Illness and treatment beliefs, cognitive functioning and Quality of Life in End Stage Renal Disease (ESRD)

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Dedication:

For my parents,

Panagiotis Grivas and Fotini Griva

Abstract

This thesis examines the neuropsychological functioning and health-related quality of life (HQoL) in patients with ESRD undergoing on different treatments (hemodialysis; peritoneal dialysis and transplantation). The aim was to investigate the effects of illness and treatment beliefs on HQoL in patients with End Stage Renal Disease. Comparisons were undertaken between dialysis and transplant patients, between patients on haemodialysis (HD) and on peritoneal dialysis (PD) and patients with a cadaver (CAD) or a living related renal transplant (LRD).

A sample of 117 transplant (mean age = 50.3 years) and 145 dialysis patients (mean age = 50.1 years) completed questionnaires assessing illness and treatment beliefs, mood and HQoL. A neuropsychological test battery was also administered and the patients' biochemistry was assessed. Haemodialysis and Peritoneal Dialysis patients were administered the neuropsychological battery test battery on 2 consecutive days (pre- and 24-hours post-dialysis) whereas transplant patients were only assessed once.

Neuropsychogical results indicated almost equivalent cognitive functioning among treatment groups. Transplant patients outperformed dialysis patients only in memory tasks. Significant improvements in neuropsychological functioning (attention, concentration, memory, and psychomotor speed) were found in hemodialysis patients 24 hours post-dialysis. No such fluctuations were found in peritoneal dialysis patients. Although biochemical changes were found in the hemodialysis patients at the same time points, these were not consistently related to the neurospychological changes.

Results also showed that illness and treatment beliefs did not differ between the dialysis groups. Transplant recipients however, were more likely to hold an acute timeline, perceive more control, less consequences, less symptoms and less illness and treatment related burden compared to dialysis. HQoL was impaired in dialysis patients, particularly in physical SF-36 dimensions compared to transplant patients and general population norms. Post-hoc analyses revealed that peritoneal dialysis patients had more compromised HQoL than both haemodialysis and transplant patients. Multiple regressions indicated that illness and treatment intrusiveness, consequences and medication concerns predicted QoL in both dialysis and transplant patients over and above the effect of sociodemographic, medical,

and mood variables. Explained variance ranged from 28.4% to 65.8%, with different variables emerging as significant predictors in emotional and physical SF-36 dimensions (mental and physical component scores) in dialysis and transplantation.

The findings suggest that although NP outcomes are roughly equivalent in ESRD treatments, dialysis and transplantation may induce distinct illness and treatment beliefs which appear to have a direct influence on HQoL.

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Table of abbreviations

A	
Alb	Albumin
Alk-P-Tase	Alkaline phosphatase
APD	Automated Peritoneal Dialysis
APKD	Adult Polycystic Kidney Disease
Adh	Adhererce
B	
BDI	Beck Depression Inventory
BMQ	Beliefs about your Medicines Questionnaire
BMQ-c	Concerns about medication subscale from the BMQ
BMQ-n	Medication necessity subscale from the BMQ
BP	Bodily Pain subscale from the SF-36
BUN	Blood Urea Nitrogen
BVRT	Benton Visual Retention test
BVRT-C	Benton Visual Retention test – number correct
BVRT-E	Benton Visual Retention test – number of errors
C	
Ca^{2+}	Calcium
CAD	Cadaver
CAPD	Continuous Ambulatory Peritoneal Dialysis
CDI	Cognitive Depression Index
Comrb	Comorbidities
Conseq	Consequences subscale from the Illness Perceptions Questionnaire
Cr	Creatinine
CRF	Chronic Renal Failure
Ctl	Controls
Cum	Cumulative
D	
DBP	Diastolic Blood Pressure
DBP-ly	Diastolic Blood Pressure – measured when lying

DBP-st	Diastolic Blood Pressure – measured when standing
DL	Dialysis
Dr	Duration
E	
Educ	Education
EPO	Erythropoietin
ESRD	End-stage renal disease
ESRD-SI	End-stage renal disease severity index
G	
GFR	Glomerular Filtration Rate
GGL	Gamma Glutamil Transferase
GH	General Health Subscale from the SF-36
GN	Glumeronephritis
GP	Grooved Pegboard
GP-DOM	Grooved Pegboard – dominant hand
GP-NDOM	Grooved Pegboard – non dominant hand
H	
Hb	Haemoglobin
HD	Haemodialysis
HsDH	Hospital Haemodialysis
Hm-HD	Home Haemodialysis
HSD	Tukey's Honest Significant Difference post hoc test
HQoL	Health related Quality of Life
I	
Ident	Identity subscale from the Illness Perceptions Questionnaire
Ident-m	Immunosuppressive medication side-effects
Ident-tx	Extended 42 items version of the identity subscale used with transplant patients
IEQ	Illness Effects Questionnaire
IPQ	Illness Perceptions Questionnaire
K	
K^+	Potassium
Kt/V	Dialysis adequacy index based on kinetic modelling procedures

L	
LRD	Living related donor
LRD-TX	Living related donor transplant recipients
M	
MCS	Mental Component Score from the SF-36
MH	Mental Health subscale from the SF-36
N	
NP	Neuropsychological
No	Number
NP-TO	Summary score of individual standardised NP score
NP-norm	Number of NP impairments relative to norms
ns	Non significant
n/s	Not stated
P	
PCS	Physical Component Score from the SF-36
PD	Peritoneal Dialysis
PF	Physical Functioning subscale from the SF-36
PNS-NA	Negative affect scale from the PANAS
PNS-PA	Positive affect Scale from the PANAS
PO^4	Phosphate
PPR	Pulse pressure rating
pts	Patients
Q	
QoL	Quality of Life
R	
REm	Role limitations due to emotional problems subscale
RPh	Role limitation s due to physical problems subscale
RRT	Renal Replacement Therapies
S	
SBP	Systolic Blood Pressure
SBP-ly	Systolic Blood Pressure – measured when lying
SBP-st	Systolic Blood Pressure – measured when standing
SCS	Subjective Cognition Scale
SCS-TO	Summary score on the Subjective Cognition Scale

