ).

Using paired samples T test there was no statistically significant change in responses over time aside from in treatment control which just reached significance ( $p=0.049$ ) and increased with time.

### **BMQ**

56 individuals completed the BMQ with regards to their prescribed medicines, overall necessity score  $20.28 \pm 4.14$ . Distributions of Necessity beliefs are shown in Figure 8 **(A)**. 4 individuals had necessity beliefs below 15 indicating adverse necessity beliefs (prescribed medicines are not necessary). Prescribed medication necessity correlated inversely with serum phosphate ( $r= - 0.644$ ,  $p<0.0005$ ) in the dialysis group. There was no correlation with number of prescribed medicines or with number of prescribed phosphate binders or with any demographic factors. The Tx participants had higher necessity beliefs  $23.31 \pm 1.89$  vs PD  $18.90 \pm 5.07$  ( $p=0.036$ ) and pre dialysis  $15.60 \pm 4.16$  ( $p=0.001$ ).

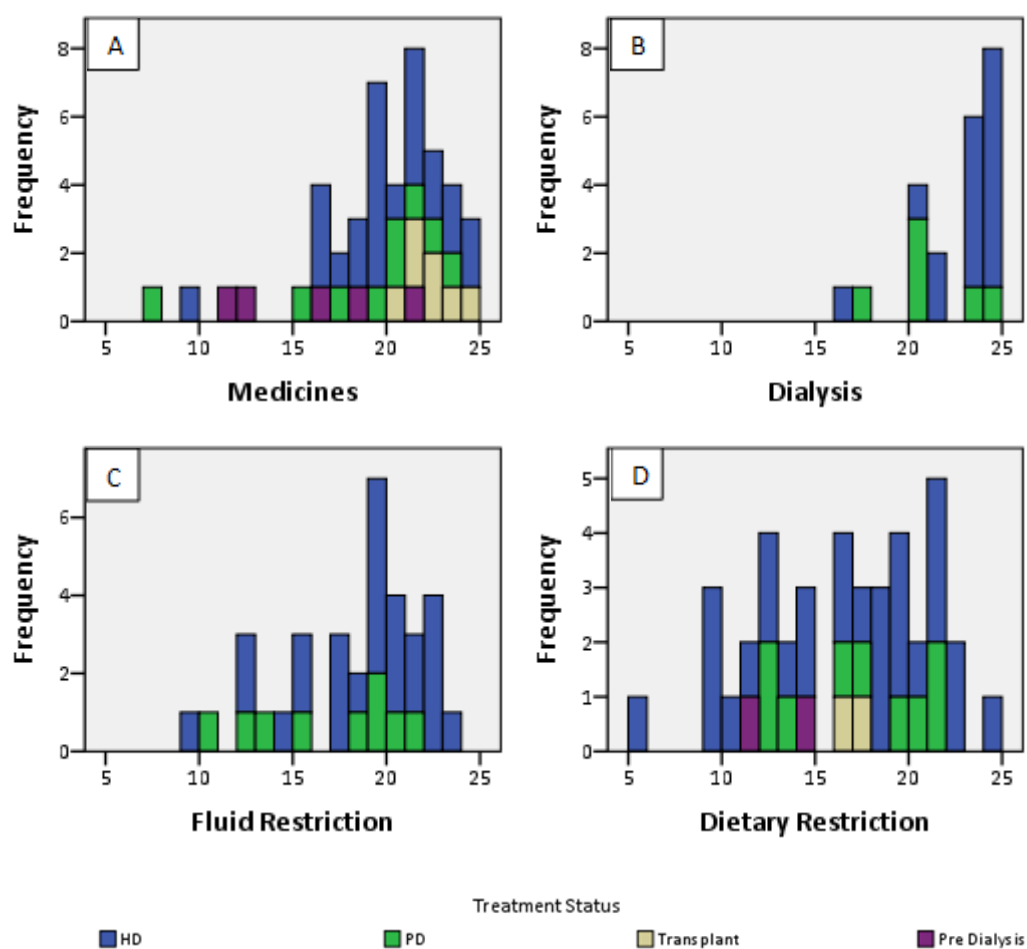
37 individuals on dialysis completed the BMQ Dialysis, overall necessity score  $23.24 \pm 2.33$  Figure 8 **(B)**. There were no significant correlations with biochemical or demographic factors. All had dialysis necessity beliefs in the range  $> 15$ .

37 individuals were on a fluid restriction with a necessity score of  $18.27 \pm 4.11$  Figure 8 **(C)**. Necessity of Fluid restriction did not correlate with interdialytic weight gain or RRT vintage. 7 had necessity beliefs  $< 15$ .

For dietary restrictions 41 individuals completed this score, with an average necessity score of  $16.17 \pm 4.67$  Figure 8 **(D)**. Necessity of Dietary Restriction did not correlate with either serum potassium or serum phosphate, there was also no correlation with any demographic factors. Almost half had necessity beliefs  $< 15$  for dietary restriction.

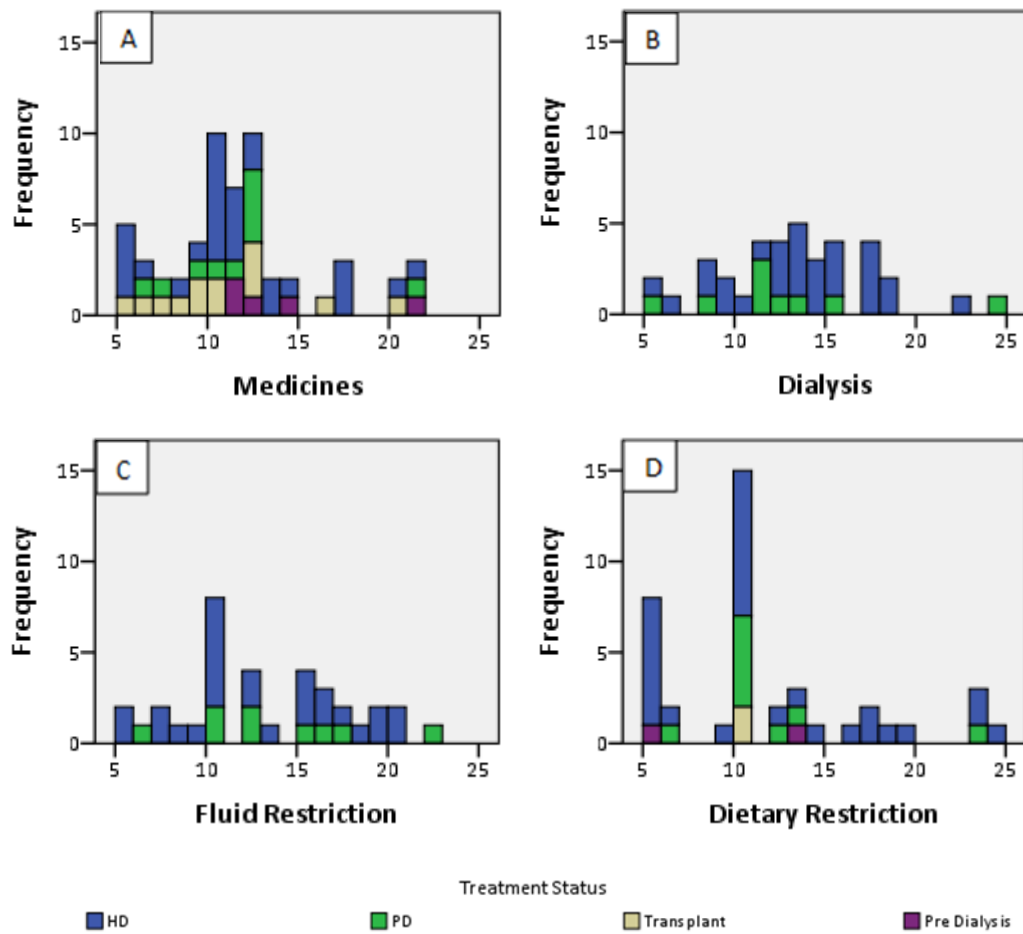
For the concerns about medicines, mean score was  $11.25 \pm 4.17$ , Figure 9 **(A)**. Concerns regarding Prescribed medications correlated inversely with age ( $r = -0.369$ ,  $p = 0.005$ ). There was no correlation with either the total number of tablets prescribed or with the number of binders. 9 individuals had a score  $> 15$  for medicines concerns. With regards to concerns about dialysis, mean score was  $12.89 \pm 4.24$  Figure 9**(B)**. Concerns regarding Dialysis correlated negatively with age ( $r = -0.420$ ,  $p = 0.010$ ). 12 had a score of  $> 15$  with 2 having very high levels of concern about dialysis.

**Figure 8** Frequency graphs for levels of Necessity beliefs



A level of < 15 indicates an absence of necessity beliefs with scores > 15 indicating increasing strength of necessity belief.  
 HD = Haemodialysis, PD = Peritoneal Dialysis

**Figure 9** Frequency graphs for levels of Concern



A level of < 15 indicates an absence of concerns with scores > 15 indicating increasing strength of concern.  
HD = Haemodialysis, PD = Peritoneal Dialysis

Mean score for concerns regarding Fluid restriction was  $13.46 \pm 5.26$  Figure 9 (C). Concerns about Fluid Restriction did not correlate with IDWG or demographic factors. For concerns regarding dietary restrictions, mean score  $11.41 \pm 5.44$  Figure 9 (D); again these concerns had no significant correlations. Around 35 % of individuals in this study had concerns about fluid restriction and 20 % had concerns about dietary restriction.

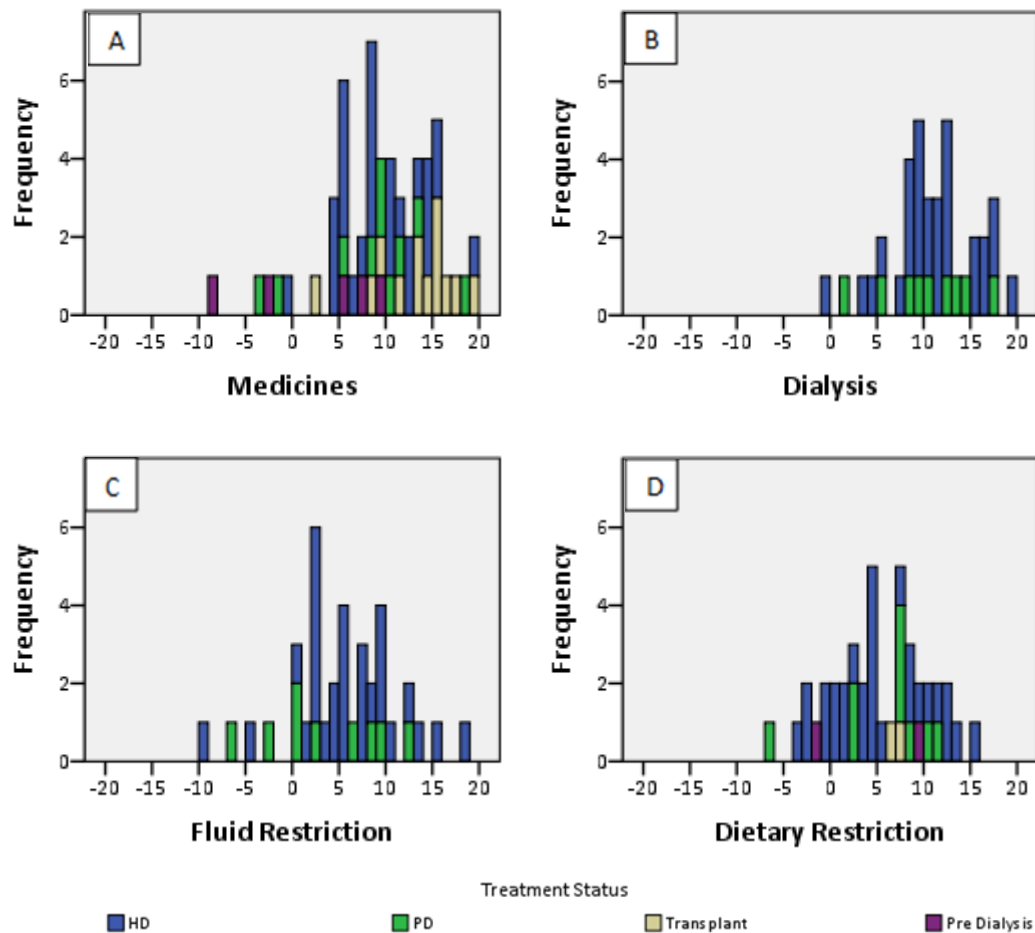
For the balance of Necessity – Concerns (N-C) these were overall in the positive indicating a dominance of beliefs around necessity over concerns. Mean N-C for Prescribed medicines was  $9.04 \pm 5.84$ , Dialysis  $10.35 \pm 4.60$ , Fluid restriction  $4.81 \pm 5.85$  and Dietary restriction  $4.76 \pm 5.14$  Figure 10.

Prescribed meds N-C correlated inversely with serum phosphate ( $r = -0.691$ ,  $p < 0.0005$ ) in the dialysis population but not with total number of prescribed medications or with number of phosphate binder tablets. There were no correlations for N-C dialysis, dietary restriction or fluid restriction. A number of individuals had values of N-C in the negative range suggesting stronger concerns than necessity beliefs in these areas. No individual in the Tx group had negative N-C values for prescribed medications.

56 participants completed the BMQ medicines in general, this is split into concerns about overuse  $11.21 \pm 3.76$  and concerns about harm  $8.95 \pm 2.79$ . BMQ general overuse did not correlate with necessity beliefs but correlated positively with concerns about prescribed medicines ( $r = 0.532$ ,  $p < 0.0005$ ), dialysis  $r = 0.501$ ,  $p = 0.002$ ) and fluid restriction ( $r = 0.473$ ,  $p = 0.003$ ). For dietary restriction this did not quite meet significance after Bonferroni correction, ( $r = 0.408$ ,  $p = 0.008$ ). BMQ general harms correlated with concerns about prescribed medicines ( $r = 0.436$ ,  $p = 0.001$ ). There was no correlation with necessity beliefs.

Using paired samples T test there was no statistically significant change in responses over time.

**Figure 10** Frequency graphs for Necessity - Concerns



A level of 0 indicates a balance of necessity and concern beliefs with scores < 0 indicating a dominance of concerns and > 0 indicating a dominance of necessity belief.  
HD = Haemodialysis, PD = Peritoneal Dialysis

## Discussion

Tx participants had higher medication necessity beliefs than dialysis or CKD patients. Increases in prescribed medication necessity belief and the balance of necessity vs concerns correlated with improvements in serum phosphate

in participants on dialysis. Necessity beliefs in the lower half (<15) which indicate that the treatment is not necessary occurred in all but the dialysis questionnaire with almost half of participants having necessity beliefs for dietary restriction in this range. Concerns diminished with age for both prescribed medications and dialysis, however around 35% had concerns about fluid restriction and 20% had concerns about dietary restriction. 32% had concerns about dialysis with 2 individuals having very high concerns. General concerns about overuse and harm of medications did correlate with concerns across the questionnaires but not with necessity.

Symptoms were common in advanced CKD although there were less overall symptoms in the Tx group who had around half the number of symptoms of the pre dialysis group. The attribution of causation of these symptoms differed such that individuals in pre dialysis attributed a large number of their symptoms to kidney disease. Individuals on HD attributed a greater number of their symptoms to dialysis compared to PD. Individuals on PD had higher beliefs around personal control compared to HD and increasing age led to lessening of perception of negative consequences with less negative emotional response with increasing personal control. Illness perceptions did not change with gender, education or dialysis vintage.

A structured approach aimed at increasing necessity beliefs and minimising concerns might reasonably be expected to result in positive changes in behaviour as has been seen in other chronic health conditions. In 2012

Petrie et al. reported on a text message intervention in chronic asthma, this intervention tested focused text messaging aimed at altering these beliefs over an 18 week period with the intervention resulting in improved concordance at the end of the study.<sup>233</sup>.

The correlations of BMQ general with disease-specific concerns would indicate that the concerns are rooted in the individuals overall understanding of health and that challenging some of these beliefs might lead to novel approaches to interventions and education even before individuals are approaching ESRD.