SF	Social Functioning subscale from the Sf-36
STAI	Spielberger State Trait Anxiety Inventory
SRM	Self Regulatory Model
T	
T1	Time 1 assessment
T2	Time 2 assessment
TEQ	Treatment Effects Questionnaire
TMT	Trail Making Test
TMT-A	Trail Making Test part A
TMT-B	Trail Making Test part B
TX	Transplantation
V	
VT	Vitality subscale from the SF-36

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CHAPTER 1: MEDICAL BACKGROUND

Section 1: Renal System and Renal Kidney Failure

Kidneys act principally to control the volume and composition of body fluids. By matching urine output to dietary salt and water intake, the kidneys regulate blood and extravascular volume, and arterial pressure. Kidneys serve key endocrine functions as well, activating vitamin D so as to regulate calcium, phosphorus and parathyroid hormone levels and synthesising erythropoeitin, the key stimulus for marrow production of red blood cells. Finally, they excrete those metabolic and mineral wastes, which might otherwise be toxic to the organism.

Normally, kidneys perform all these tasks flawlessly. But sometimes the kidneys lose their ability to filter fluids and waste, causing dangerous levels of these substances to accumulate in the body. This condition is known as kidney (renal) failure. There are three types of kidney failure: acute, chronic and end-stage renal disease.

Acute or reversible renal failure develops suddenly in previously normal kidneys due to physical trauma (such as crush injuries or major surgery), drugs or other chemical agents, in the presence of overwhelming infection, or if the blood supply to the kidneys is compromised by failure of the heart's pumping action, or losses of blood, salt or water so that the blood pressure drops and the kidneys are no longer supplied with blood. If the underlying problem can be successfully treated, complete recovery of the kidneys is possible. In this case, renal support is needed only for days or weeks before renal function returns.

More common is chronic irreversible renal failure, which involves the progressive deterioration of kidney function over time. It develops slowly and often imperceptibly, yet it can affect almost every system in the body. Over time, chronic kidney failure can lead to congestive heart failure, bone disease, and damage to the central nervous system. Unfortunately, signs and symptoms often do not appear until irreversible damage has

occurred. Renal failure of this kind may either be the result of primary renal disease or of renal damage in a systemic disorder.

When people with irreversible loss of kidney function reach that point in the course of their illness that their kidneys fail to support life, they are said to have End-stage renal disease (ESRD). In ESRD total or nearly total and irreversible kidney failure has occurred. Nephrons are lost to the extent that the retention of non-volatile, metabolic waste products, salt, and water is potentially fatal. ESRD can lead rapidly to death unless renal replacement treatment (RRT) is started (Mallick & Gokal, 1999).

Section 2: Treatments for ESRD

There are two forms of RRT: kidney transplantation and dialysis (Will & Johnson 1994). Dialysis involves the removal of waste products from the blood by allowing these products to diffuse across a thin membrane into dialysis fluid, which is then discarded along with the waste products. The fluid is composed to draw or "attract' excess salts and water from the blood to cross the membrane, without the blood itself being in contact with the fluid (Pastan & Bailey, 1998). There are two principle models of dialysis: haemodialysis (HD) and peritoneal dialysis (PD).

2.1 Haemodialysis (HD)

HD may be performed in a hospital setting, in a free-standing outpatient dialysis unit, in a satellite unit run by nursing staff or at home.

2.1.a Hospital HD

The method first used to achieve dialysis was the artificial kidney, or haemodialysis. This involves the attachment of the patient's circulation to a machine through which fluid is passed, and exchange can take place (see Figure 1.1).

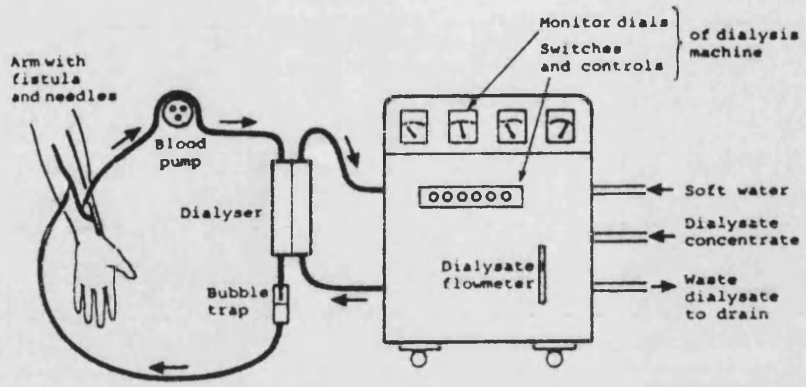


Figure 1.1: Diagram of Haemodialysis procedure

Haemodialysis requires an extracorporeal filter or dialyser, consisting of a synthetic semipermeable membrane to which blood is taken and returned through sterile tubing. Dialysis fluid, which has an electrolyte composition similar to that of the extracellular fluid, is passed in the opposite direction across the outside of the membrane channels of the dialyser through which the blood is circulating. Electrolytes and non-volatile waste products diffuse into this dialysis fluid from the blood across the membrane, which is then returned to the body (Gokal & Hutchinson, 2002). At the same time alkali can be restored to the body by diffusion from dialysis fluid to blood across the membrane (Mallick & Gokal, 1999).

This procedure requires permanent easy access to the patients' blood circulation, which is usually achieved by creating an arteriovenous fistula in the forearm. When this fistulae cannot be formed, several other options are available, including the placement of synthetic grafts subcutaneously or of a long central line into a large vein or indwelling vascular catheter. The process entails some discomfort and may at times be technically difficult. Repeated surgical procedures or sepsis may occur (Feldman *et al.*, 1996; Nolph, 1993).
Several types of dialysers, dialysates and 'dialysis machines' which monitor the procedure are commercially available and the frequency, duration of dialysis sessions, and dialysis schedules vary from centre to centre. The most common frequency is three times a week for a three to four hour-long session.

2.1.b Home HD

The same techniques as described above apply to home hemodialysis but sessions take place at home and hence can be scheduled at patients' convenience (Mackenzie & Mactier, 1998; Oberley & Schatell, 1995).

Although home HD appears attractive, the current lack of easy-to-use HD machines poses a significant disincentive for patients. Blood access is usually obtained through a fistula or a graft puncture (which requires a helper). A training period of at least 6 weeks is necessary to learn the technique and appropriate living arrangements are required. There is a risk, albeit low, of air embolism associated with the procedure, making the process stressful for the patient and the helper. The overall dialysis procedure is more time consuming simply because a significant percentage of the time is spent in setting up, priming, taking down and cleaning the HD machine. The effective treatment makes up only a small portion of the total time spent on dialysis-related tasks.

Only a small proportion of patients reaching ESRD receives home HD; partly because such patients need suitable space, vascular access, which they can cannulate reliably, and also the ability to learn and use the relatively complicated equipment and procedures necessary for safe and high quality hemodialysis.

2.2 Peritoneal Dialysis (PD)

In PD, there is an exchange of solutes and fluid between the peritoneal blood and the dialysis solution in the peritoneal cavity across the peritoneal membrane, which acts as a filter (Gokal, 1987; Gokal & Mallick, 1999). It requires placement of a catheter into the abdominal cavity and repeated instillation and drainage of sterile dialysate.

The crucial components of the peritoneal dialysis system are peritoneal blood flow, the highly vascular membrane and the flow rate and volume of peritoneal dialysis solutions.
Since neither peritoneal blood flow nor the vascularity of the membrane can be manipulated, the only factor that can be adjusted to achieve maximum solute and fluid

removal is the flow rate of dialysis solutions, i.e. how often exchanges are performed. To increase clearance for example the amount of fluid and the frequency of exchange can be increased, but both maybe limited by the patient's comfort and convenience. Success of PD is dependent on the long-term viability of the peritoneal membrane and lies in preserving the peritoneum as a dialysing membrane for as long as possible.

PD is often regarded and has been advocated as the preferred initial modality of choice for patients with co-morbidities, particularly those with impaired cardiac function (Blake, 2001; Burkart, 2001). In addition, more prolonged preservation of residual renal function, less strict control of diet and fluid intake and increased independence makes this treatment attractive in some patients starting dialysis. The two main types of PD are discussed in the following sections.

2.2.a Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD has been used as an alternative to HD since 1976 (Popovich *et al.*, 1976) and is the most common form of PD.

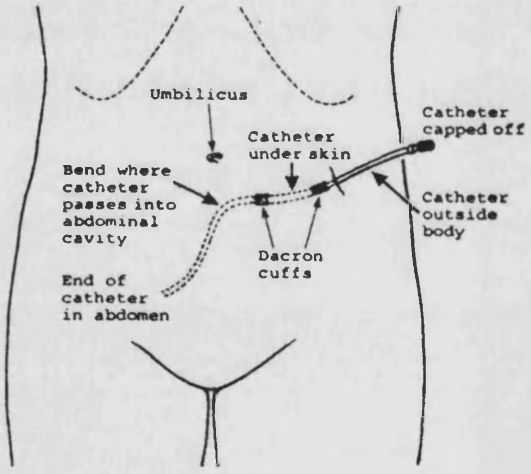


Figure 1.2: Diagram of Peritoneal Dialysis

CAPD involves a closed system (see Figure 1.2) in which fluid is initially instilled by gravity into the peritoneal cavity and then drained out after several hours. The basic CAPD system consists of a plastic bag containing 0.5-3.0L PD fluid, a transfer set and a permanent

catheter. The solutions contain glucose as an osmotic agent and lactate, sodium, potassium and calcium in differing concentrations (Hutchinson & Gokal, 1992). Various catheters are available designed to keep complications to a minimum. The connection between the bag and the transfer is broken several times a day and the procedure must be carried out by a strict, sterile, non-touch technique.

CAPD is carried out by the patient, who has to perform on a daily basis the required fluid exchanges, typically 4 or 5, requiring scrupulous attention to sterile technique. This typically requires no machine and does not involve visiting the hospital or dialysis unit. Various advantages have been claimed for CAPD and PD in comparison for HD (see Table 1.1).

Table 1.1: Advantages and disadvantages of CAPD (PD) in comparison to HD

Advantages	Disadvantages
• Home based without a complex machine	• Mechanical complications (abdominal wall hernia, back pain, fluid leaks, abdominal fullness occasional pain with drainage)
• Easy to teach and learn	• Infections (peritonitis, exit site infection)
• Easier for travel	• Lower long term viability
• More liberal diet and fluid allowance	• Metabolic complications, malnutrition
• Continuous fluid and solute removal	• Risk for inadequate dialysis, limited possibilities to increase adequacy
• Longer preservation of residual renal function	• Peritoneal membrane damage
• More suitable for specific patients groups (children, elderly, patients with diabetes and cardiovascular instability)	• Fatigue and burn out from the continuous and rigorous schedule of bag exchanges especially in the elderly
• Low cost (cheaper than HD)	• Psychological problems related to indwelling catheter
	• Lower long term technique viability

2.2.b Automated Peritoneal Dialysis (APD)

APD is a modification of the technique described above in which exchanges are performed overnight by a machine. It is used to refer to all forms of PD that use a mechanical device to assist in the delivery infusion and drainage of dialysate from the peritoneum cavity (Diax-Buxo & Suki, 1994; Ronco & Diaz-Buxo, 2001).

APD obviates the need for intensive manual involvement and limits the process of PD to two procedures–setting up of the dialysis regimen with an initial connection of the catheter to the machine and disconnection from the patient with dismantling of the machine at the end of dialysis. It is a home-based, self-care treatment and is predominantly done during the night. Thus, patients (and their helpers) are free during the day with short-dwell cycles run in and out of the peritoneum cavity by the cycler machine. APD treatment can offer several options, diurnal or nocturnal, tidal, with diurnal full or void abdomen, with different fluid volumes and dwell times and can be tailored to peritoneal transport characteristics and to the patient's psychological needs.

However, because there is often a need to provide additional dialysis to achieve adequate dialysis, daytime exchanges may become necessary, thereby complicating the procedure and intruding in the patients' daytime routine. Higher adequacy targets have been set by the National Kidney Foundation-DOQI and the UK renal registry and some APD patients have problems in reaching the selected targets (National Kidney Foundation Dialysis Outcome Quality Initiative: NKF-DOQI 1997a). Moreover, APD is much more expensive than CAPD.