Previous studies have shown a relationship between medication beliefs about phosphate binders and serum phosphate and/or poor self-reported phosphate binder adherence with low necessity beliefs<sup>240, 241, 296</sup>. Three studies reported educational interventions aimed at improving phosphate control and also assessed perceptions of medicines necessity. A study in 2008 by Karamanidou et al. involved a small group of individuals and was successful in improving knowledge, medication necessity perception and self-reported adherence immediately post a single intervention, however the change in necessity perception was not sustained despite persistent improvement in knowledge at 4 months<sup>297</sup>. Another study evaluated a longer intervention based on a single educational session followed by weekly personalised counselling sessions on 4 occasions. At the end of the intervention phosphate binder adherence had increased, however there

were no data on adherence at longer time intervals to understand the duration of effect<sup>298</sup>. A more recent study undertaken in Norway involved a pharmacy led single time point intervention; this increased necessity beliefs but had no overall effect on the mean serum phosphate, although the levels were already very close to target and medication adherence was also high before the study<sup>242</sup>.

The finding that age but not experience (dialysis vintage) correlated inversely with perception of negative consequences and emotional response would suggest that there is the potential to adapt these perceptions possibly in response to social context, society accepts increasing “illness” with increasing age. The finding that individuals on PD had more perception of personal control is not unexpected for a home based therapy.

There were no detectable relationships between Illness perceptions and clinical outcomes that might be linked to behaviours (phosphate, potassium or IDWG) in this study. This is consistent with a previously published meta-analysis which reported that individual Illness perception domains do not predict illness behaviours across a variety of acute and chronic health conditions<sup>299</sup>. However in smaller studies perception of personal control has been shown to be associated with self-care in diabetes<sup>300</sup> and perception of control has also been shown to be associated with attendance at cardiac rehabilitation post myocardial infarction<sup>285</sup>. In 2002 a RCT in individuals post-acute myocardial infarction showed that a structured program to

address illness perceptions delivered over three sessions (in addition to conventional cardiac rehabilitation) was successful in modifying illness perceptions and resulted in earlier return to work<sup>286</sup>.

This study is limited by the relatively small numbers of participants particularly in the pre dialysis group. The fact that biochemical and treatment data was retrieved from the routine clinical record within 3 months of the study visit meant that no additional data could be collected. This cohort did not include individuals on home HD or assisted PD and exploring this element of home based therapy would be interesting. The observation around phosphate is interesting but would be strengthened by data on medication adherence such as pill count which should be included in any further study.

Developing an understanding of an individual's illness perceptions and treatment beliefs in ESRD may help in delivering targeted education/information in a more effective manner. Further work will be needed to explore these concepts to understand if the development of interventions targeted at these beliefs and perceptions may impact on individual's physical and emotional wellbeing. Specific areas of interest include targeted early pre dialysis education specific to individual's beliefs and concerns about medicines in general, delivered alongside conventional pre dialysis counselling, which might offer additional benefits and should be explored. Further work to explore if individuals choosing home based

therapies start from a position of increased perception of personal control which might lead to improvements in pre dialysis education and planning.

## Chapter 5. Symptoms or Survival? A Systematic Exploration of Individual Renal Replacement Therapy Patient Preferences for Treatment Outcome.

### Abstract

#### *Introduction*

Individual preferences for treatment outcomes vary but there are few data on how these preferences vary and the factors that might influence the balance of preferences between symptom control and survival. We therefore systematically explored the treatment outcome preferences of a cohort of individuals with advanced CKD, utilising established methodology to compare and quantify the subconscious trade off in decision making.

#### *Methods*

Prevalent haemodialysis (HD; n=25), peritoneal dialysis (PD; n=9), transplant (Tx; n=12) and CKD 5 patients (n=5) completed an outcome preference set comprising 25 possible treatment outcome profiles, each scored for overall acceptability. All profiles contained the same 6 attributes (pain, tiredness, breathing, depression, survival and treatment burden (TB)). Standard full profile conjoint analysis was used to derive % importance weights (IW) for each attribute, allowing the relative contribution of each to be determined

for every individual. Individuals also completed the dialysis symptom index and a visual analogue scale to rate their treatment burden. Additional demographics and treatment history were collected from medical records.

Where relevant, the individuals were split into a dialysis group (n=34) and non-dialysis (n=17). These groups had similar demographics; mean age of the dialysis group was  $62.17 \pm 13.31$  years vs non-dialysis  $57.44 \pm 11.68$  years (p=ns), gender split was dialysis 62.9% male vs non-dialysis 62.5 % male (p = ns).

### *Results*

In the whole study population there is a clear preference for survival (IW 16.57 [9.40 – 37.27]) vs treatment burden (IW 9.07 [4.11 – 16.81]) (p=0.001). The IW's for survival were much lower in the dialysis versus non-dialysis group (15.32 [6.42 – 24.28] vs 29.80 [13.69 – 58.53] (p = 0.010). IWs for pain were higher in the dialysis group versus non-dialysis ( $20.20 \pm 10.18$  vs.  $10.14 \pm 7.38$ ; p = 0.001). Pain and breathlessness were more important in older patients ( $\geq 65$  years vs  $< 65$  years): pain  $20.71 \pm 12.09$  vs  $13.92 \pm 7.92$  (p=0.019), breathlessness  $21.59 \pm 14.05$  vs  $14.51 \pm 10.20$  (p=0.042). Tiredness was less important in older patients:  $10.53 \pm 6.76$  vs  $16.31 \pm 10.49$  (p=0.029). The preference IW's were not influenced by demographic factors aside from age or by symptom burden. In the non-dialysis population 58.8% ranked survival in the top two whereas for individuals on dialysis the corresponding figure is 29.4% (p=0.008). These trends are strong but on an

individual level people had very strong preferences for either symptoms or survival that do not necessarily reflect the population trends.

### *Discussion*

This study demonstrates that the balance of outcome preferences can be measured in individuals with advanced CKD. In this study participants on dialysis placed greatest importance on symptoms whereas those not currently receiving dialysis had a greater preference for survival. There was however large variation at the individual level that was not explained by demographic or treatment related factors. Understanding these preferences and how they are influenced and change may lead to novel approaches for improving the treatment outcomes and quality of life of people with kidney disease.

### **Introduction**

Individuals are making choices about aspects of their lives all the time and this is no different when it comes to healthcare related decisions. People on dialysis are unfortunately faced with an imperfect treatment that continues to be associated with markedly decreased survival and a very high prevalence of ongoing symptoms. These impacts are lessened for patients with a functioning renal Tx but there is still a high prevalence of symptoms even in this group. However people with ESKD are asked to accept these demanding treatments and or symptoms with the attendant issues of transport, time demands and restrictions on daily life.

Whilst some choices are simple such as, “should I go to work today?”, and some really have little consequence (was your choice of breakfast really that critical?), healthcare decisions are usually neither simple nor without consequence. They are complex and multifaceted, with no clearly ‘correct’ option and thus a trade-off or compromise is required balancing those aspects that are important to the individual. Whereas the medical profession would traditionally consider the hard-endpoint of mortality to be the most critical outcome, patients may favour factors contributing to quality, not quantity of life. In addition we as clinicians often make assumptions about the choices that our patients would make and at times we make those decisions on their behalf.

There are some obvious points in an individual’s CKD journey where conscious treatment decisions are made, most notably at the time of choosing an RRT modality, however there are many other times when the choice is less obvious. The illness related choices that people with kidney disease make affect all aspects of care ranging from choosing to attend our clinics, to take their prescribed medications, or to turn up for dialysis, or not, based upon which aspects of their management are important to them. Ultimately they choose whether to listen to the advice we provide. In truth these decisions and trade-offs are often made subconsciously.

This is, of course, not limited to kidney disease, but is a feature of many chronic diseases. We know that these decisions (and the process underlying

them) are individually highly variable in many other conditions such as heart failure and cancer treatment but also smoking cessation<sup>251, 258-260</sup>. However there are little data relating to the balance of decision making (choices) in advanced kidney disease. It would seem reasonable that many of these individual trade-offs frequently include aspects of outcome. We therefore set out to systematically investigate the balance of these choices with regards to treatment outcome preferences in a cohort of people receiving or about to receive RRT

## Methods

We designed a study to explore individuals' subconscious decision making as it related to treatment for their kidney disease and the balance of symptoms, treatment burden and survival. There are surprisingly few techniques available to systematically explore patients subconscious decision-making and preferences. One such technique is to use conjoint analysis.

Individuals were recruited as part of the INTUITIVE study. They were recruited from our prevalent outpatient population either currently receiving or likely to receive renal replacement therapy within one year. They were studied at a time convenient to them, either at home or at the hospital.

For this study we utilised full-profile conjoint analysis to explore the competing importance placed on survival, treatment burden, and the separate symptoms of breathlessness, pain, tiredness and depression. The specific attributes were chosen based on the results of a previous patient survey asking for patient priorities and published data on symptom prevalence. Full profile and other conjoint methodologies were originally developed for use in market research and product design. However over the last 10 - 15 years it has been increasingly used to examine the relative contribution of multiple variables in healthcare related decisions.

Conjoint design and analysis was undertaken using the specific conjoint software module within SPSS (V24). This uses a specially tailored version of multiple regression analysis to derive importance weights for individual attributes. 25 theoretical outcome combinations were generated and participants were asked to score each of these outcome cards on a scale of 0 (as bad as or worse than being dead) to 10 (best possible outcome). Each outcome card represented the change from the individual's current state as a result of a hypothetical change in treatment. The software had the potential to vary each attribute across 4 levels of change, for survival this was +/- 6 or 12 months and for all others it was a little or lot, more or less, than currently experienced, it was assumed that changes to less symptoms, lower treatment burden and longer survival were preferable. See Figure 11 for an example outcome card.

**Figure 11**                      **Example outcome preference card**

| Card ID | Pain          | Tiredness     | Depression | Breathlessness | Survival       | Treatment burden |
|---------|---------------|---------------|------------|----------------|----------------|------------------|
| 1       | a LITTLE less | a LITTLE less | a LOT more | a LOT less     | Minus 6 months | a LOT less       |

Once completed the scores for each outcome card were inputted back into the conjoint analysis model which then derives the relative value of each attribute in the decision making process, these are reported as the individual attribute, percentage importance weights. Thus if all attributes carried equal weight in this study they would each score around 16.

The derived IW for all attributes were tested for normality, IW for survival, burden and depression are non-normally distributed, so results from non-parametric tests (Mann-Whitney U test with median and interquartile range and spearman's rho) have been reported, for all other attributes the IW's were normally distributed and standard parametric tests applied.

At the same visit basic demographic and treatment data were collected alongside data on symptom prevalence (using the DSI) and perceived treatment burden. A subset of patients repeated the testing at 12 months looking at stability of preference.

## Results

All 58 participants enrolled within the wider study were asked to complete the outcome preference questionnaire as part of their first visit. The questionnaire took about ten minutes to complete but was part of a wider

set that took around two hours. A total of 51 individuals completed the full questionnaire on the first visit. Two patients completed the questions with the help of a translator and some required additional explanation than that originally given with the questionnaire. Seven people did not complete the questionnaire: two reported that they did not want to contemplate the questionnaire as they found the subject distressing, two found it difficult to understand the instructions and three did not want to complete any further questionnaires as they were tired and wanted to rest. Seven of the 51 individuals repeated the questionnaire at one year.

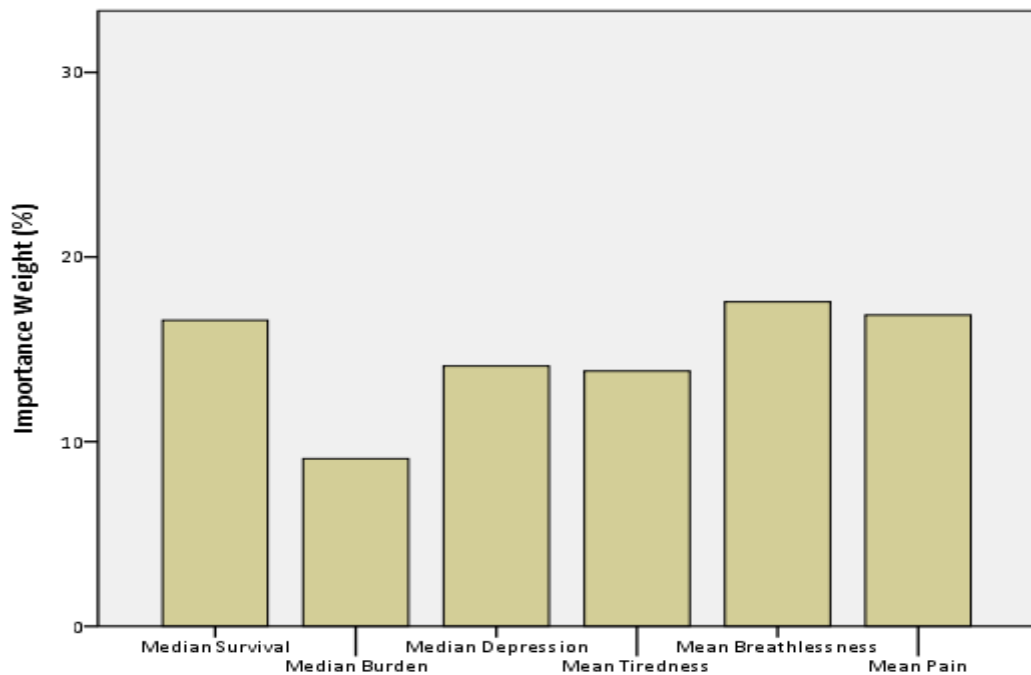
There were no significant differences between the Tx and pre dialysis patients or between the different dialysis modalities, the results are therefore presented as dialysis vs non-dialysis patients where relevant. Demographic and relevant PROM data are presented in Table 11.

A summary graph of all participants is shown in Figure 12; this shows the average importance for each attribute across the population. There was a clear preference for increased survival (16.57 [9.40 – 37.27]) vs decreased treatment burden (9.07 [4.11 – 16.81]) ( $p=0.001$ ) with a smaller difference between survival and tiredness 13.38 [6.16 – 19.15] ( $p=0.027$ ) and no difference between the other symptom preferences and survival preference.

**Table 11****Basic demographics for individuals who returned outcome preference data.**

|                                                                    |                               | Total (n=51)    |           | Dialysis (n=34) |           | Non-dialysis (n=17) |           |
|--------------------------------------------------------------------|-------------------------------|-----------------|-----------|-----------------|-----------|---------------------|-----------|
|                                                                    |                               | Mean $\pm$ SD   | N (%)     | Mean $\pm$ SD   | N (%)     | Mean $\pm$ SD       | N (%)     |
| Age (years)                                                        |                               | 61 $\pm$ 13     |           | 63 $\pm$ 13     |           | 57 $\pm$ 12         |           |
| Gender                                                             | Male                          |                 | 32 (62.7) |                 | 22 (64.7) |                     | 10 (58.8) |
| Renal Replacement Therapy Vintage (years) (excluding pre dialysis) |                               | 5.04 $\pm$ 6.59 |           | 3.65 $\pm$ 4.66 |           | 9.00 $\pm$ 9.47     |           |
| Status                                                             | Haemodialysis                 |                 | 25 (49.0) |                 | 25 (73.5) |                     |           |
|                                                                    | Peritoneal dialysis           |                 | 9 (17.6)  |                 | 9 (26.5)  |                     |           |
|                                                                    | Transplant                    |                 | 12 (23.5) |                 |           |                     | 12 (70.6) |
|                                                                    | Pre Dialysis                  |                 | 5 (9.8)   |                 |           |                     | 5 (29.4)  |
|                                                                    | Active on the Transplant List |                 | 2 (3.9)   |                 | 2 (5.1)   |                     |           |
| Diabetes                                                           | Yes                           |                 | 18 (35.3) |                 | 16 (47.1) |                     | 2 (11.8)  |
| Heart Failure                                                      | Yes                           |                 | 4 (7.8)   |                 | 4 (11.8)  |                     | 0 (0.0)   |
| Religious                                                          | Religious Belief              |                 | 36 (70.6) |                 | 25 (73.5) |                     | 11 (64.7) |
| Highest Education                                                  | Pre 16                        |                 | 10 (20.4) |                 | 8 (25.0)  |                     | 2 (11.8)  |
|                                                                    | Post 16                       |                 | 14 (28.6) |                 | 9 (28.1)  |                     | 5 (29.4)  |
|                                                                    | Degree                        |                 | 6 (12.2)  |                 | 3 (9.4)   |                     | 3 (17.6)  |
|                                                                    | Professional Qualifications   |                 | 7 (14.3)  |                 | 2 (6.3)   |                     | 5 (29.4)  |
|                                                                    | No Formal Qualifications      |                 | 12 (24.5) |                 | 10 (31.3) |                     | 2 (11.8)  |
| Employment Status                                                  | In work                       |                 | 12 (24.0) |                 | 8 (23.5)  |                     | 4 (25.0)  |
|                                                                    | Retired                       |                 | 27 (54.0) |                 | 18 (52.9) |                     | 9 (56.3)  |
|                                                                    | Unemployed                    |                 | 11 (22.0) |                 | 8 (23.5)  |                     | 3 (18.8)  |

**Figure 12** Average percentage importance weights for each attribute



Analysis of subgroups revealed a clear distinction between those currently receiving dialysis and those with a functioning Tx or CKD. The IW's for survival were much lower in the dialysis versus non-dialysis group (15.32 [6.42 – 24.28] vs 29.80 [13.69 – 58.53] ( $p = 0.010$ )). IWs for pain were higher in the dialysis group versus non-dialysis ( $20.20 \pm 10.18$  vs.  $10.14 \pm 7.38$ ;  $p = 0.001$ ). There was no statistical difference in the IW for the other attributes between dialysis and non-dialysis Figure 13 and

Figure 14. There were no significant differences in IWs with regards to gender, comorbidity, religious belief, education achievement or employment status. Pain and breathlessness were more important in older patients ( $\geq 65$  years vs  $< 65$  years): pain  $20.71 \pm 12.09$  vs  $13.92 \pm 7.92$  ( $p=0.019$ ), breathlessness  $21.59 \pm 14.05$  vs  $14.51 \pm 10.20$  ( $p=0.042$ ). Tiredness was less important in older patients:  $10.53 \pm$

6.76 vs  $16.31 \pm 10.49$  ( $p=0.029$ ). There were no age related differences in IW for survival, burden or depression

**Figure 13** Average percentage importance weights for each attribute for individuals on Dialysis

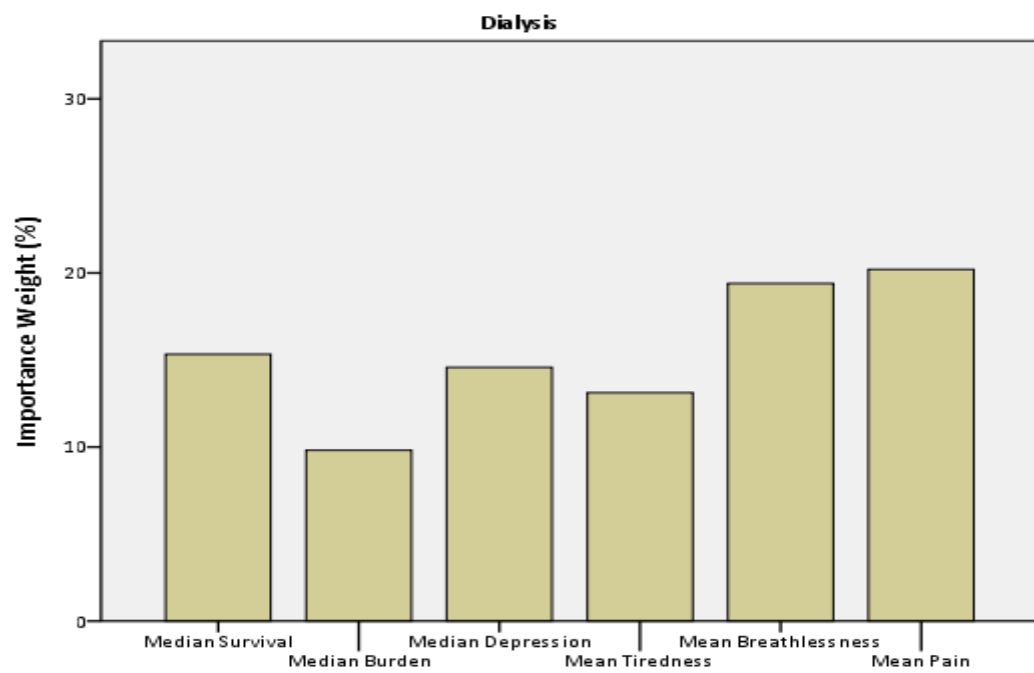
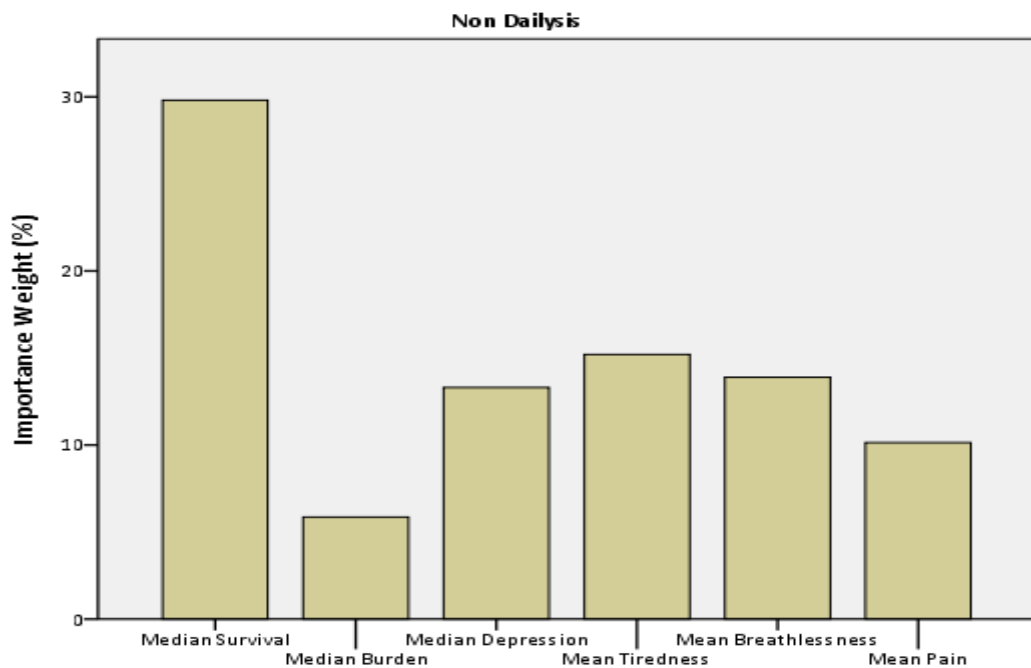


**Figure 14**  
**Non-Dialysis**

**Average percentage importance weights for each attribute for**

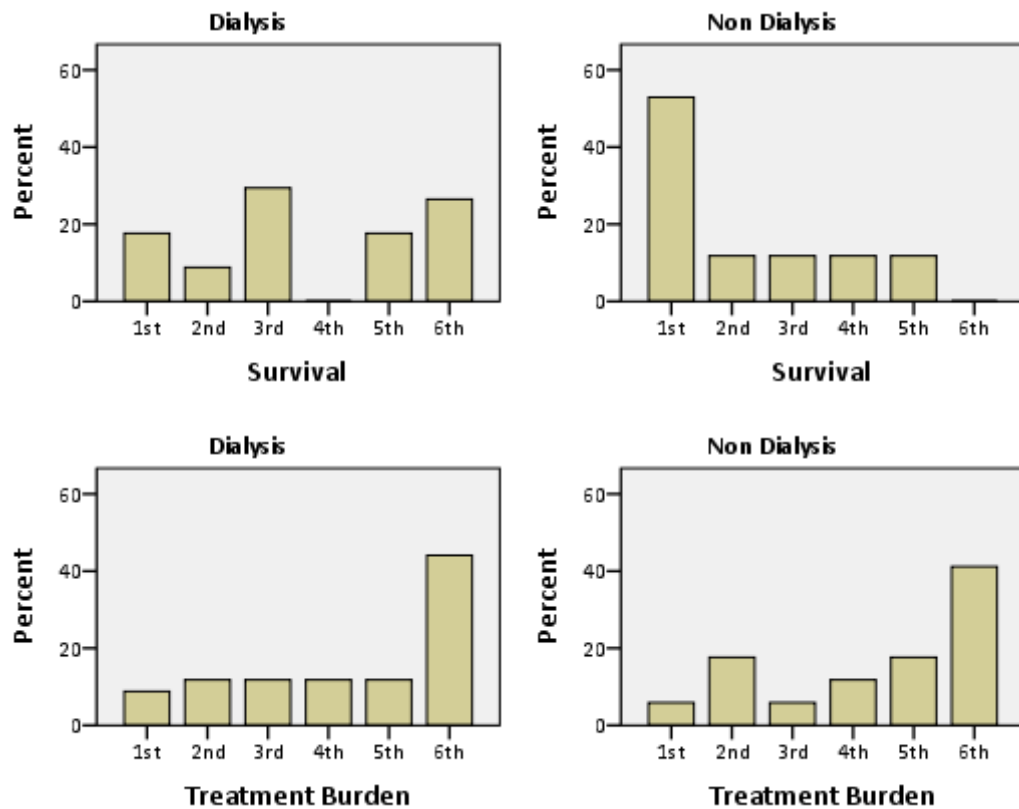


Importance weights for symptoms of pain, breathlessness and tiredness were analysed in relation to DSI, there was no correlation between either total symptom scores or burden or between the self-reported presence or both of the specific symptoms. There was also no correlation of the IW's with perceived treatment burden as reported on the 100 point VAS.

The IWs of individual participants were then ranked in order of importance: The most highly ranked attributes were survival in 29.4% and breathlessness in 27.5%. However this was highly influenced by whether or not the participants were on dialysis. In the non-dialysis population 58.8% rank survival in the top two whereas for individuals on dialysis the corresponding

figure was 29.4% ( $p=0.008$ ). This contrasts with the fact that for both populations considerations around treatment burden were commonly of lower ranking (55.9 in 5<sup>th</sup> or 6<sup>th</sup> place for dialysis and 58.8% for those not on dialysis;  $p=ns$ ). Survival appeared more frequently in the bottom two ranking for dialysis (44.1%) vs non-dialysis (11.8%) ( $p=0.021$ ). Figure 15 sets out the ranking of survival and treatment burden according to if the individual was receiving dialysis or not.

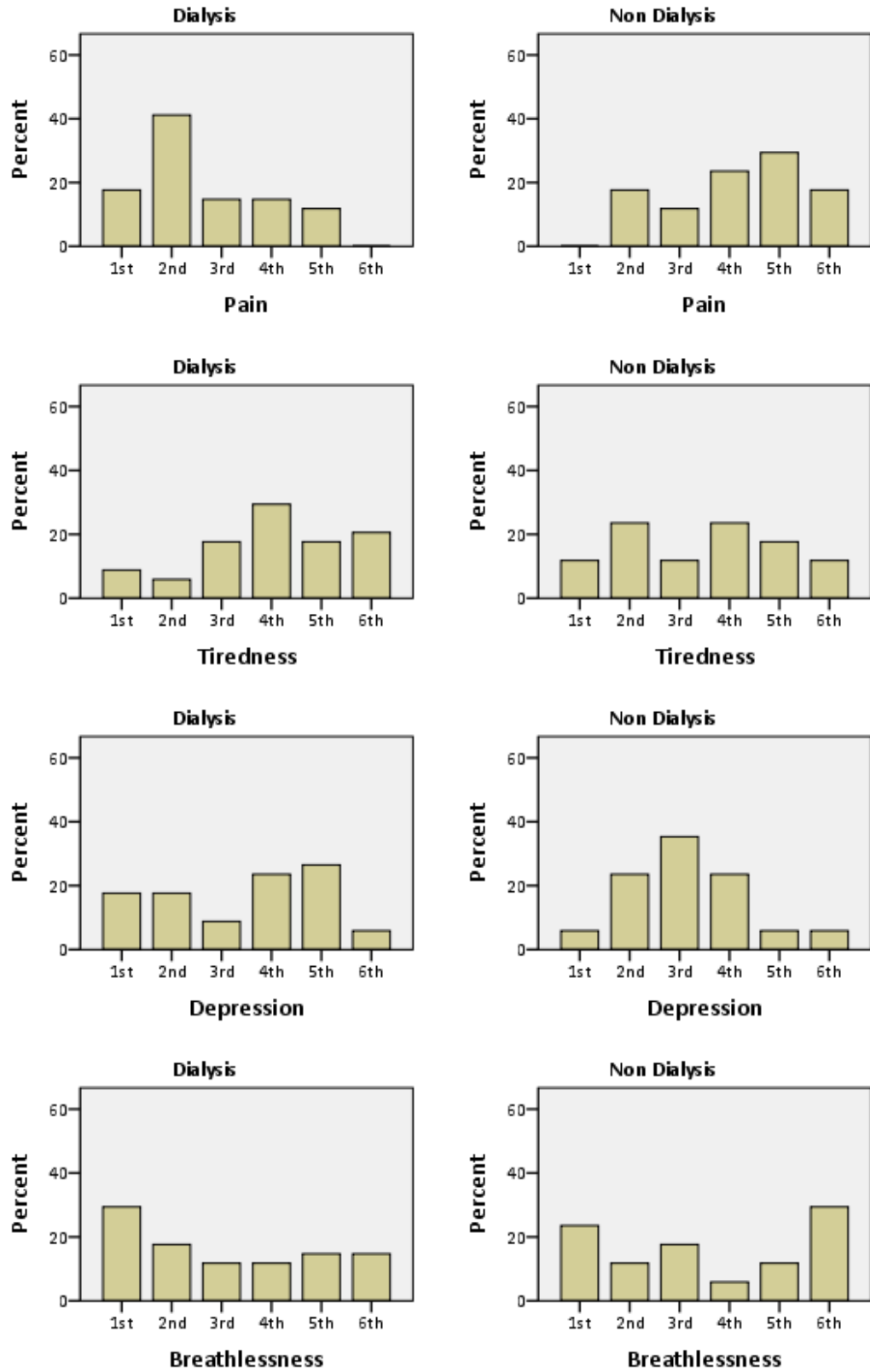
**Figure 15** Importance ranking of survival and treatment burden when making decisions about future treatments split by dialysis or non-dialysis.



As regards specific symptoms there was also a wide variation between the dialysis population and those not on dialysis. IW Pain was an important (top

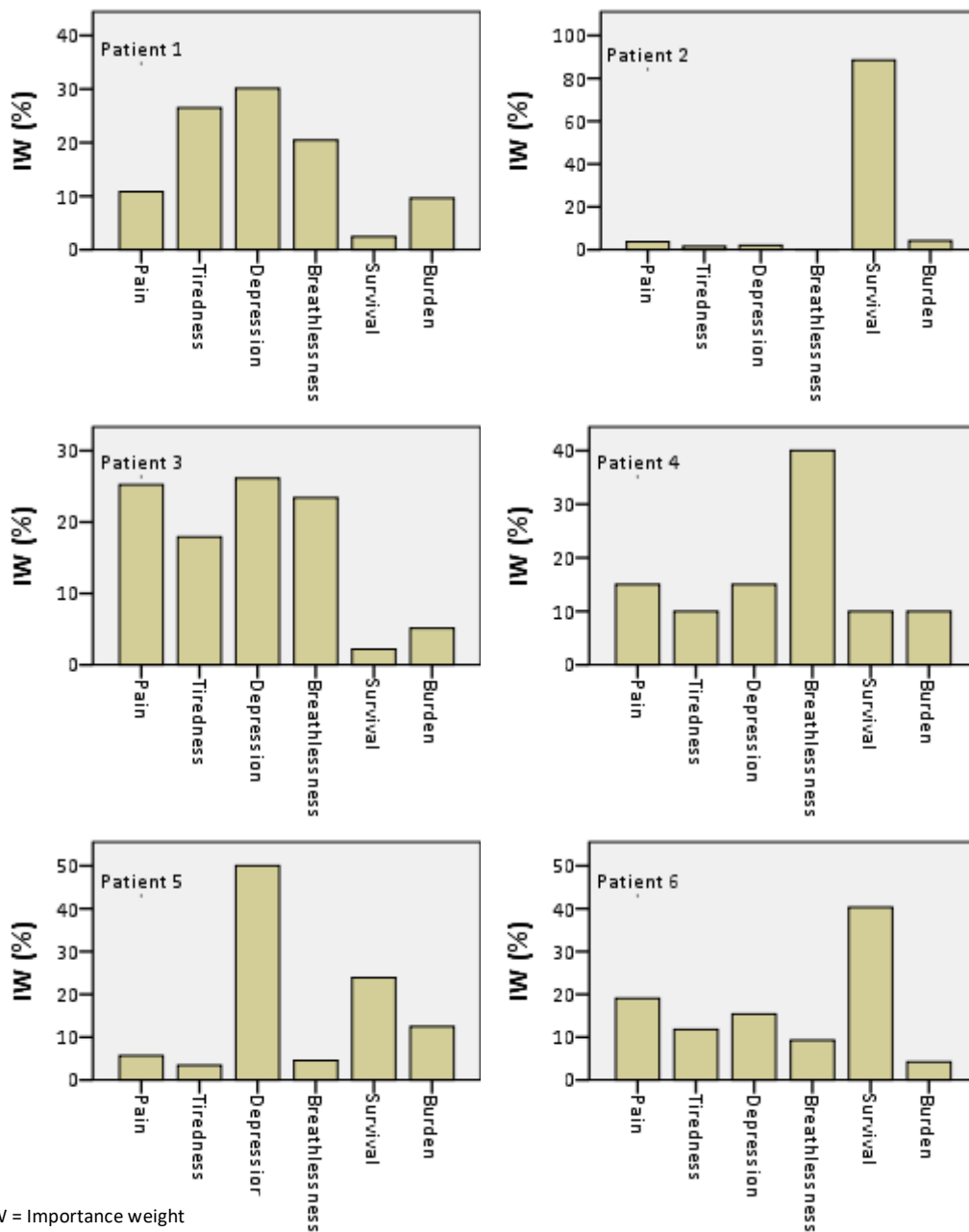
2) factor in 58.8% of dialysis patients but only for 17.6% of non-dialysis patients ( $p=0.005$ ) (and not the primary factor in any non-dialysis patients). IW Breathlessness was ranked in the top 2 for 47.1% of dialysis patients but only 35.3% of non-dialysis ( $p=ns$ ). IW Tiredness was ranked in the top 2 for only 14.7% of dialysis patients but 35.3% non-dialysis ( $p=ns$ ) and for IW depression this was 35.3% individuals on dialysis vs 29.4% non-dialysis ( $p=ns$ ). Figure 16 shows the detailed breakdown between symptoms and ranking for both dialysis and non-dialysis.