The most important consideration in the selection of APD other than the patient's preference, lifestyle needs and the availability of equipment, is the individual's peritoneal transporter status. For patient with low peritoneal permeability, APD may be inappropriate especially when there is little residual renal function. These patients are unable to remove adequate amounts of solute and are best managed with haemodialysis (Gokal, 1996; Gokal & Mallick, 1999).

2.3 Biochemistry and dialysis

The uraemic syndrome is the prototype of a slowly progressive endogenous intoxication, when a detoxifying organ (in this case the kidney) fails. It is characterised by the gradual retention of a host of metabolites and solutes that interfere with various biochemical functions. Roughly, three groups of solutes can be distinguished: (i) small, water-soluble, non-protein-bound molecules such as urea and creatinine; (ii) large molecules with a

molecular weight between 300 and 12000 D, classically referred to as middle molecules, and (iii) small protein-bound compounds.

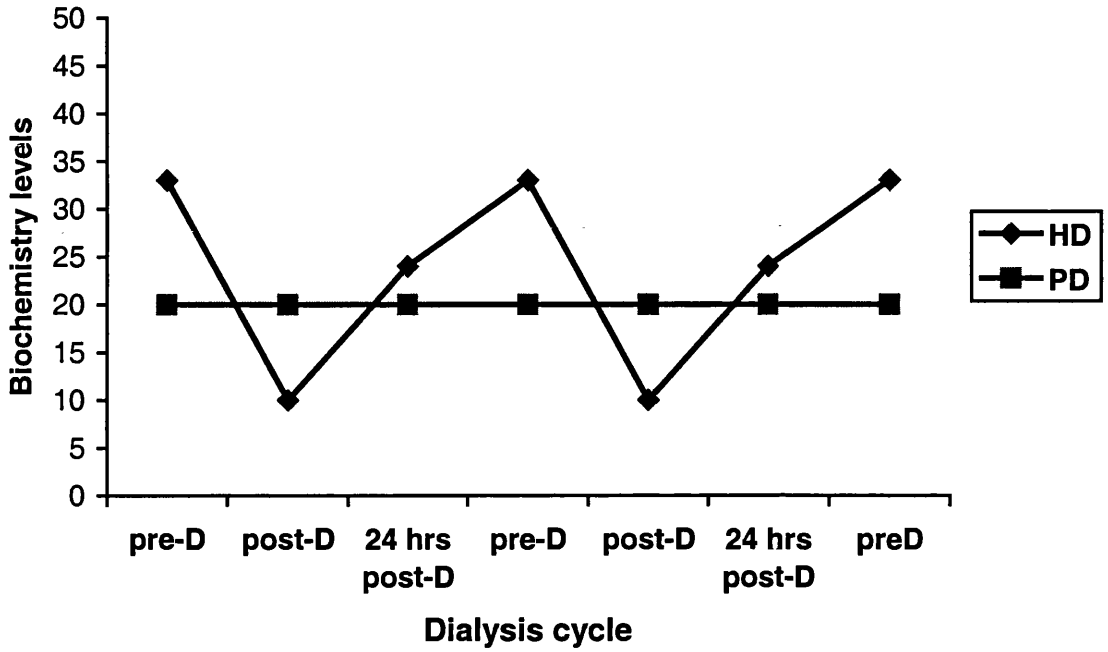
The uraemic syndrome is biochemically indexed by this range of solutes, but relatively little is known about the exact mechanisms leading to uraemia, the unique contribution of each of these types of solutes to uraemia manifestation and their interrelations (Lesaffer *et al.*, 2000). There is also no clear consensus on the role of these different solutes in the uraemic syndrome. In general, urea only becomes toxic at concentrations that are higher than those found in uraemic patients (Bergström, 1997; Vanholder *et al.*, 1994).

HD (hospital and home) is performed intermittently, usually three times a week, for periods of three or more hours at a time. This results in periods of very high rates of artificial kidney function or 'clearance', alternating with longer inter-dialytic periods of poor kidney function. HD produces massive fluid shifts and metabolic alterations over a limited time span. Waste products and fluid are removed during dialysis and gradually accumulate again between treatments. As a result it is not uncommon for a patient's weight to increase by 2-4 kgs between treatments.

The intermittent HD results in a "sawtooth" effect (see Figure 1.3), producing a dramatic alkalinisation and reduction in urea during treatment, followed by a degree of rebound as the molecules equilibrate from the extravascular compartment (Nehemkis & Gerber, 1986). In fact, the fluctuation induced in the body (internal milieu) are so rapid and therefore so unphysiological that the phenomena were aptly termed 'the unphysiology of dialysis' in a paper published by Kjellstrand *et al.* in 1975. It was Kjellstrand and colleagues who first drew attention to the issues of possible negative effects of the unphysiology of intermittent dialysis treatment.

Studies that have analysed the brain density in HD patients showed that it decreases after HD with an influx of water in the tissue but similar changes were not observed for patients on CAPD. This effect leads to normalisation of the brain tissue that shows severe dehydration on the pre-dialysis phase (La Greca *et al.*, 1980; 1982).

Figure 1.3: HD and PD biochemical profile



Removal of toxins by PD also differs in many aspects from that of HD, the most important being the continuous or nearly continuous nature of treatment. PD clearance is slow but continuous, with uraemic solutes and organic acids reaching a stable concentration in the blood (Ronco *et al.*, 1998). As such PD is claimed to provide a more physiologic renal replacement as it provides effective control of uraemia and electrolyte disturbances and effectively corrects various forms of acidosis (Gokal & Mallick, 1999).

It is also the case that HD achieves more efficient clearance of small molecules, such as urea (Lessafer *et al.*, 2000), whereas PD may achieve more efficient clearance of larger molecules (Berkoben & Schwab, 1999).

2.4 Renal Transplantation (TX)

Renal TX is considered the 'ultimate renal replacement therapy (RRT)'. Successful renal TX represents the 'closest' return to normality and certainly the fullest resolution of uraemic state. In contrast with dialysis treatments, which only approximate the function of healthy kidneys, TX replaces all functions of the kidney. Renal TX usually restores

erythropoeitin production, corrects anaemia (Besarab *et al.*, 1987) and renal excretory, metabolic and endocrine function are recovered and nutritional status is improved (Miller *et al.*, 1987).