**Figure 16** Importance ranking of specific symptoms in decisions about future treatments, split by dialysis or non-dialysis.



These trends hide the fact that some (total 8 of 51) individuals had very strong > 50% IW for survival whilst only one individual had an IW for pain > 50 and none reached this threshold for any of the other outcomes. Figure 17 shows representative importance weights on an individual level for 6 sequential individuals on dialysis from the study group.

**Figure 17** Individual Participant importance weight distributions



When the responses of the 7 individuals who completed the follow up questionnaire at one year were analysed there were no statistically significant differences between the importance weights at baseline and follow up.

## Discussion

Participants showed a variety of outcome preferences which were strongly influenced by whether or not they were on dialysis. Individuals not on dialysis were twice as likely to be focused on survival whereas those on dialysis were more focused on symptoms. Individuals on dialysis were twice as likely to be focused on pain. In both the symptom focused and the survival focused participants there was the willingness and ability to consider increased treatment burden in order to achieve their optimal outcome. A small cohort of individuals from across the groups strongly valued survival over all other aspects of outcome presented. Although preference for the symptoms of pain, shortness of breath and tiredness varied with age there were no firm demographic or treatment factors that predicted preference strongly. The presence or otherwise of the individual symptoms and reported treatment burden also had no relationship to the individual outcome preferences. Although there were clear trends to symptom preference in individuals on dialysis there were still some individuals that were very survival focused.

The finding that individuals on dialysis are more symptom focused is not explained by the demographics or by the presence or degree of symptoms. I propose that it may be influenced by prior experience and symptoms as well as the observation of others on dialysis. It is possible that there is a difference between those that are transplant listed and on dialysis and those not listed; however only 2 of our cohort were active on the list at the time of study so we were unable to explore this further.

There are no data with which to directly compare this study, however in 2010 Stanek et al. examined the balance of symptoms versus survival preferences in patients with congestive heart failure. They showed that in symptomatic patients there was a clustering into either a preference for survival or a preference for symptom control with the majority falling into the latter group. There were no predictors of which group an individual patient would be in (age, gender, ethnicity, severity of heart failure, cause, QOL or objective measure of heart function)<sup>262</sup>. Another study in advanced or recurrent ovarian cancer had progression free survival as an outcome; in this study women predominantly chose chemotherapy regimens based on progression free survival but they were willing to trade a significant reduction in survival for reductions in treatment related toxicity<sup>260</sup>. In both of these studies, as in our study, individuals were making complex judgements about potential outcomes and separated into groups that were

defined by their outcome preferences that were not related to demographic factors.

The sample size in this pilot study limited the ability to perform more complex analysis. In particular the small numbers of individuals that were followed up at one year means that no real conclusion can be drawn on the stability of outcome preferences over time and there are no published data looking at what happens when there is intercurrent illness or a change of treatment. The choice of a little or lot more or less than current with regards to symptoms assumed that each individual had these symptoms and might have resulted in them overlooking the options that included less symptoms as not relevant to them. This might have led to an underestimate of the significance of symptoms in the final analysis. In future work the questionnaire should be revised to give a scale response for the symptoms and treatment burden. Published data suggest that while around 40% of people on dialysis are unsure of their prognosis, 33% felt it was likely > 10 years with only 11% thinking it was less than 5 years. In this context the choice of plus or minus 6 or 12 months survival may be more relevant to some than to others who think they will live longer overall anyway<sup>301</sup>. Future work should include an assessment of individual's prognostic expectations.

This work has demonstrated that it is possible to systematically elicit the relative importance of competing outcomes for our patients in complex

treatment decisions and that there is wide variation in the balance of priorities. It potentially provides us as clinicians with another tool with which to approach our discussions with patients and a way of targeting interventions to get the optimal outcome for the individual patient. In particular we should not assume that our patients will be unwilling to accept an increase in treatment burden in order to achieve their objective. Further work needs to be undertaken to explore the utility of this methodology in more detail and to refine the outcome choices in order to elicit the most relevant preferences.

## **Chapter 6. Collection of daily patient reported outcomes is feasible and demonstrates differential patient experience in chronic kidney disease**

This work was published in Haemodialysis international in April 2017<sup>302</sup>.

### **Abstract**

#### *Introduction*

Patient reported outcomes (PROs) are a critical metric documenting the impact of disease and treatment from the patient's perspective. A variety of generic and disease specific PRO measures (PROMs) are used in chronic kidney disease (CKD) but studies are primarily cross-sectional. None of the available PROMs are designed for frequent iterative application.

#### *Methods*

An online PROM for daily use in dialysis and CKD 4/5 patients was developed. The custom website utilised visual analogue scales to capture 6 PROs (general well being (GWB), pain, sleep, breathing, energy and appetite). Participants were asked to complete the online form daily. Outcomes of interest were uptake, response rates, inter-modality variation and change in PRO corresponding to predefined events.

## *Results*

43 of 84 patients submitted at least once and 34 submitted daily beyond 30 days. Median follow-up was 247 days, 64% were male, age  $62 \pm 12$  yrs. In individuals submitting for >30 days, dialysis patients had significantly worse median scores compared to CKD for sleep (47[32 – 80] vs. 97[76 – 99],  $p=0.003$ ), appetite (66[50 – 96] vs. 97[88 – 100],  $p=0.008$ ), energy (47[40 – 89] vs. 84[67 – 96],  $p=0.031$ ) and GWB (63[49 – 94] vs. 93[71 – 98],  $p=0.026$ ). Patients demonstrated a variety of stable amplitudes of response, deviations from this were associated with specific events e.g. acute admission, vascular procedures, disturbed fluid status and dialysis start.

## *Discussion*

We successfully introduced an online, patient acceptable, iterative PROM that discriminates symptom burden, cross-sectionally and longitudinally. Further work will prospectively examine the predictive power of changes in PRO and more rigorously investigate the potential use of these methods to optimise patient care.

## **Introduction**

### *Background/rationale*

Within nephrology our clinical decisions are increasingly based on a growing body of research, ranging from large registry datasets to small investigator led but high resolution studies. However, most work uses either hard

endpoints (mortality, MI, stroke, change in eGFR) or surrogates (vascular calcification, arterial stiffness, intra-dialytic myocardial performance). In reality, our treatments/interventions are often aimed at reducing symptoms and/or improving quality of life and thus recently there has been an increased interest in these more patient orientated outcomes. Patient reported outcome measures (PROMs) offer a means of measuring outcomes that can only be assessed by the patients themselves.

There are a large number of PROMs available to the clinician, measuring a range of outcomes with reference to the individual's perceptions of their functional status, wellbeing and/or experience. The defining feature that all PROMs share is that they are intended for completion by the patient; most comprise of one or more questions where response is obtained either using the Likert or Visual Analogue (VAS) scales. They have been developed and utilised in a variety of different clinical and research contexts <sup>64</sup>. PROMs can be generic or disease specific and measure a variety of constructs such as health-related quality of life (HRQOL), functional status, health utilities, or disease specific symptoms. PROMs have been used in clinical trials as either the primary or secondary endpoint for many years and are now increasingly used as a measure of effectiveness <sup>65</sup>. Recently, national bodies have mandated collection of PROMs in several settings to assess the quality of care provided at facility level. In 2008 the Centres for Medicare and Medicaid Services adopted a set of clinical performance measures to assess

the quality of dialysis care in the United States, including a requirement for regular measurement of HRQOL. Since 2009 it has been mandatory within the UK to collect PROMs data pre- and post- elective hip and knee replacements, inguinal hernia repair and varicose vein surgery <sup>67</sup>. The role of PROMs as an individual health outcome measure in long-term conditions is likely to be more complex and to date there is a paucity of research in this field.

The majority of studies involving PROMs in renal disease are in patients receiving renal replacement therapy (RRT). The PROMs most widely reported in this context are the European Quality of Life instrument (EQ 5D) and instruments based around the Short Form 36 (SF 36), including the Kidney Disease Quality of Life (KDQOL) <sup>93, 303-305</sup>. There are also a variety of symptom based PROMs that have been developed for, or used in, the CKD population including the dialysis symptoms index (DSI) <sup>306</sup>. The bulk of these studies are cross sectional, thus there is limited data from longitudinal studies <sup>84</sup>.

The authors are not aware of any frequent longitudinal PRO assessment in CKD or RRT despite the often fluctuating course of the disease and the intermittent nature of the treatment (especially haemodialysis (HD)). Indeed, there is an issue with frequent iterative use of many PROMs in that patients are felt to “learn” the answers. In addition, the usefulness of these PROMs in CKD patients is potentially limited by marked ceiling and floor

effects, in part due to the high symptom burden, resulting in a large proportion of respondents at the extremes of a scoring system <sup>84</sup>. The resulting low sensitivity to change makes it very difficult to identify trends in the data, either of the individual or a population. One review looked at validated physical symptom focused PROMs in dialysis patients and identified 23 such instruments, 13 dialysis specific and 10 generic <sup>307</sup>. The recall period for completing these PROMs varied but was rarely less than a week and often much longer. The review concluded that “a valid symptom focused instrument with short recall and assessment of multiple symptom attributes is needed to improve symptom assessment among maintenance dialysis patients.”

We believe that an instrument that is specific for outcomes of relevance to renal patients and is sensitive to change over a short time course, allowing iterative application, would be desirable not just in the dialysis population but also in the CKD 4/5 setting. However, no such PROM is currently available.

### *Objectives*

To develop and test the ‘Derby Evaluation of Illness’ web based platform, the key attributes of which needed to be: patient acceptability, easy integration into clinical care and responsiveness to changing clinical condition. This paper presents the results of our initial feasibility testing.

## Methods

### *Study design*

A custom website was built to capture daily patient reported outcomes (PROs) utilising VAS. An archived copy of the complete website can be found at <http://v1.kidneypatientsurvey.com>. The use of VAS for PRO assessment is well validated and has been used extensively in clinical and research practice for frequent (even hourly) repeated measures especially in symptom assessment<sup>63, 68, 69, 308, 309</sup>. The outcomes were selected following a review of published data on symptom burden in CKD and information on patient priorities from our own patient survey (unpublished)<sup>124, 188, 310</sup>. This process resulted in 6 separate domains: general well being (GWB), pain, sleep, breathing, energy and appetite. The anchors for GWB, sleep and appetite were 'very poor' – 'excellent', for pain and breathing 'extreme' – 'no problem' and for energy 'extremely fatigued' – 'full of energy'. There were no other marks on the line. For each domain the VAS allowed free selection of status along a line from worst (0) to best (100). The website also contained options for participants to send a message to the project team to provide feedback, highlight a problem or request re-advice of their username/PIN.

**Figure 18** Screenshot of the data submission page of the website.

**LOGIN DETAILS**

Username:

PIN:

[Forgot your details?](#)

[Problem submitting?](#)

**DATA FORM**

For each item below click on the line to show your current status from worst to best possible

Please answer all questions based only on the previous 24 hours

|                                                                          |                    |       |                   |
|--------------------------------------------------------------------------|--------------------|-------|-------------------|
| Feeling of general well-being                                            | Very Poor          | _____ | Excellent         |
| Presence and severity of bodily pain                                     | Extreme            | _____ | No Problem        |
| Feeling washed out or drained                                            | Extremely Fatigued | _____ | Full of Energy    |
| Sleep quality                                                            | Very Poor          | _____ | Excellent         |
| Difficulty breathing or shortness of breath                              | Extreme            | _____ | No Problem        |
| Appetite                                                                 | Very Poor          | _____ | Excellent         |
| If you have a current fistula, how well do you think it is working today | Not working        | _____ | Working Perfectly |

[Submit Answers](#)

**LATEST NEWS**

**Mar 12th, 2012**  
Further Extended scope  
Project news update  
Fistula question added

**Sep 30th, 2012**  
News update  
Project news update

All patients were approached by the nursing team with the option to speak to a clinician. Each potential participant was given a set of simple written instructions and a unique username and password with which to register on the site. Once registered, the website issued them with a four digit PIN to use with their username for all subsequent data submission. Registration took no more than five minutes and each visit to the website took less than two minutes to complete data submission. A news section of the website was updated at intervals to keep patients informed about the project. The website also provided for electronic feedback and problem reporting. For the purpose of this initial evaluation recurrent efforts to reinforce repeated engagement with this PROM were not made.

### *Setting*

This project was undertaken in a single renal unit in the UK and patients were approached between December 2011 and May 2012. After seeking

appropriate advice this work was considered not to require formal ethical approval as it was regarded as an extension to our current patient care processes and was not considered to be a clinical trial.

### *Participants*

Use of the website was initially offered to all patients undergoing unit based HD within our unit who reported having regular access to the internet and could understand spoken and written English. The project was subsequently rolled out to include patients attending our pre dialysis clinics and to peritoneal dialysis (PD) patients. Our total unit based HD population at this time was around 200 patients with around 100 on PD.

### *Variables*

Supplementary information on HD day and dialysis treatments, hospital admissions (date, reason and length of stay), additional treatments (vascular access procedures, additional HD sessions, PD peritonitis events) and routine laboratory investigations (eGFR, Potassium (K) Adjusted Calcium (adj Ca), Phosphate ( $\text{PO}_4$ ), Albumin (Alb), Parathyroid hormone (PTH), and Haemoglobin (Hb)) were collected from the electronic patient record.

### *Data sources/measurement*

Each PRO data point contained the username, a date and time stamp and the numerical value (0-100) for each domain. A copy of the master key table linking each username with a specific individual patient identity remained

on a separate secure internal hospital computer system, inaccessible from the internet. The PRO data was downloaded from the website server after 11 months and matched with the supplemental clinical data.

### *Sample size*

This was a feasibility project with an aim to recruit > 30 patients across HD, PD and CKD (pre-dialysis). All eligible (self-reported regular access to the internet) HD patients were approached. PD and CKD patients were approached in routine clinic appointments.

### *Statistical methods*

Demographic data are presented as mean  $\pm$  SD, all PRO data are reported as median and inter quartile range (IQR) unless otherwise specified. Spearman's correlations were used to determine association between PROs and demographic and clinical data, the Mann-Whitney U test was used when comparing distributions across groups. Statistical significance was set at 5% and all data were analysed using SPSS, Version 19.0.0.1 (IBM Corp, Armonk, NY).

## **Results**

### *Participants*

Initial written information was given to 84 patients (45 HD, 11 PD and 28 CKD) who reported having regular access to the internet. 43 patients (19 HD, 5 PD and 19 CKD) submitted at least one set of data via the website with a

median follow up at analysis of 247 days (range 10 – 312 days). 80% submitted data for > 30 days, 2 HD patients withdrew at <30 days (1 death, 1 transplant), 65% of all registered patients continued to submit data at 90 days.

### *Descriptive data*

For the entire cohort 64% were male and the mean age was  $62 \pm 12$  years. All further analysis focused on those that submitted for > 30 days, where 62 % were male with a mean age of  $61 \pm 11$  years. Patient demographics split by renal function (dialysis vs CKD) are summarised in Table 12

**Table 12** Baseline patient demographics for patients submitting for > 30 days categorised by RRT status.

|                                   | CKD (N = 17)     | Dialysis (N = 17)         | p value |
|-----------------------------------|------------------|---------------------------|---------|
| Age (years)                       | $59.6 \pm 9.7$   | $60.8 \pm 12.6$           | 0.762   |
| Gender (% male)                   | 58               | 65                        | 0.734   |
| RRT Vintage (months)              | -                | $39.8 \pm 48.6$ (0 – 184) | -       |
| Ischemic heart disease (%)        | 12               | 24                        | 0.384   |
| Diabetes (%)                      | 29               | 41                        | 0.488   |
| Active follow-up (days)           | $186 \pm 64$     | $168 \pm 95$              | 0.508   |
| HD session length (hrs)           | -                | $4.2 \pm 0.8$             | -       |
| UF per HD session (L)             | -                | $1.44 \pm 2.10$           | -       |
| eGFR (ml/min/1.73m <sup>2</sup> ) | $16.2 \pm 5.4$   | -                         | -       |
| Haemoglobin (g/dL)                | $11.12 \pm 1.61$ | $11.27 \pm 1.27$          | 0.754   |

### *Main results*

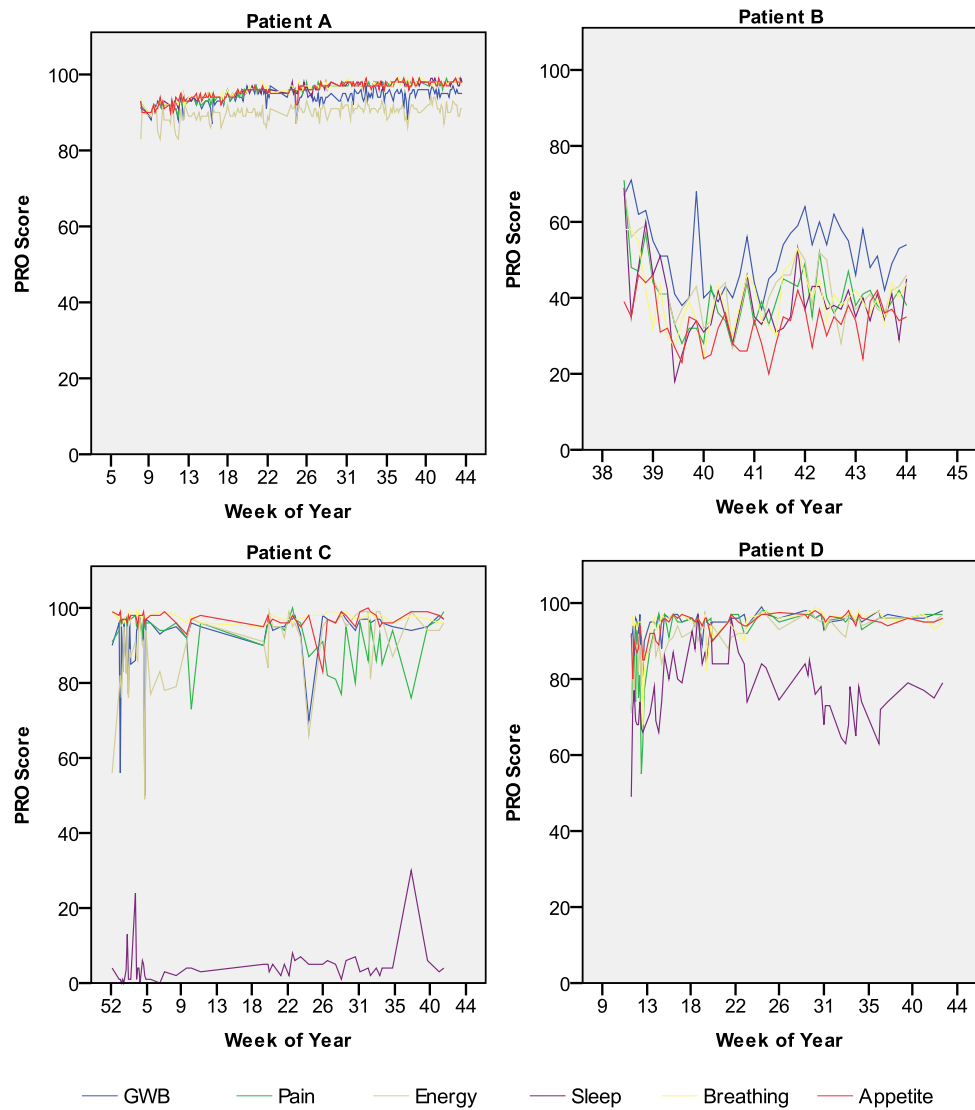
Around 40% of those submitting for more than 30 days (13/34) submitted  $\geq$  three times per week for the duration of follow up. At the time of censure (death, transplant or data collection) 7 patients had submitted within the previous 24 hours and 18/34 within the past 30 days.

The initial stage of investigation focused on general trends in PRO scores. Dialysis patients had significantly worse median scores compared to CKD for sleep (47[32 – 80] vs. 97[76 – 99],  $p=0.003$ ), appetite (66[50 – 96] vs. 97[88 – 100],  $p=0.008$ ), energy (47[40 – 89] vs. 84[67 – 96],  $p=0.031$ ) and GWB (63[49 – 94] vs. 93[71 – 98],  $p=0.026$ ). The degree to which there was inter-submission variability fluctuated considerably according to PRO, and between individual patients. Individual patients demonstrated a variety of stable bandwidths of response as demonstrated in Figure 19. Patient A remained very stable with relatively little fluctuation with all domains closely matched. Patient B might also be described as stable about a point but had much greater variability across all domains. Patient C, in contrast, clearly demonstrates one domain (sleep) that was consistently poor, as compared to Patient D for whom there was deterioration in sleep even while the other parameters improved. However for the entire cohort, dialysis patients had a greater overall amplitude in the range of response compared to CKD in three of the six domains; GWB (41 [23 – 55] vs. 64 [43 – 80],  $p=0.037$ ), sleep (35 [15 – 59] vs. 57 [48 – 90],  $p=0.011$ ) and appetite (15 [6 – 60] vs. 63 [20 – 76],  $p=0.018$ ), indicating greater variability.

Examination of individual patient responses revealed a number of additional patterns of interest. We initially looked for signal change associated with specific events (admission, procedure, unscheduled medical review, RRT start) in the CKD cohort. There were 12 recorded events in this group, in six

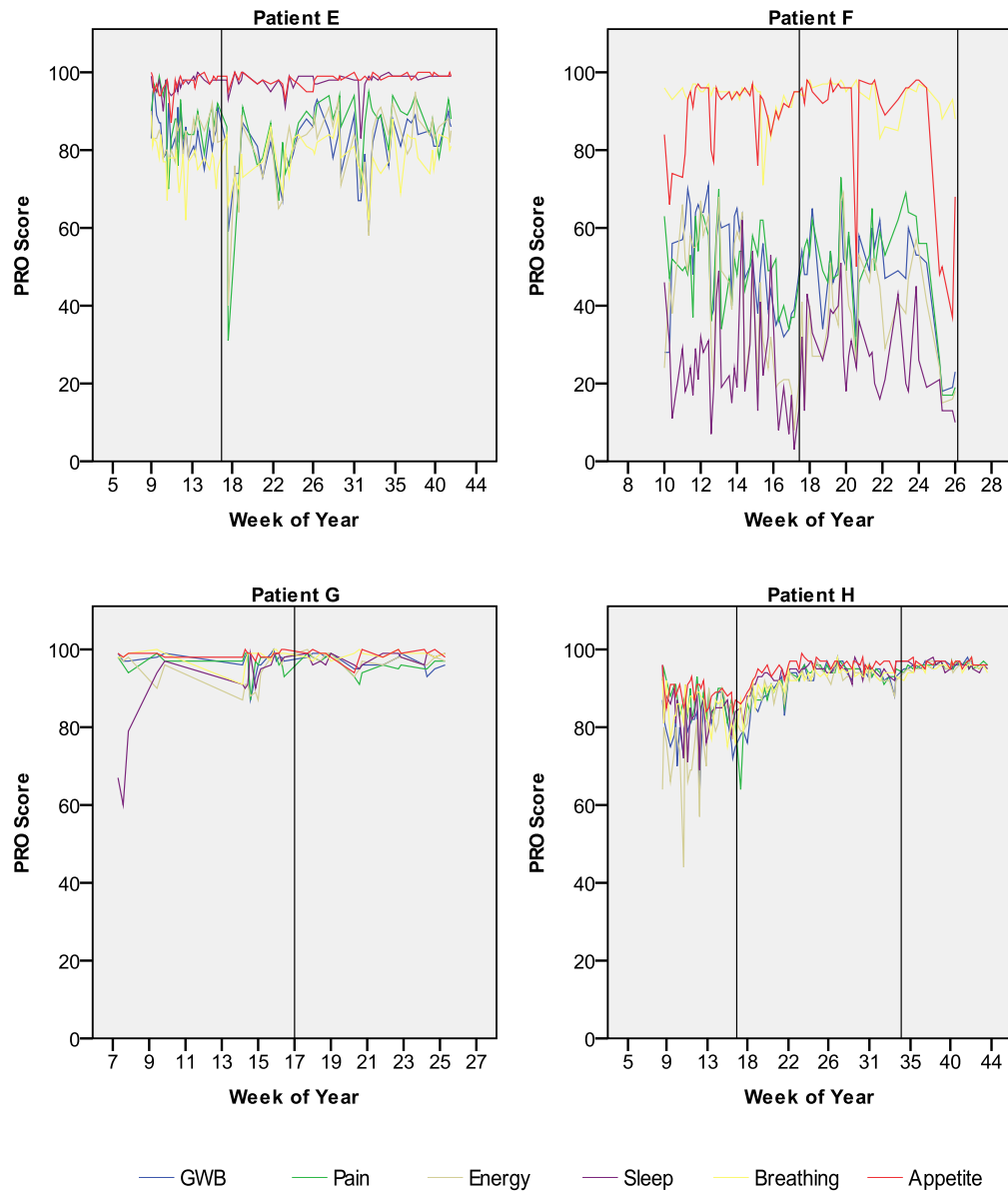
patients. Figure 20 shows the responses of four of these patients. The events were fistula formation (Patient E), RRT commencement (Patients F–G) (Patient F had a subsequent acute medical admission and patient H later transferred to Home HD), one patient had recurrent admissions for investigation and management of anaemia, and one patient 2 admissions for elective surgical procedures.

**Figure 19** This figure demonstrates the range of responses and trends in a selection of participants



Patient A is a stable CKD patient with an eGFR of 14 to 16 ml/min. Patient B is an established CAPD patient. Patient C is an established hospital HD patient. Patient D is a hospital HD patient training for Home HD.

**Figure 20** Demonstrates the PRO changes at the time of specific events in CKD patients



Vertical lines represent events. Patient E had a fistula formation (brachiobasilic transposition). Patient F had a planned start to HD at the first time point, the second represents a hospital admission. Patient G had an elective PD catheter insertion and planned start on PD two weeks later. Patient H had a planned start to HD and subsequently started Home HD (second line).

Analysis in the dialysis group also examined specific events, but furthermore explored differing responses dependent on dialysis vs. non-dialysis day. There were 10 specific events in four patients. Figure 21 demonstrates a selection of these responses. The events were an unplanned medical review and initiation of training for home HD with increased frequency of HD (Patient I), an admission and an unplanned medical review both related to fluid balance (Patient J), a patient who had an acute surgical admission (Patient K) and a patient with a series of unplanned medical reviews for fluid balance (graph not shown). Patient L demonstrates the differential response of an individual patient in energy on HD and non HD days.

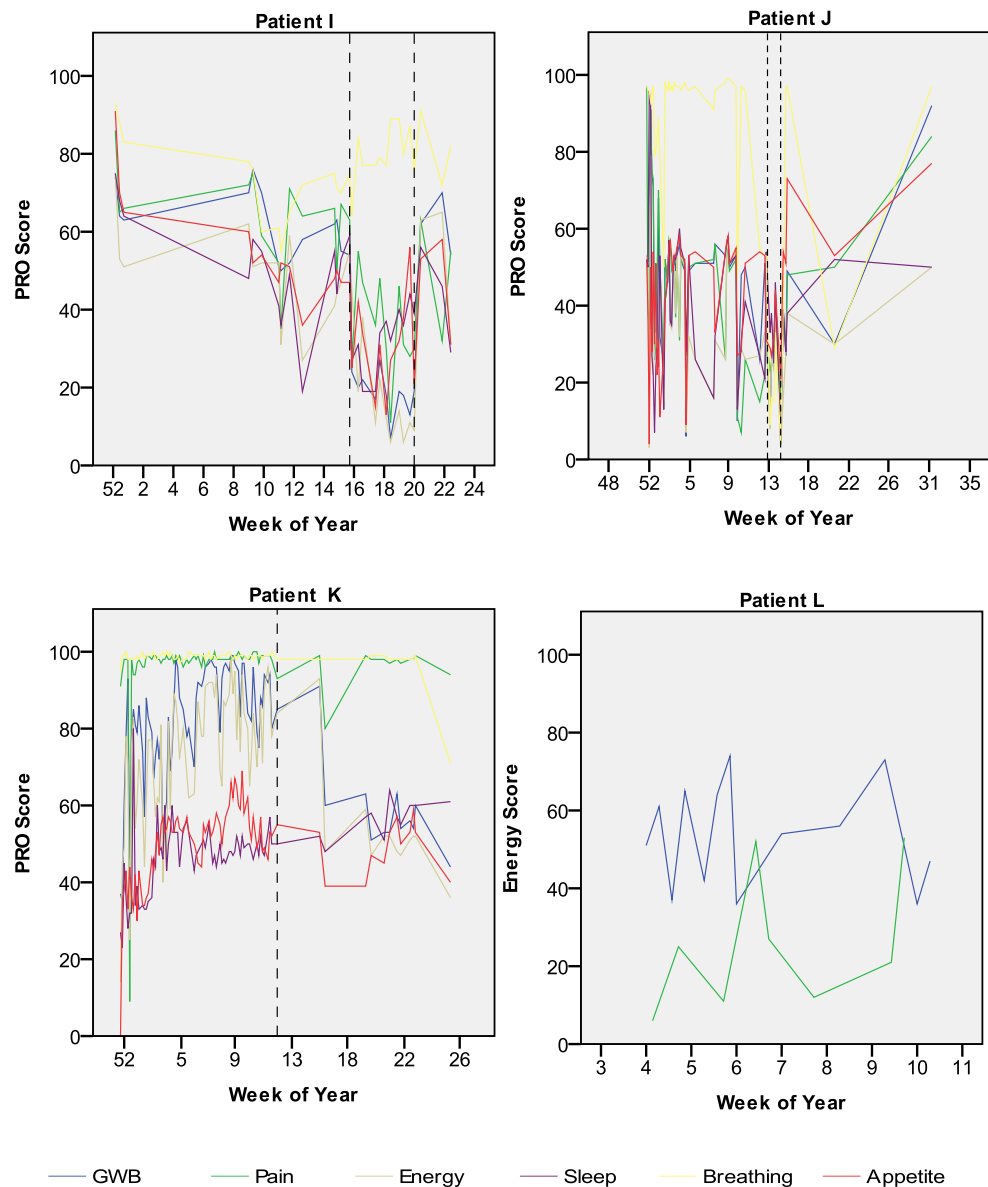
### *Other analyses*

We evaluated correlations between selected serially measured variables (haemoglobin (Hb) concentration, ultrafiltration (UF) volume and rate (UFR), and eGFR) and specific or total PRO scores for individual patients. Adequate Hb data were available for 31 patients. Hb had a significant correlation with GWB in 12 patients, and with Energy in 12 patients. Eight patients' Hb demonstrated correlation with both GWB and Energy. The strength and direction of the correlation varied between individual patients and with Hb range. Of the 13 HD patients for whom there were sufficient data ( $\geq 6$  HD sessions with PRO recording on the same day) 3 had a significant correlation between their breathing PRO and dialysis UF volume ( $r=-0.264$   $p=0.001$ ,  $r=0.777$   $p=0.040$ ,  $r=0.350$   $p=0.039$ ). 5 CKD patients had a change in eGFR  $\geq 5$

ml/min/m<sup>2</sup> (one additional patient was excluded from this analysis due to AKI). 3 displayed a significant correlation between at least two PROs (pain and breathing) and eGFR.