A single kidney is placed usually in the pelvis close to the bladder to which the ureter is connected, without disturbance of the patient's own kidneys. The kidney is attached to a nearby artery and vein. This surgery leads to a hospital stay of 2 to 3 weeks if uncomplicated.

Rejection continues to be the single largest impediment to success in TX (Matas, 1988; Pelletier *et al.*, 1998) which has largely been overcome during the first few months using drugs such steroids and cyclosporin. Acute rejection still occurs in approximately 20–50% of kidney recipients during the first year post-transplantation (Sollinger, 1995) although year graft survival rates improved significantly over the last 20 years (Cecka, 2000).

Immunosuppressive drugs are taken on a permanent basis following TX to reduce the likelihood of rejection. Maintenance immunosuppression traditionally involves the use of a Calcineurin Inhibitor (CNI) either cyclosporin or tacrolimus. There is no consensus about whether the regimen with cyclosporin or tacrolimus is more effective; both are considered effective in preventing acute rejection (Keown, 2001). Major side-effects are associated with each of the traditional immunosuppressive drugs used in transplantation, particularly cyclosporin (and related tacrolimus) and corticosteroids. Complications include the acceleration of vascular disease so that myocardial infarction and strokes are commoner in transplant patients than in age-matched controls. TX recipients also suffer from multiple other complications including bone loss (Julian *et al.*, 1992), increased incidence of fractures (Ramsey-Goldman *et al.*, 1999) and increased risk for the development of malignancy and infection as compared with age-matched population. During subsequent years there is also a steady loss of transplanted kidneys through rejection; and many patients require a second or even a third graft, and have to rely on dialysis between transplants.

There are two types of kidney transplantation:

2.4.a Cadaver transplantation (CAD TX)

CAD TX is the type of transplantation where the graft comes from a cadaver donor. A cadaver donor is a person who is brain dead but who is maintained on artificial life support, such as an accident victim. The average time for ESRD patients to receive a cadaver transplant is long, typically greater than 2 years, and it continues to increase.

2.4.b Living related donor transplantation (LRD TX)

In LRD TX, the kidney is donated by a living donor often related but sometimes unrelated to the recipient. It can be scheduled electively and is more likely to be an early treatment, or even the initial modality of RRT.

Renal transplantation from living donors accounts for approximately 9% of all renal transplants performed in Europe (Mallick *et al.*, 1995) although rates in the UK are 15% (International figures on organ donation and transplantation activities, 1998). Living donors are predominantly blood relatives, although there has been an increase in recent years in genetically unrelated kidney donations from emotionally related persons such as a recipient's friend or partner.

Living related donor transplants have been considered to offer a number of advantages over cadaver kidney transplants, which affect their outcome.

(a) The elective nature of the surgery allows a more complete evaluation and preparation of the recipient and donor and can be performed when donor's and recipient's health is optimal.

(b) It may also permit a shorter delay between starting dialysis and transplantation and also offers a chance to avoid the potential negative consequences and medical risks of chronic dialysis (Asderakis *et al.*, 1998).

(c) The donor kidney incurs minimal ischaemic damage because the donor and recipient surgeries are scheduled together.

(d) The clinical outcomes of kidney transplantation such as graft and recipient survival rates have been found to be substantially better when organs are from living donors (Berkoven & Schwab, 1999; Cecka, 2000; 2001; Medin *et al.*, 2000; Melchor & Gracida, 1999; Ojo *et al.*, 1995). Receiving a kidney from living related donor confers up to 7%

increase in survival in Europe (EBPG European Expert Group on Renal Transplantation, 2000). Even a poorly matched kidney graft fares better than a well-matched cadaver graft (Terasaki *et al.*, 1995; 1997).

The physical disadvantages of LRD TX are borne by the donor. In general for a completely healthy kidney donor the risk of death is extremely low and major complications are uncommon but the physical impact of a successful surgical operation should not be underestimated.

Section 3: Incidence and Prevalence rates of ESRD and RRTs

3.1 ESRD

The number of patients with ESRD is increasing worldwide (Schena, 2000; van Dijk *et al.*, 2001) and is expected to double over the next decade (Briggs *et al.*, 2000; USRDS, 2001). Across Europe, approximately 50-80 people per million of the population (pmp) develop ESRD each year requiring some form of RRT (Brunner & Selwood, 1990). The current estimated rate of adult patients reaching ESRD and starting RRT in the UK is 90 pmp and approximately 5350 patients started RRT in 1999 (Feest *et al.*, 1990; Internet UK renal registry report, 2000 see also http://www.renalreg.com/home.htm). The incidence of ESRD is three times greater for people with Afro-Caribbean or Indian origin (Roderick *et al.*, 1994) and it further increases six-fold to ten-fold from age 30-50 to age 70-90 (Stengel *et al.*, 2003).

The prevalence of ESRD (patients with transplants or treated with dialysis) was 477 pmp in UK in 1994/1995 (Horl *et al.*, 1999).

This increase in ESRD population is inevitable because of population ageing and the age-related increase in the incidence of ESRD, improvements in the technology of dialysis, and better immunosuppression for TX that cut down mortality rates (Roderick *et al.*, 1998).

The criteria for RRT acceptance have broadened to include older patients and those with comorbidities. Contemporary patients receiving RRT in Europe bear little resemblance to

those given treatment up to the mid-1980s. Recognition of these demographic shifts is key to interpreting the literature on the clinical, psychological and neuropsychological outcomes of ESRD in that the current ESRD patients now are quite different from their counterparts 10 or 20 years ago.

The following two sections review the breakdown of patients in the various treatment modalities.

3.2 Transplantation

The main bar to expanding transplantation is organ availability. The supply of donor organs (cadaver and living donor) which averages 28 pmp per year in the UK is greatly outstripped by demand which is 79 pmp (United Kingdom Transplant Support Service Authority, UKTSSA, 1993). At the end of 1999 in Great Britain and Ireland, 4740 patients were awaiting a kidney transplant, but only 1602 transplants were performed in that calendar year (UKTSSA, 1999). The majority of organ donation is carried out posthumously. In the UK in 2001, 2717 received an organ transplant; 378 of which were from a living related donor. Therefore, in the UK in 2001, 2339 patients received their kidney transplant from a cadaver donor.