Feedback was sent via the website 8 times by 5 different patients, their comments generally focused on requests for additional items – such as a “comment box” or for the ability to view previous results. The problem report function was used 12 times, twice to request registration details, one person used the function to report being on holiday (and therefore a data gap). Six reports (4 people) related to problems entering data (this was diagnosed to be due to a bug in an old version of a popular web browser, allowing deployment of a site modification), and three had issues with the registration process (this was tracked to incorrect entry of a *case sensitive* password, allowing an update to the website wording helping to highlight this to users).

**Figure 21** Demonstrates the PRO changes at the time of specific events in dialysis patients



Vertical lines represent events. Patient I was initially established on conventional thrice weekly hospital HD, The first event line represents an unplanned medical review triggered by general decline in health, the second when they commenced Home HD training and concurrently switched to 5\*3 hours per week HD. Patient J was an established hospital HD patient who had an acute medical admission related to fluid status and a subsequent unplanned medical review where their target weight had a further downward adjustment. Patient K had an acute surgical admission following a fall. The graphs for Patient L show the differing PRO score dependent on if they dialysed or not at the time point (day).

## Discussion

This preliminary work has demonstrated the successful utilization of the first online iterative renal PROM. Our PROM has been shown to be acceptable to patients as revealed by sustained and regular use in a diverse group of individuals. We have demonstrated for the first time the degree of individual patient variability in these clinically relevant PROs, with some patients displaying a very narrow (<10) range of response while others appear much less stable (>40).

We have shown, in reasonably well-matched groups (co-morbidity, age, gender, Hb, serum albumin and phosphate), that patients receiving dialysis have both worse and more variable PRO scores. This observation is particularly concerning as a primary aim of RRT initiation is to improve patient symptoms including appetite and sleep. Reassuringly, we did indeed observe an improvement in PRO for some of our patients initiating dialysis (with no change in the others). These observations are limited by the small numbers of patients initiating RRT. We note that the mean eGFR in our CKD 4/5 cohort was 16.2 ml/min/1.73m<sup>2</sup> with an associated deterioration in scores with worsening renal excretory function. Mean dialysis vintage of our patients was a little over four years and we propose that the observed differences can also be explained in part by increasing burden of disease for those receiving RRT. Longer studies would help explore this.

At the individual patient level we have demonstrated that this PROM is sensitive enough to detect clinically relevant change in PROs over both the short (days) and longer (months) term. We have also demonstrated significant correlation of these PROs with measured parameters (Hb, eGFR, UF rate) at levels of change that have not been previously described, suggesting that the use of frequent PRO assessment via VAS may be more responsive to these subtle changes. These preliminary observations lead us to propose that the data items collected are relevant and the tool sensitive enough to detect a clinically relevant change in our patient group. Further development to provide a platform that is both accessible and fully integrated into routine care is desirable to fully explore the utility of this novel instrument.

The 'Derby Evaluation of Illness' website was not compared to other PROMs such as the EQ 5D or the DSI as our PROM is measuring a different part of the patient experience and none of the available instruments offer the same functionality of iterative use. Nevertheless, we feel that the above observations would indicate that care needs to be taken when interpreting currently available PROMs, as the assessment might look very different depending on when the 'snapshot' of patient experience was taken utilising a standard established PROM.

This study is supportive of the contention that there is potential for integrating specific iterative PROMs into clinical systems to give a semi-

automated 'early warning' prompt for review on issues as diverse as dry weight/ fluid status, or to "flag" those patients that are failing to thrive either on dialysis or in the pre dialysis setting. This method for collecting PRO data is potentially applicable to a wide cohort of patients, especially after addressing accessibility issues relating to active/passive completion and IT platform selection.

Robust conclusions, beyond an initial description of a signal that dynamically collected PRO scores might be associated with laboratory values and clinical outcomes, was beyond the scope of this initial feasibility study. At the time of the study only around one quarter of our patients self reported regular access to the internet and of these just under half engaged with the website. However the use and availability of technology has changed very rapidly and now a majority of people have regular access to the internet either in their own homes or via smart phones. In addition there is now increasing use of portable devices within renal units. In 2016, approximately 60% of our prevalent HD patients have requested access to a national online NHS patient results portal (Renal Patient View). However, only approximately one-half remain active users. We made a conscious decision at the start of this project not to provide reminders or prompts to either register or continue to submit data and there was no reinforcement or incentive given to participate beyond the initial contact. In this context we feel that the numbers choosing to register and maintain engagement are

encouraging. Although the patients in this study were self-selecting as IT literate and engaged with their care, we feel that this has the potential to be accessible to a much broader cohort of patients especially those on unit based HD where the technology is often already present within the unit. Further work will look at providing real time feedback to those submitting data and to the clinical team looking after them with alerting of abnormal returns. It will also explore the use of different platforms and models of delivery to enhance patient take-up and participation. Simultaneously our ongoing work will now look at more rigorously testing the potential use of these methods in dealing with key challenges of patient care including event prediction, transfer to conservative care, dialysis start time selection and assessing impact of changing dialysis modality.

## Chapter 7. Discussion

I have confirmed that HRQOL, especially the PCS is poor in advanced CKD and is related to the number and burden of symptoms and also to the presence of high scores for depression. This study suggests that the most significant symptoms are muscle cramp, shortness of breath, restless legs, tiredness, dry mouth, dry skin and itching. There is a loss of the normal variation in HRQOL that is seen in the general population with age, gender and education. The way that individuals make sense of their illness and treatment influences how they interact; this was shown to be particularly true of necessity beliefs around medicines for transplant recipients and the relationship of necessity beliefs to serum phosphate in dialysis patients. In addition all individuals had positive necessity beliefs in relation to dialysis but far fewer to the need for fluid or dietary restriction. Concerns about medicines, dialysis and fluid restriction were all related to the underlying beliefs from the BMQ general about medicines overuse. Individuals who were pre dialysis had a greater number of symptoms and attributed more of these to their kidney disease. People undertaking PD had higher perception of personal control over their kidney disease. In addition individuals on HD attributed more symptoms to the dialysis than those on PD. When it came to outcome preferences these varied markedly but individuals not on dialysis were twice as likely to favour survival as those on dialysis. I have also

described development of online frequent symptom tracking that was acceptable to patients and able to demonstrate that deviations from an individual's normal response amplitude were associated with specific events e.g. acute admission, vascular procedures, disturbed fluid status and dialysis start.

The lack of the normal patterns of variation seen with age, gender and employment suggest that advanced CKD by itself is a stronger determinant of HRQOL than these other demographic factors. The finding that advanced CKD is associated with poor QOL is not new but the understanding that this is related to symptom burden and in particular to a few specific symptoms gives a focus to efforts to improve HRQOL in this population. Depression was also a big contributor to poor QOL; the diagnosis of depression in advanced CKD is difficult as many of the physical symptoms of depression are also common symptoms in this population. In addition there is little evidence that conventional treatment with antidepressants is effective and some evidence of harm as these drugs have a tendency to prolong the QTc interval and so increase the risk of cardiac arrhythmia in a population already known to be at high risk of sudden cardiac death. The use of cognitive therapies is also under studied and under resourced. Further work to understand the treatment of depression in advanced CKD is warranted.

The relationship of BMQ general to concerns raises the possibility of targeted interventions early in an individual's renal journey aimed at

modifying these concerns. The finding that BMQ prescribed medicines necessity correlates with serum phosphate fits with previous data regarding phosphate binder necessity<sup>240, 241</sup>. Published data suggest that necessity and concern beliefs are modifiable and that this change can persist in other health conditions; there are no studies to date that have shown a sustained benefit to an approach aimed at altering health beliefs in this way in CKD. However the use of the BMQ in regards to individual's beliefs about medicines prescribed for renal disease in the pre dialysis clinic as well as in dialysis might allow targeted interventions aimed at modifying beliefs and improving concordance with medical therapy as demonstrated in populations with asthma<sup>233</sup>. Further use of the BMQ to understand beliefs about dialysis as well as fluid and dietary restrictions may again lead to the development of a targeted individualised approach to patient education aimed at increasing necessity beliefs and minimising concerns. I suggest that these interventions need to be individualised and sustained over a period of time with frequent reinforcement of the messaging. The exact methodology for delivery of this type of intervention is an area for future work and it is likely that a combination of different interventions may be required at different time points.

Understanding perceptions might lead to improved patient education by allowing the educator to structure the information around the individual's pre-existing framework of belief. Targeted education based on illness

perceptions has been used in the past to modify behaviours in other populations and the development of a similar approach in advanced CKD (potentially aimed initially at those in the pre dialysis setting) could lead to improved understanding with increased participation in decision making and engagement<sup>292, 311</sup>.

An appreciation that individuals with advanced CKD are willing to balance the often competing outcomes of symptom control, survival and treatment burden, often having a strong preference for either symptoms or survival and attaching low importance to changes in treatment burden should allow health care professionals involved in the care of these individuals to be bolder in the discussions about the potential consequences of changing treatments and to tailor these changes to better match the individuals preferences. More work needs to be done to develop the outcome preference questionnaire into something that can be used easily in clinical practice but the observations in this study give the first indications of a way to assess this important aspect of care.

Since the initial design of the daily web based PROM the use of computers and internet connected devices has become almost ubiquitous across the population. The system that we implemented allowed for collection of frequent data on symptoms that was able to distinguish important events. The next stage of work will focus on expanding this to allow for the development of flags within the system to prompt clinical review in much

the same way that historically changes in biochemical parameters have been used. In addition there is a plan to develop the concept to include a mobile application. This will widen access and could also allow for the introduction of prompts for completion alongside development of other feedback mechanisms.

A limitation of this work was that INTUITIVE was slow to recruit to due to the fact that a number of individuals were not prepared to commit to two hours completing questionnaires. Whilst some haemodialysis patients were more than happy to participate during a dialysis session some felt that they just wanted to rest. Individuals in the other target groups were often unwilling to commit the time. Although efforts were made to recruit non English speakers with the use of interpreters this was not successful. For a small number of those that did consent the volume of questions in one sitting was sometimes overwhelming and they were unable to complete the entire set. The effects of this are that the data collected may not truly reflect the experience of the entire population as only those with the willingness to devote the time and motivation or psychological stamina to complete all questionnaires will have been included in the analysis. In order to improve recruitment and increase completion rates future work should focus on a smaller number of questionnaires targeted to specific areas of interest. This could involve the development of a number of parallel workstreams but could also involve the use of different questionnaires at

different timepoints in an individual's journey. This would focus on collection of symptom data, illness perception, beliefs and outcome preferences using changes in HRQOL as an outcome. Questionnaire fatigue is recognised in many areas however we found that participants were very willing to continue to respond on a regular and frequent basis on the Derby evaluation of illness site. Although each of the questionnaires' in this study has had merit, caution should be used in choosing which questionnaire is relevant at a particular time in a patient's journey to best facilitate the conversations around their care.

Recent work by the renal registry has been looking to explore the options of incorporating PROM data into routine clinical care within Nephrology. This work is in the early stages but there is a recognition within the community that this is an important and expanding area of investigation that has the potential to positively impact on patient care and experience.

Since this study was first designed, it has been recognised that frailty is an increasingly important concept within advanced CKD management and has many interactions with HRQOL and symptoms as well as ability to engage with health care professionals. Any future work will need to take this important concept into account.

With this work we are now able to identify the symptoms most likely to negatively affect HRQOL in advanced CKD and have demonstrated a

methodology for tracking symptoms that is acceptable to patients and has been shown to track changes in health status. In addition we have tested and developed the tools to explore the individual's health beliefs and outcome preferences showing that that they are both highly individual and that beliefs have an impact on clinically relevant measures. The next steps will be to further develop the use of these tools, testing their acceptability to a wider demographic including healthcare professionals and to combine them with targeted intervention strategies as implemented in other health settings with the aim of improving outcomes including HRQOL.

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## Appendix

### Copy Questionnaires

#### KDQOL\_SF

Influence of Illness beliefs and Treatment outcome preferences  
In patients with End Stage Renal Disease.

Pt No:  
Date:

#### **Kidney Disease and Quality of Life Short Form (KDQOL – SF™) Version 1.3 (UK)**

**Patient Study Number** \_\_\_\_\_

**Date of Completion** \_\_\_\_\_

**Patient Visit Number** \_\_\_\_\_

#### **Instructions:**

- a) 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.
- b) 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.
- c) Please answer the questions by marking the appropriate box or by filling in the answer as requested.

#### d) Example:

During the past four weeks, how much back pain have you had?

(Mark one box)

|           |                                     |
|-----------|-------------------------------------|
| None      | <input checked="" type="checkbox"/> |
| Very mild | <input type="checkbox"/>            |
| Mild      | <input type="checkbox"/>            |
| Moderate  | <input type="checkbox"/>            |
| Severe    | <input type="checkbox"/>            |

- e) Several items in the survey ask about the effect of kidney disease on your life. Some items will ask about limitations related to your kidney disease, and some items will ask about your well-being. Some questions may look like others, but each one is different. Please answer every question as honestly as possible. If you are unsure about how to answer a question, please give the best answer you can. This will allow us to have an accurate picture of the different experiences of individuals with kidney disease.

### 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                     |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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

| Much better<br>now than one<br>year ago | Somewhat<br>better now<br>than one year<br>ago | About the<br>same as<br>one year ago | Somewhat<br>worse now<br>than one year<br>ago | Much worse<br>now than one<br>year ago |
|-----------------------------------------|------------------------------------------------|--------------------------------------|-----------------------------------------------|----------------------------------------|
| <input type="checkbox"/>                | <input type="checkbox"/>                       | <input type="checkbox"/>             | <input type="checkbox"/>                      | <input type="checkbox"/>               |

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,<br>limited<br><u>a lot</u> | Yes,<br>limited<br><u>a little</u> | No,<br>not limited<br><u>at all</u> |
|-----------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------|-------------------------------------|
| a) <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports.....  | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| b) <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf..... | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| c) Lifting or carrying groceries .....                                                                          | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| d) Climbing <u>several</u> flights of stairs .....                                                              | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| e) Climbing <u>one</u> flight of stairs .....                                                                   | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| f) Bending, kneeling, or stooping .....                                                                         | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| g) Walking <u>more than a mile</u> .....                                                                        | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| h) Walking <u>500 metres</u> .....                                                                              | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| i) Walking <u>100 metres</u> .....                                                                              | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |
| j) Bathing or dressing yourself .....                                                                           | <input type="checkbox"/>        | <input type="checkbox"/>           | <input type="checkbox"/>            |

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 on the <u>amount of time</u> you spent on work or other activities? .....                       | <input type="checkbox"/> | <input type="checkbox"/> |
| b) <u>Accomplished less</u> than you would have liked?.....                                                 | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Were limited in the <u>kind</u> of work or other activities? .....                                       | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)? ..... | <input type="checkbox"/> | <input type="checkbox"/> |

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 on the <u>amount of time</u> you spent on work or other activities? ..... | <input type="checkbox"/> | <input type="checkbox"/> |
| b) <u>Accomplished less</u> than you would like?.....                                 | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Didn't do work or other activities as <u>carefully</u> as usual?.....              | <input type="checkbox"/> | <input type="checkbox"/> |

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

| Not at all               | Slightly                 | Moderately               | Quite a bit              | Extremely                |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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

| None                     | Very mild                | Mild                     | Moderate                 | Severe                   | Very severe              |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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

| Not at all               | A little bit             | Moderately               | Quite a bit              | Extremely                |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

9. 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<br>of the<br>time    | Most<br>of the<br>time   | A good bit<br>of the<br>time | Some<br>of the<br>time   | A little of<br>the time  | None<br>of the<br>time   |
|------------------------------------------------------------------------------------|--------------------------|--------------------------|------------------------------|--------------------------|--------------------------|--------------------------|
| a) Did you feel full of life? .....                                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Have you been a very<br>nervous person? .....                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Have you felt so down in<br>the dumps that nothing<br>could cheer you up? ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Have you felt calm<br>and peaceful? .....                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Did you have a lot of<br>energy? .....                                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Have you felt downhearted<br>and unhappy? .....                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) Did you feel worn out? .....                                                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Have you been a happy<br>person? .....                                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) Did you feel tired? .....                                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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<br>of the time       | Most<br>of the time      | Some<br>of the time      | A little<br>of the time  | None<br>of the time      |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

11. Please choose the answer that best describes how true or false each of the following statements is for you.

|                                                                        | Definitely<br>true       | Mostly<br>true           | Don't<br>know            | Mostly<br>false          | Definitely<br>false      |
|------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) I seem to catch things a little more easily than other people ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) I am as healthy as anybody I know.....                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) I expect my health to get worse.....                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) My health is excellent .....                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

### Your Kidney Disease

12. How true or false is each of the following statements for you?

|                                                                            | Definitely<br>true       | Mostly<br>true           | Don't<br>know            | Mostly<br>false          | Definitely<br>false      |
|----------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) My kidney disease<br>interferes too much<br>with my life .....          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Too much of my time<br>is spent dealing with<br>my kidney disease ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) I feel frustrated dealing<br>with my kidney disease .....               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) I feel like a burden on my<br>family .....                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

13. These questions are about how you feel and how things have been going 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...

|                                                                    | None<br>of the<br>time   | A little<br>of the<br>time | Some<br>of the<br>time   | A good bit<br>of the<br>time | Most<br>of the<br>time   | All<br>of the<br>time    |
|--------------------------------------------------------------------|--------------------------|----------------------------|--------------------------|------------------------------|--------------------------|--------------------------|
| a) Did you isolate yourself from<br>people around you? .....       | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Did you react slowly to things<br>that were said or done? ..... | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Did you act irritable toward<br>those around you? .....         | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Did you have difficulty<br>concentrating or thinking? .....     | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Did you get along well with<br>other people? .....              | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Did you become<br>confused? .....                               | <input type="checkbox"/> | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |

14. During the past 4 weeks, to what extent were you bothered by each of the following?

|                                                | Not at all<br>bothered   | Somewhat<br>bothered     | Moderately<br>bothered   | Very much<br>bothered    | Extremely<br>bothered    |
|------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) Soreness in your<br>muscles? .....          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Chest pain? .....                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Cramps? .....                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Itchy skin? .....                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Dry skin? .....                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Shortness of breath? .....                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) Faintness or<br>dizziness? .....            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Lack of appetite? .....                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) Washed out or<br>drained? .....             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) Numbness in hands<br>or feet? .....         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| k) Nausea or upset<br>stomach? .....           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <br><b>l) Haemodialysis patient only</b>       |                          |                          |                          |                          |                          |
| Problems with your<br>access site? .....       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <br><b>m) Peritoneal dialysis patient only</b> |                          |                          |                          |                          |                          |
| Problems with your<br>catheter site? .....     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

### 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 bother you in each of the following areas?

|                                                                    | Not at all<br>bothered   | Somewhat<br>bothered     | Moderately<br>bothered   | Very much<br>bothered    | Extremely<br>bothered    |
|--------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) Fluid restriction? .....                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Dietary restriction? .....                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Your ability to work<br>around the house? .....                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Your ability to travel? .....                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Being dependent on<br>doctors and other<br>medical staff? ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Stress or worries<br>caused by kidney<br>disease? .....         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) Your sex life? .....                                            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Your personal<br>appearance? .....                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

16. The next two questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

How much of a problem was each of the following in the past 4 weeks?

|                                        | Not a<br>problem         | A little<br>problem      | Somewhat of<br>a problem | Very<br>much a<br>problem | Severe<br>problem        |
|----------------------------------------|--------------------------|--------------------------|--------------------------|---------------------------|--------------------------|
| a) Enjoying sex? .....                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> |
| b) Becoming sexually<br>aroused? ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>  | <input type="checkbox"/> |

17. 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 your 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.]

| Very bad                 |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          | Very good |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------|
| 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       |                          |           |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |           |

18. How often during the past 4 weeks did you...

|                                                                               | None<br>of the<br>time   | A Little of<br>the time  | Some<br>of the<br>time   | A good bit<br>of the<br>time | Most<br>of the<br>time   | All<br>of the<br>time    |
|-------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|------------------------------|--------------------------|--------------------------|
| a) Awaken during the night<br>and have trouble falling<br>asleep again? ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Get the amount of<br>sleep you need? .....                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Have trouble staying awake<br>during the day? .....                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/> |

19. Concerning your family and friends, how satisfied are you with...

|                                                                                       | Very<br>dissatisfied     | Somewhat<br>dissatisfied | Somewhat<br>satisfied    | Very<br>satisfied        |
|---------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) The amount of time you are<br>able to spend with your<br>family and friends? ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) The support you receive<br>from your family and<br>friends? .....                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

20. During the past 4 weeks, did you work at a paying job?

Yes                  No

☐                  ☐

21. Does your health keep you from working at a paying job?

Yes                  No

☐                  ☐

22. Overall, how would you rate your health?

Worst possible  
(as bad or worse  
than being dead)

Half-way  
between worst  
and best

Best  
possible  
health

|                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

### 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<br>poor             | Poor                     | Fair                     | Good                     | Very<br>good             | Excellent                | The<br>Best              |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

24. How true or false is each of the following statements?

|                                                                       |                          |                          |                          |                          |                          |
|-----------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                                                       | Definitely<br>True       | Mostly<br>true           | Don't<br>know            | Mostly<br>false          | Definitely<br>false      |
| a) Dialysis staff encourage me to be as independent as possible ..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Dialysis staff support me in coping with my kidney disease.....    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

## TT and DRT

Influence of Illness beliefs and Treatment outcome preferences  
In patients with End Stage Renal Disease.

Pt No:  
Date:

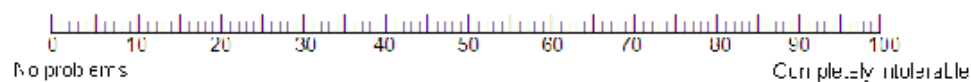
### Treatment Tolerability

Patient Study Number \_\_\_\_\_

Date of Completion \_\_\_\_\_

Patient Visit Number \_\_\_\_\_

Please mark on the scale of 0 to 100 how you rate the overall tolerability of your treatment.  
Where 0 is no problems and 100 is completely intolerable.



### Dialysis recovery time

How long does it take you to recover from a dialysis session? \_\_\_\_\_

Not Applicable ☐

### Treatment Burden

Patient Study Number

Date of Completion

Patient Visit Number

Please mark on the scale of 0 to 100 how you rate the overall **burden of treatment** for your kidney disease over the last 4 weeks. The scale runs from no problems to completely intolerable.



### Adapted Illness Intrusiveness Ratings(IIRS)

Patient Study Number

Date of Completion

Patient Visit Number

The following items ask about how much your kidney disease and/or its treatment interfere with your life. Please circle the one number that best describes your current life situation. If an item is not applicable, please check (✓) the box to indicate that this aspect of your life is not affected.

Please do not leave any item unanswered.

*How much does your kidney disease and/or its treatment interfere with:*

1. Your feeling of being healthy?

Not very much ► 1 2 3 4 5 6 7 ◄ Very much      Not applicable ☐

2. The things you eat and drink?

Not very much ► 1 2 3 4 5 6 7 ◄ Very much      Not applicable ☐

3. Your work, including job, house work, chores, or errands?

Not very much ► 1 2 3 4 5 6 7 ◄ Very much      Not applicable ☐

4. Playing sports, gardening, or other physical recreation or hobbies?

Not very much ► 1 2 3 4 5 6 7 ◄ Very much      Not applicable ☐

5. Quiet recreation or hobbies, such as reading, TV, music, knitting, etc.?

Not very much ► 1 2 3 4 5 6 7 ◄ Very much      Not applicable ☐

*How much does your kidney disease and/or its treatment interfere with:*

6. Your financial situation?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

7. Your relationship with your spouse or domestic partner?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

8. Your sex life?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

9. Your relationship and social activities with your family?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

10. Social activities with your friends, neighbours, or groups?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

11. Your religious or spiritual activities?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

12. Your involvement in community or civic activities?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

13. Your self-improvement or self-expression activities?

Not very much ► 1 2 3 4 5 6 7 ◀ Very much Not applicable ☐

### Dialysis Symptom Index(DSI)

Patient Study Number \_\_\_\_\_

Date of Completion \_\_\_\_\_

Patient Visit Number \_\_\_\_\_

Below is a list of physical and emotional symptoms that people on dialysis may have. For each symptom, please indicate if you had the symptom during the past week by circling "yes" or "no."

If "yes", please indicate how much that symptom bothered you by circling the appropriate number.

| During the past week:<br><br>Did you experience this symptom? |     |    | If "yes":<br><br>How much did it bother you? |                    |               |                |              |
|---------------------------------------------------------------|-----|----|----------------------------------------------|--------------------|---------------|----------------|--------------|
|                                                               |     |    | Not At<br>All                                | A<br>Little<br>Bit | Some<br>-what | Quite<br>a Bit | Very<br>Much |
|                                                               |     |    |                                              |                    |               |                |              |
| Constipation                                                  | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Nausea                                                        | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Vomiting                                                      | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Diarrhea                                                      | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Decreased appetite                                            | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Muscle cramps                                                 | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Swelling in legs                                              | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Shortness of breath                                           | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Light headedness or dizziness                                 | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Restless legs or difficulty keeping legs still                | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Numbness or tingling in feet                                  | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |
| Feeling tired or lack of energy                               | YES | NO | 1                                            | 2                  | 3             | 4              | 5            |

| During the past week:<br><br>Did you experience this symptom? |     |    | If "yes":<br><br>How much did it <u>bother</u> you? |                    |               |                |              |
|---------------------------------------------------------------|-----|----|-----------------------------------------------------|--------------------|---------------|----------------|--------------|
|                                                               |     |    | Not At<br>All                                       | A<br>Little<br>Bit | Some<br>-what | Quite<br>a Bit | Very<br>Much |
|                                                               |     |    |                                                     |                    |               |                |              |
| Cough                                                         | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Dry mouth                                                     | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Bone or joint pain                                            | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Chest pain                                                    | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Headache                                                      | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Muscle soreness                                               | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Difficulty concentrating                                      | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Dry skin                                                      | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Itching                                                       | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Worrying                                                      | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Feeling nervous                                               | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Trouble falling asleep                                        | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Trouble staying asleep                                        | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Feeling irritable                                             | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Feeling sad                                                   | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Feeling anxious                                               | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Decreased interest in sex                                     | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |
| Difficulty becoming sexually aroused                          | YES | NO | 1                                                   | 2                  | 3             | 4              | 5            |

## PHQ-9

Influence of Illness beliefs and Treatment outcome preferences  
In patients with End Stage Renal Disease.

Pt No:  
Date:

### Patient Health Questionnaire – 9 (PHQ-9)

Patient Study Number \_\_\_\_\_

Date of Completion \_\_\_\_\_

Patient Visit Number \_\_\_\_\_

| Over the last 2 weeks, how often have you been bothered by any of the following problems?<br>(Use ✓ to indicate your answer)                                                | Not<br>At all | Several<br>days | More<br>than half<br>the days | Nearly<br>every<br>day |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------------|-------------------------------|------------------------|
| 1. Little interest or pleasure in doing things                                                                                                                              |               |                 |                               |                        |
| 2. Feeling down, depressed, or hopeless                                                                                                                                     |               |                 |                               |                        |
| 3. Trouble falling or staying asleep, or sleeping too much                                                                                                                  |               |                 |                               |                        |
| 4. Feeling tired or having little energy                                                                                                                                    |               |                 |                               |                        |
| 5. Poor appetite or overeating                                                                                                                                              |               |                 |                               |                        |
| 6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down                                                                          |               |                 |                               |                        |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television                                                                                    |               |                 |                               |                        |
| 8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual |               |                 |                               |                        |
| 9. Thoughts that you would be better off dead or of hurting yourself in some way                                                                                            |               |                 |                               |                        |

If you ticked any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

|                                                  |                                                |                                            |                                                 |
|--------------------------------------------------|------------------------------------------------|--------------------------------------------|-------------------------------------------------|
| Not difficult<br>at all <input type="checkbox"/> | Somewhat<br>Difficult <input type="checkbox"/> | Very<br>Difficult <input type="checkbox"/> | Extremely<br>Difficult <input type="checkbox"/> |
|--------------------------------------------------|------------------------------------------------|--------------------------------------------|-------------------------------------------------|

### Outcome Preferences Questionnaire

**Patient Study Number** \_\_\_\_\_

**Date of Completion** \_\_\_\_\_

**Patient Visit Number** \_\_\_\_\_

Below you will find a series of theoretical treatment outcomes. You are asked to rate each separately on a scale of 0 to 10, with a score of 0 representing the least desirable and 10 the most desirable outcome of a change to your treatment.

| Card ID | Pain          | Tiredness     | Depression | Breathlessness | Survival       | Treatment burden |
|---------|---------------|---------------|------------|----------------|----------------|------------------|
| 1       | a LITTLE less | a LITTLE less | a LOT more | a LOT less     | Minus 6 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival      | Treatment burden |
|---------|------------|------------|------------|----------------|---------------|------------------|
| 2       | a LOT less | a LOT more | a LOT less | a LOT less     | Plus 6 months | a LITTLE less    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness     | Depression | Breathlessness | Survival        | Treatment burden |
|---------|------------|---------------|------------|----------------|-----------------|------------------|
| 6       | a LOT less | a LITTLE more | a LOT more | a LITTLE more  | Minus 12 months | a LITTLE more    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival       | Treatment burden |
|---------|------------|------------|------------|----------------|----------------|------------------|
| 7       | a LOT more | a LOT more | a LOT less | a LITTLE more  | Plus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression    | Breathlessness | Survival       | Treatment burden |
|---------|------------|------------|---------------|----------------|----------------|------------------|
| 8       | a LOT less | a LOT more | a LITTLE less | a LITTLE less  | Minus 6 months | a LITTLE more    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness  | Depression    | Breathlessness | Survival       | Treatment burden |
|---------|---------------|------------|---------------|----------------|----------------|------------------|
| 9       | a LITTLE more | a LOT less | a LITTLE more | a LOT less     | Plus 12 months | a LITTLE more    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness  | Depression    | Breathlessness | Survival        | Treatment burden |
|---------|---------------|------------|---------------|----------------|-----------------|------------------|
| 10      | a LITTLE less | a LOT less | a LITTLE less | a LITTLE more  | Minus 12 months | a LITTLE less    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness  | Depression | Breathlessness | Survival      | Treatment burden |
|---------|---------------|------------|------------|----------------|---------------|------------------|
| 11      | a LITTLE less | a LOT less | a LOT less | a LOT less     | Plus 6 months | a LITTLE more    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness     | Depression    | Breathlessness | Survival       | Treatment burden |
|---------|------------|---------------|---------------|----------------|----------------|------------------|
| 12      | a LOT less | a LITTLE less | a LITTLE less | a LOT less     | Plus 12 months | a LOT more       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness  | Depression | Breathlessness | Survival        | Treatment burden |
|---------|---------------|------------|------------|----------------|-----------------|------------------|
| 13      | a LITTLE more | a LOT more | a LOT more | a LOT less     | Minus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness     | Depression | Breathlessness | Survival        | Treatment burden |
|---------|---------------|---------------|------------|----------------|-----------------|------------------|
| 14      | a LITTLE more | a LITTLE less | a LOT less | a LITTLE less  | Minus 12 months | a LITTLE less    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression    | Breathlessness | Survival        | Treatment burden |
|---------|------------|------------|---------------|----------------|-----------------|------------------|
| 15      | a LOT more | a LOT less | a LITTLE less | a LOT less     | Minus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness     | Depression    | Breathlessness | Survival      | Treatment burden |
|---------|------------|---------------|---------------|----------------|---------------|------------------|
| 16      | a LOT less | a LITTLE less | a LITTLE more | a LITTLE more  | Plus 6 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness     | Depression | Breathlessness | Survival        | Treatment burden |
|---------|------------|---------------|------------|----------------|-----------------|------------------|
| 17      | a LOT less | a LITTLE more | a LOT less | a LOT less     | Minus 12 months | a LOT more       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness     | Depression    | Breathlessness | Survival       | Treatment burden |
|---------|------------|---------------|---------------|----------------|----------------|------------------|
| 18      | a LOT more | a LITTLE more | a LITTLE more | a LOT less     | Minus 6 months | a LITTLE less    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression    | Breathlessness | Survival        | Treatment burden |
|---------|------------|------------|---------------|----------------|-----------------|------------------|
| 19      | a LOT less | a LOT less | a LITTLE more | a LITTLE less  | Minus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival       | Treatment burden |
|---------|------------|------------|------------|----------------|----------------|------------------|
| 20      | a LOT less | a LOT less | a LOT more | a LOT more     | Plus 12 months | a LITTLE less    |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival        | Treatment burden |
|---------|------------|------------|------------|----------------|-----------------|------------------|
| 21      | a LOT less | a LOT less | a LOT less | a LOT less     | Minus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible outcome  
(as bad or worse than being dead)

Half-way between worst and best

Best possible outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival       | Treatment burden |
|---------|------------|------------|------------|----------------|----------------|------------------|
| 22      | a LOT less | a LOT less | a LOT less | a LOT more     | Minus 6 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible outcome  
(as bad or worse than being dead)

Half-way between worst and best

Best possible outcome

| Card ID | Pain       | Tiredness  | Depression | Breathlessness | Survival      | Treatment burden |
|---------|------------|------------|------------|----------------|---------------|------------------|
| 23      | a LOT more | a LOT less | a LOT more | a LITTLE less  | Plus 6 months | a LOT more       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible outcome  
(as bad or worse than being dead)

Half-way between worst and best

Best possible outcome

| Card ID | Pain          | Tiredness  | Depression    | Breathlessness | Survival        | Treatment burden |
|---------|---------------|------------|---------------|----------------|-----------------|------------------|
| 24      | a LITTLE less | a LOT more | a LITTLE more | a LOT more     | Minus 12 months | a LOT more       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

| Card ID | Pain          | Tiredness     | Depression | Breathlessness | Survival       | Treatment burden |
|---------|---------------|---------------|------------|----------------|----------------|------------------|
| 25      | a LITTLE less | a LITTLE more | a LOT less | a LITTLE less  | Plus 12 months | a LOT less       |

(Circle One Number)

0 1 2 3 4 5 6 7 8 9 10

Worst possible  
outcome  
(as bad or worse  
than being dead)

Half-way  
between  
worst and best

Best possible  
outcome

Thank you for completing this questionnaire.