3.3 Dialysis treatment distribution

Given the shortage of donor organs, most ESRD patients rely on some form of dialysis as treatment for their condition. There is considerable international and inter-regional variation in the distribution of the different dialysis modalities (HD vs. PD) (Dalziel & Garrett, 1987). In England & Wales 66% of dialysis patients are on HD compared with 73% in Scotland. After an initial expansion and popularity in home HD during the 1970s and early 1980s, the number of patients receiving home HD has decreased progressively over the last decade (Blagg, 1996; MacKenzie & Mactier, 1998).

By world standards, the UK has relatively high PD utilisation (Internet address: http:/www/oanda.com/cgi_bin/ncc. 1998; Jassal *et al.*, 2002). This contrasts with other

European countries and the US where CAPD is used in less than 20% of patients (MacLeod *et al.*, 1998). The rate on increase in CAPD is lower than in HD, producing proportional falls in these modalities in the UK (UK renal registry report, 2000).

APD has been the fastest growing method of renal replacement therapy, with the number of APD patients doubled since 1996 to 30,000 worldwide (Gokal & Mallick, 1999). The growth of APD has been paralleled by the development of new automatic machines which have made possible personalised treatment prescription and perhaps have improved treatment acceptability and adherence (Ronco & Diaz-Buxo, 2001). APD is utilised by 31.9% of all PD patients, including the daytime dwell mode, daytime empty mode and schedules with one or more additional manual exchanges (Ronco & Diaz-Buxo, 2001; USRDS, 1999).

A wide range of factors both medical and non-medical would influence choice of treatment (Horl *et al.*, 1999). In certain patients only one form of dialysis therapy (HD or PD) is possible and for some kidney transplantation may be difficult but in the majority of cases the choice of dialysis modality is based on non-medical factors (Jassal *et al.*, 2002; Stack, 2002). These include financial reimbursement, facilities, physician bias and patients' preferences (MacLeod *et al.*, 1998; Wuerth *et al.*, 2002).

Not all patients receiving dialysis are suitable for TX and there is evidence that selection criteria vary widely throughout the UK (McMillan & Briggs, 1995). This is reflected in the variation in the proportion of dialysis patients who are on the transplant waiting list in different regions. In some areas patients not yet on dialysis are accepted for TX and compete for organs with patients who may have been on dialysis for many years.
Practice guidelines regarding suitability for transplantation have been available in the United States for some years (Kasiske *et al.*, 1995) and European Best Practice Guidelines have recently been published (EBPG European Expert Group on Renal Transplantation, 2000)
In the UK definitive criteria for acceptance onto the cadaver transplant waiting list have yet to be agreed although major co-morbid factors reduce the likelihood of acceptance in many Transplant Units.

Section 4: Renal Replacement Treatments (RRTs) and Survival

The increase in numbers of patients on RRT has 'inevitably' been accompanied by a decline in overall survival as treatment becomes available for patients of all ages and with a range of comorbidities. On average the yearly mortality among patients being treated with dialysis is nearly 25% (USRDS, 1999) with deaths being mainly due to cardiovascular diseases (50%) and infections (15%). The rates of death among patients undergoing dialysis in the US are 25-50% higher than those in Japan and Europe (Friedman, 1996; Schena, 2000).

4.1 Dialysis vs. Transplantation

Studies that compared clinical outcomes between dialysis and TX patients have focused mainly on survival and mortality rates. Studies from the pre-cyclosporin era (before 1984) were unable to show a substantial survival advantage of TX compared with dialysis. However immunosuppression treatment, Human Leukocyte Antigen (HLA) matching and organ preservation have fuelled an increase in graft survival with the result that survival in kidney TX is much superior to that experienced by dialysis patients. The comparison is biased by the fact that preferentially relatively young and healthy patients receive transplants, whereas the individuals who remain on dialysis comprise a precipitate of elderly with one or several co-morbidities severe enough to prevent acceptance for transplantation.

To minimise such selection biases several studies compared TX patients with dialysis patients on TX waiting lists. These results produced convincing evidence that TX improved long term survival relative to dialysis (Johnson *et al.*, 2000; Mallick *et al.*, 1995; Medin *et al.*, 2000; Ojo *et al.*, 1994; 2001; Rabbat *et al.*, 2000; Schaubel *et al.*, 1995; Schnuelle *et al.*, 1998). The death rate for waiting-listed dialysis patients was found to be twofold to eightfold greater than it is for TX recipients (Becker *et al.*, 2000). The estimated additional life-years gained from TX vary from 8 years in a diabetic recipient who is 60 years old or

older to 31 years in a non-diabetic recipient who is 20 years old to 44 years old (Port *et al.*, 1993; Wolfe *et al.*, 1999). Studies have also shown that failed TX terminates the patient survival benefit accruable from kidney transplantation and patients who lose graft function are at increased mortality risk unless repeat transplantation is performed (Ojo *et al.*, 1998).

4.2 Different dialysis treatments (HD vs. PD)

Ever since the introduction of PD as a treatment modality for ESRD, there has been considerable debate about its success and the comparability of outcomes between PD and HD (Maiorca *et al.*, 1989). Numerous studies have evaluated and compared the clinical outcomes associated with the different dialysis treatments. The major difficulty in objectively assessing treatment outcomes is that there are no randomly allocated prospective trials comparing the different treatments.

4.2.a Survival

The first serious attempt to look at outcome after correction for confounding variables was made by Burton and Walls (1987) who concluded that on an intention to treat basis there was no difference in mortality between PD and HD. Subsequently numerous studies have been published (examples of these are summarised in Table 1.2) which have found conflicting results.