**Beliefs about Medicines(BMQ)****Patient Study Number** \_\_\_\_\_**Date of Completion** \_\_\_\_\_**Patient Visit Number** \_\_\_\_\_**Your views about the medicines you have been prescribed for your kidney disease**

- We would like to ask you about your personal views about the medicines.
- Below are statements that other people have made about these medicines.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box
- There are no right or wrong answers. We are interested in your personal views

|                                                                      | Strongly<br>Agree        | Agree                    | Uncertain                | Disagree                 | Strongly<br>Disagree     |
|----------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) My health, at present, depends on my medicines                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Having to take these medicines worries me                         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) My life would be impossible without these medicines               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Without these medicines I would be very ill                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) I sometimes worry about long-term effects of the medicines        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) These medicines are a mystery to me                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) My health in the future will depend on these medicines            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) These medicines disrupt my life                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) I sometimes worry about becoming too dependent on these medicines | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) My medicines protect me from becoming worse                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Your views about the dialysis you have been prescribed for your kidney disease**

- We would like to ask you about your personal views about the dialysis.
- Please indicate the extent to which you agree or disagree with the statements below by ticking the appropriate box
- There are no right or wrong answers. We are interested in your personal views

|                                                               | Strongly<br>Agree        | Agree                    | Uncertain                | Disagree                 | Strongly<br>Disagree     |
|---------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) My health, at present, depends on my dialysis              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Having to undertake dialysis worries me                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) My life would be impossible without dialysis               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Without dialysis I would be very ill                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) I sometimes worry about long-term effects of the dialysis  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Dialysis is a mystery to me                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) My health in the future will depend on my dialysis         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Dialysis disrupts my life                                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) I sometimes worry about becoming too dependent on dialysis | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) My dialysis protect me from becoming worse                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Your views about the fluid restriction you have been prescribed for your kidney disease**

- We would like to ask you about your personal views about the fluid restriction.
- Please indicate the extent to which you agree or disagree with the statements below by ticking the appropriate box
- There are no right or wrong answers. We are interested in your personal views

|                                                                           | Strongly<br>Agree        | Agree                    | Uncertain                | Disagree                 | Strongly<br>Disagree     |
|---------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) My health, at present, depends on my fluid restriction                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Having to undertake fluid restriction worries me                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) My life would be impossible without fluid restriction                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Without fluid restriction I would be very ill                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) I sometimes worry about the long-term effects of the fluid restriction | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Fluid restriction is a mystery to me                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) My health in the future will depend on my fluid restriction            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Fluid restriction disrupts my life                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) I sometimes worry about becoming too dependent on fluid restriction    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) My fluid restriction protects me from becoming worse                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Your views about the dietary restriction you have been prescribed for your kidney disease**

- We would like to ask you about your personal views about the dietary restriction.
- Please indicate the extent to which you agree or disagree with the statements below by ticking the appropriate box
- There are no right or wrong answers. We are interested in your personal views

|                                                                             | Strongly<br>Agree        | Agree                    | Uncertain                | Disagree                 | Strongly<br>Disagree     |
|-----------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) My health, at present, depends on my dietary restriction                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) Having to undertake dietary restriction worries me                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) My life would be impossible without dietary restriction                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Without dietary restriction I would be very ill                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) I sometimes worry about the long-term effects of the dietary restriction | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) Dietary restriction is a mystery to me                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) My health in the future will depend on my dietary restriction            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) Dietary restriction disrupts my life                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i) I sometimes worry about becoming too dependent on dietary restriction    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| j) My dietary restriction protects me from becoming worse                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Your views about medicines in general**

- We would like to ask you about your personal views about medicines in general
- These are statements other people have made about medicines in general
- Please indicate the extent to which you agree or disagree with the statements below by ticking the appropriate box
- There are no right or wrong answers. We are interested in your personal views

|                                                                                          | Strongly<br>Agree        | Agree                    | Uncertain                | Disagree                 | Strongly<br>Disagree     |
|------------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a) Doctors use too many medicines                                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) People who take medicines should stop their treatment for a while every now and again | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Most medicines are addictive                                                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d) Natural remedies are safer than medicines                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e) Medicines do more harm than good                                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f) All medicines are poisons                                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g) Doctors place too much trust on medicines                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h) If doctors had more time with patients they would prescribe fewer medicines           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**ILLNESS PERCEPTION QUESTIONNAIRE (IPQ-R)****Patient Study Number****Date of Completion****Patient Visit Number****YOUR VIEWS ABOUT YOUR KIDNEY DISEASE**

Listed below are a number of symptoms that you may or may not have experienced in the last three months. Please indicate by circling **Yes** or **No**, whether you have experienced any of these symptoms in the last three months, and whether you believe that these symptoms are related to your Kidney Disease.

| I have experienced this symptom in the last three months |               |   | This symptom is related to my<br>(tick all that apply) |          |            |                   |                       |
|----------------------------------------------------------|---------------|---|--------------------------------------------------------|----------|------------|-------------------|-----------------------|
|                                                          | Please circle |   | Kidney Disease                                         | Dialysis | Medication | Fluid restriction | Other health problems |
| Pain                                                     | Y             | N |                                                        |          |            |                   |                       |
| Sore Throat                                              | Y             | N |                                                        |          |            |                   |                       |
| Nausea                                                   | Y             | N |                                                        |          |            |                   |                       |
| Breathlessness                                           | Y             | N |                                                        |          |            |                   |                       |
| Weight Loss                                              | Y             | N |                                                        |          |            |                   |                       |
| Fatigue                                                  | Y             | N |                                                        |          |            |                   |                       |
| Stiff Joints                                             | Y             | N |                                                        |          |            |                   |                       |
| Sore Eyes                                                | Y             | N |                                                        |          |            |                   |                       |
| Wheeziness                                               | Y             | N |                                                        |          |            |                   |                       |
| Headaches                                                | Y             | N |                                                        |          |            |                   |                       |
| Upset stomach                                            | Y             | N |                                                        |          |            |                   |                       |
| Sleep difficulties                                       | Y             | N |                                                        |          |            |                   |                       |
| Dizziness                                                | Y             | N |                                                        |          |            |                   |                       |
| Loss of Strength                                         | Y             | N |                                                        |          |            |                   |                       |

We are interested in your own personal views of how you now see your Kidney Disease.

Please indicate how much you agree or disagree with the following statements about your Kidney Disease by ticking the appropriate box.

|      | <b>VIEWS ABOUT<br/>YOUR KIDNEY<br/>DISEASE</b>                    | <b>STRONGLY<br/>DISAGREE</b> | <b>DISAGREE</b> | <b>NEITHER<br/>AGREE<br/>NOR<br/>DISAGREE</b> | <b>AGREE</b> | <b>STRONGLY<br/>AGREE</b> |
|------|-------------------------------------------------------------------|------------------------------|-----------------|-----------------------------------------------|--------------|---------------------------|
| IP1* | My Kidney Disease will last a short time                          |                              |                 |                                               |              |                           |
| IP2  | My Kidney Disease is likely to be permanent rather than temporary |                              |                 |                                               |              |                           |
| IP3  | My Kidney Disease will last for a long time                       |                              |                 |                                               |              |                           |
| IP4* | This Kidney Disease will pass quickly                             |                              |                 |                                               |              |                           |
| IP6  | I expect to have Kidney Disease for the rest of my life           |                              |                 |                                               |              |                           |
| IP8  | My Kidney Disease is a serious condition                          |                              |                 |                                               |              |                           |
| IP7  | My Kidney Disease has major consequences on my life               |                              |                 |                                               |              |                           |
| IP8* | My Kidney Disease does not have much effect on my life            |                              |                 |                                               |              |                           |
| IP8  | My Kidney Disease strongly affects the way others see me          |                              |                 |                                               |              |                           |
| IP10 | My Kidney Disease has serious financial consequences              |                              |                 |                                               |              |                           |

|           | VIEWES ABOUT<br>YOUR KIDNEY<br>DISEASE                                 | STRONGLY<br>DISAGREE | DISAGREE | NEITHER<br>AGREE<br>NOR<br>DISAGREE | AGREE | STRONGLY<br>AGREE |
|-----------|------------------------------------------------------------------------|----------------------|----------|-------------------------------------|-------|-------------------|
| IP11      | My Kidney Disease causes difficulties for those who are close to me    |                      |          |                                     |       |                   |
| IP12      | There is a lot which I can do to control my symptoms                   |                      |          |                                     |       |                   |
| IP13      | What I do can determine whether my Kidney Disease gets better or worse |                      |          |                                     |       |                   |
| IP14      | The course of my Kidney Disease depends on me                          |                      |          |                                     |       |                   |
| IP15<br>• | Nothing I do will affect my Kidney Disease                             |                      |          |                                     |       |                   |
| IP16      | I have the power to influence my Kidney Disease                        |                      |          |                                     |       |                   |
| IP17<br>• | My actions will have no affect on the outcome of my Kidney Disease     |                      |          |                                     |       |                   |
| IP18<br>• | My Kidney Disease will improve in time                                 |                      |          |                                     |       |                   |
| IP19<br>• | There is very little that can be done to improve my Kidney Disease     |                      |          |                                     |       |                   |
| IP20      | My treatment will be effective in curing my Kidney Disease             |                      |          |                                     |       |                   |

|           | <b>VIEWS ABOUT<br/>YOUR KIDNEY<br/>DISEASE</b>                                       | <b>STRONGLY<br/>DISAGREE</b> | <b>DISAGREE</b> | <b>NEITHER<br/>AGREE<br/>NOR<br/>DISAGREE</b> | <b>AGREE</b> | <b>STRONGLY<br/>AGREE</b> |
|-----------|--------------------------------------------------------------------------------------|------------------------------|-----------------|-----------------------------------------------|--------------|---------------------------|
| IP21      | The negative effects of my Kidney Disease can be prevented (avoided) by my treatment |                              |                 |                                               |              |                           |
| IP22      | My treatment can control my Kidney Disease                                           |                              |                 |                                               |              |                           |
| IP23<br>• | There is nothing which can help my condition                                         |                              |                 |                                               |              |                           |
| IP24<br>• | The symptoms of my condition are puzzling to me                                      |                              |                 |                                               |              |                           |
| IP25      | My Kidney Disease is a mystery to me                                                 |                              |                 |                                               |              |                           |
| IP26      | I don't understand my Kidney Disease                                                 |                              |                 |                                               |              |                           |
| IP27      | My Kidney Disease doesn't make any sense to me                                       |                              |                 |                                               |              |                           |
| IP28<br>• | I have a clear picture or understanding of my condition                              |                              |                 |                                               |              |                           |
| IP29      | The symptoms of my Kidney Disease change a great deal from day to day                |                              |                 |                                               |              |                           |
| IP30      | My symptoms come and go in cycles                                                    |                              |                 |                                               |              |                           |

|      | <b>VIEWS ABOUT<br/>YOUR KIDNEY<br/>DISEASE</b>                        | <b>STRONGLY<br/>DISAGREE</b> | <b>DISAGREE</b> | <b>NEITHER<br/>AGREE<br/>NOR<br/>DISAGREE</b> | <b>AGREE</b> | <b>STRONGLY<br/>AGREE</b> |
|------|-----------------------------------------------------------------------|------------------------------|-----------------|-----------------------------------------------|--------------|---------------------------|
| IP31 | My Kidney Disease is very unpredictable                               |                              |                 |                                               |              |                           |
| IP32 | I go through cycles in which my Kidney Disease gets better and worse. |                              |                 |                                               |              |                           |
| IP33 | I get depressed when I think about my Kidney Disease                  |                              |                 |                                               |              |                           |
| IP34 | When I think about my Kidney Disease I get upset                      |                              |                 |                                               |              |                           |
| IP35 | My Kidney Disease makes me feel angry                                 |                              |                 |                                               |              |                           |
| IP36 | My Kidney Disease does not worry me                                   |                              |                 |                                               |              |                           |
| IP37 | Having Kidney Disease makes me feel anxious                           |                              |                 |                                               |              |                           |
| IP38 | My Kidney Disease makes me feel afraid                                |                              |                 |                                               |              |                           |

### CAUSES OF MY KIDNEY DISEASE

We are interested in what you consider may have been the cause of your Kidney Disease.

As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your Kidney Disease rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your Kidney Disease.

Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

|     | POSSIBLE CAUSES                                        | STRONGLY DISAGREE | DISAGREE | NEITHER AGREE NOR DISAGREE | AGREE | STRONGLY AGREE |
|-----|--------------------------------------------------------|-------------------|----------|----------------------------|-------|----------------|
| C1  | Stress or worry                                        |                   |          |                            |       |                |
| C2  | Hereditary - it runs in my family                      |                   |          |                            |       |                |
| C3  | A Germ or virus                                        |                   |          |                            |       |                |
| C4  | Diet or eating habits                                  |                   |          |                            |       |                |
| C5  | Chance or bad luck                                     |                   |          |                            |       |                |
| C6  | Poor medical care in my past                           |                   |          |                            |       |                |
| C7  | Pollution in the environment                           |                   |          |                            |       |                |
| C8  | My own behaviour                                       |                   |          |                            |       |                |
| C9  | My mental attitude e.g. thinking about life negatively |                   |          |                            |       |                |
| C10 | Family problems or worries caused my Kidney Disease    |                   |          |                            |       |                |
| C11 | Overwork                                               |                   |          |                            |       |                |

|     | POSSIBLE<br>CAUSES                                                    | STRONGLY<br>DISAGREE | DISAGREE | NEITHER<br>AGREE NOR<br>DISAGREE | AGREE | STRONGLY<br>AGREE |
|-----|-----------------------------------------------------------------------|----------------------|----------|----------------------------------|-------|-------------------|
| C12 | My emotional<br>state e.g. feeling<br>down, lonely,<br>anxious, empty |                      |          |                                  |       |                   |
| C13 | Ageing                                                                |                      |          |                                  |       |                   |
| C14 | Alcohol                                                               |                      |          |                                  |       |                   |
| C15 | Smoking                                                               |                      |          |                                  |       |                   |
| C16 | Accident or injury                                                    |                      |          |                                  |       |                   |
| C17 | My personality                                                        |                      |          |                                  |       |                   |
| C18 | Altered immunity                                                      |                      |          |                                  |       |                   |

In the space below, please list in rank-order the three most important factors that you now believe caused YOUR Kidney Disease. You may use any of the items from the box above, or you may have additional ideas of your own.

The most important causes for me:-

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

#### Reference

Weinman, J., Petrie, KJ, Sharpe, N & Walker, S . (2000) Causal attributions in patients and spouses following first-time myocardial infarction and subsequent lifestyle changes. *Br. J. Health Psychology*, 5, 263-273