Table 1.2: Survival comparisons: HD vs. PD

Study	Year	Outcome
Picolli	1995	No difference
Bloembergen	1995	CAPD worse except for younger patients
Locatelli	1995	CAPD worse
Disney	1995	CAPD worse
Maiorca	1996b	No difference; CAPD better only in elderly
Fenton	1997	CAPD better
Collins	1999	CAPD better
Vonesh	1999	No difference
Murphy	2000	CAPD better
Van Biesen	2000	No difference
Keshaviah	2002	No difference
Termorshuizen	2003	CAPD worse for elderly patients

Recent reviews of the literature concluded that survival rates among patients treated with PD or PD are similar (Alloatti *et al.*, 2000; Coles & Williams 1998; Gokal *et al.*, 1999).

4.2.b Dialysis technique failure

It is common for ESRD patients to change RRT modalities during the course of their treatment. Reasons for transfer include: complications of the therapy, inability to perform the therapy (lack of suitable access, medical contraindications), and patient request or lifestyle issues. In some cases it may be medically appropriate to transfer from PD to HD rather than a technique failure.

In terms of retention of patients on the original therapy (technique survival), there is consistent data to show that PD patients do not stay on their original therapy (Blake *et al.*, 2000; Churchill *et al.*, 1998; Gentil *et al.*, 1991; Gokal *et al.*, 1987; Maiorca *et al.*, 1996a; Serkes *et al.*, 1990). Only 1-4% of patients who start PD continue for longer than 8 years (Gokal & Oreopoulos, 1996), largely due to technique-related complications such as peritonitis (Davies *et al.*, 1998; Kim *et al.*, 2002; Maiorca *et al.*, 1996a; Schaubel *et al.*, 2001). Although APD is associated with lower peritonitis rate than CAPD (Huang *et al.*, 2001; Van Biesen *et al.*, 2002) technique survival is still lower than figures reported for HD. It should however be acknowledged that at times peritonitis is the "precipitating" event for transfer, while the real underlying reason might be patient burnout, poor adherence, inadequate dialysis, a request based on lifestyle, or an underlying exit site infection. Two papers for example (Maiorca *et al.*, 1995a; 1996c) commented on the increased incidence of CAPD drop out compared to drop out rates in HD. This was almost entirely due to patients' or partners' choice to discontinue PD treatments for several reasons (psychological, working, social).

Access problems are also frequent in HD and are responsible for 50% of the hospitalisations of HD patients (Ifudu *et al.*, 1996). Without an adequate vascular access, HD efficiency is reduced, which results in increased morbidity and mortality (Santoro, 2000).

CHAPTER 2: HEALTH RELATED QUALITY OF LIFE IN ESRD

In the early days of the RRT the challenge faced by the Nephrologists was to overcome the technical difficulties and provide a safe environment for more patients on RRT. To some extent this challenge has been met although it remains a difficult task to provide high quality care for the large heterogeneous group of patients on RRT.

Outcomes other than morbidity and mortality may provide a significant contribution to the discussion regarding the allocation of health care resources and medical decision processes. The following chapters review the literature on the health related quality of life (HQoL), illness and treatment beliefs, and neuropsychological functioning in ESRD and its treatments.

Section 1: The concept of Quality of Life (QoL) and its measurement

1.1 Definition/Conceptualisation of QoL/HQoL

Although QoL is increasingly assessed in research and clinical practice no consensus exists concerning the definition or the measurements of this multidimensional concept. Only a very small proportion of the studies that examined HQoL in ESRD have defined the term or have discussed how this term would be conceptualised and put in operation (Cagney *et al.*, 2000).

QoL or HQoL are often used interchangeably to describe the effects that diseases, treatments or other interventions may have on person's functioning and well-being. But the concept of QoL may be considered distinct from health, although related to it. QoL is a multidimensional phenomenon including but not restricted to health (Welch, 1994). It can include a number of dimensions that refer to physical, psychological, mental, emotional, social, spiritual, and vocational function. Patients actually perceive and react to many health and non health-related aspects of their lives, such as family life, finances, housing

work and others aspects of human experience, that are not related to the domain of health. Hence only the subset of the overall QoL that relates specifically to a person's health status that is more sensitive to changes in health refers to the measure of the patients' HQoL.

Based on the WHO definition of health, defined as 'a state of complete physical, mental and social well-being and not merely absence of disease or infirmity' (WHO 1948; 1958), HQoL is operationalised by assessing the domains of physical, mental/cognitive, and social functioning. It is the health-related quality of life that is traditionally measured in clinical trials and medical research to evaluate the benefit/burden ratio of available treatment modalities. The physical domain is typically considered to encompass ambulation, mobility, fatigue, pain, sleep, and ability to perform daily activities. Depression, anxiety, emotional well-being and cognitive status fall within the mental/cognitive domain. The social domain of HQoL includes, for example, work status, role functioning, personal relationships, and sexual functioning.

In this thesis the focus will be on HQoL since this construct has been applied in ESRD research to date. The terms subjective and objective HQoL, a distinction commonly used in clinical ESRD literature, will be avoided and where appropriate the terms physical and emotional HQoL will be employed.

1.2 Measurement of HQoL

Two main approaches have been used to measure HQoL: generic and disease-specific instruments:

- Disease-specific instruments are those which include the dimensions most relevant to patients affected by particular condition (disease or treatment). They tend to be more sensitive to clinical changes than generic instruments but do not allow comparisons between patients with different pathologies (Guyatt *et al.*, 1989).
- Generic instruments include different dimensions of HQoL considered generally imported and broadly applicable across types and severities of disease, across different treatments and medical interventions and across demographic and social subgroups (Patrick & Deyo, 1989). Generic instruments enable comparisons across studies and

disease groups which help judge the severity of problems associated with disease (Guyatt & Jaeschke, 1990), but they may not focus adequately on specific areas of interest or particular problems/issues among different populations and illness groups (Tsevat *et al.*, 1994). Commonly used generic tools in HQoL research include the Sickness Illness Profile (SIP; Bergner *et al.* 1981; 1993) and the 36-item short form of the Medical Outcomes Survey (SF-36; Ware & Sherbourne, 1992).

There is no ideal instrument to measure HQoL in all circumstances. A combined approach using generic instruments augmented by disease-specific measurements or items as suggested by Kutner (1994) may be the preferred approach (Garratt *et al.*, 1993; Valderrabano *et al.*, 2001).

It should nevertheless be kept in mind that QoL and HQoL instruments will never capture all aspects of life that are important to the individual, although systems in which patients specify all or at least some of the qualities are likely to come closest. The individual nature and the shortcomings of many existing measures have been highlighted by many investigators (Carr *et al.*, 2001). The increasing interest in developing individualised measures reflect the perception that QoL is unique to the individual and cannot be adequately assessed using standardised measures. Individual measures such as the Schedule for the Evaluation of Individualised Quality of Life (SEIQoL; O'Boyle *et al.*, 1992) have been advocated but are limited by difficulties in making group comparisons. Although the debate is still ongoing, several disease-specific and generic (assessing health concepts relevant to everyone's health status and well-being) measures have been demonstrated to be valid, reliable, and robust across languages, cultures and clinical settings and as such this will be the focus of this work.

Previous research in HQoL in ESRD has employed a range of generic and disease-specific HQoL measures. It is beyond the scope of this chapter to describe available HQoL instruments; detailed reviews have been published elsewhere (Cagney *et al.*, 2000; Edgell *et al.*, 1996; Rettig *et al.*, 1997; Salek, 1996) but irrespective of the type or the focus of the instruments (generic vs. disease-specific) used, the need for comprehensiveness, reliability, validity and responsiveness cannot be overstated. This unfortunately has not always been demonstrated or reported in ESRD studies (Cagney *et al.*, 2000; Edgell *et al.*, 1996). Of the

101 studies reviewed by Edgell *et al.* (1996) only 35 reported satisfactory psychometric properties for the instrument used and 45 papers reported no psychometric evidence at all.

This review will focus on some of the most common HQoL measures used in ESRD research. It is not intended to be comprehensive and only a subset of the large literature will be directly cited. Emphasis will be given on those studies, which used well-established generic instruments (such as the SF-36, NHP or the SIP) or kidney-specific measures that have undergone adequate evaluation and development such as the Kidney Disease Questionnaire (KDQ; Laupacis *et al.*, 1992), or the Kidney Disease Quality of Life (KDQoL; Hays *et al.*, 1994). These so called new generation of generic and disease-specific measures have had extensive testing in the ESRD population and have been advocated as reasonable choices (Cagney *et al.*, 2000; Nissenson, 1994).

1.3 The place of HQoL in ESRD research

Recent work used/treated measures of HQoL as outcomes per se and as predictors of other outcomes.

1.3.a HQoL as a predictor of clinical outcomes

HQoL scores are strong predictors of clinical outcomes in ESRD including survival and hospitalisation (Kalantar-Zadeh *et al.*, 2001; Knight *et al.*2003; Lopes *et al.*, 2003; Merkus *et al.*, 2000; Parkerson & Gutman, 2000).

Lowrie *et al.* (1997; 2003) for instance, have demonstrated that dialysis patients with scores lower than 51 on the Mental Component Scale (MCS) of the SF-36 have progressively increasing risks of death. Patients with scores of 0–37 have twice the relative risk of death than those patients with scores of 51 or higher. In a prospective study of 1000 HD patients, a 10% increase in death risk and a 5.8% in hospitalisation rate for every five-point decrease in PCS was found (De Oreo, 1997). MCS was not associated with survival, but a five point decrease in MCS correlated with a 2% increase in hospitalisation rate.

A large prospective study using the SF-36 and the short form KDQoL, was carried out in 17,236 HD patients in the United States, Europe and Japan (Mapes *et al.*, 1999; 2003).

Results indicated that a five-point increase in HQoL scores for PCS, MCS and kidney disease targeted issues was associated with a 4 % to 8% reduction in risk of hospitalisation, and a 9% to 29% reduction in mortality after adjusting for sociodemographic, clinical, and laboratory factors.

1.3.b HQoL as an outcome

The bulk of studies have treated HQoL as an outcome per se of ESRD and associated treatment. These will be selectively reviewed in the following two sections.

Section 2: Research in HQoL and Dialysis

There have been numerous HQoL studies in dialysis and kidney transplantation although relatively few studies have been conducted on PD and Home HD patients. Diabetic patients, elderly patients and those who return to dialysis after failure of a renal graft have also been the subject of several studies.

With a few exceptions, data on HQoL of dialysis and renal transplant patients are derived from cross-sectional studies. The few longitudinal studies have either assessed only hospital HD or CAPD patients (Kutner *et al.*, 1986; Meers *et al.*, 1996) or compared HQoL before and after kidney TX (Laupacis *et al.*, 1996; Parfrey *et al.*, 1988a; Russell *et al.*, 1992). A selective overview of the most relevant studies will be presented.

2.1 Comparisons between dialysis and general population

Overall the observed mean scores of dialysis patients on HQoL instruments fall below those of general population indicating that HQoL is substantially compromised (Beusterien *et al.*, 1996a; Diax-Buxo *et al.*, 2000; Gudex, 1995; Khan *et al.*, 1995; Moreno *et al.*, 1996a; Wight *et al.*, 1998).

The research was spurred on by Evans and colleagues in 1985, when they published a 'landmark' paper that focused the attention of the medical community on HQoL in ESRD patients. In that paper, HQoL data from the classic National Kidney Dialysis and Kidney Transplantation study of 859 patients showed that physical functioning scores of dialysis patients were worse than those of the population, although emotional well-being was less affected (Evans *et al.*, 1985). These early data on the lack of congruence between physical and mental indicators of HQoL was confirmed in later studies using generic HQoL instruments (e.g. SF-36; SIP).

HQoL impairments were found to be particularly pronounced with respect to physical dimensions of HQoL (DeOreo, 1997; DeWit *et al.*, 2001; Fukuhara *et al.*, 2003; Khan *et al.*, 1995; Perneger *et al.*, 2003; Wight *et al.*, 1998), whereas emotional HQoL remains generally intact. Mean scores in the emotional dimensions of HQoL are typically close or equivalent to those of general population (Diax- Buxo *et al.*, 2000; Lamping *et al.*, 2000; Merkus *et al.*, 1999b; Mingardi., 1998; Mingardi *et al.*, 1999; Mittal *et al.*, 2001a), but not always within normal range (Beusterien *et al.*, 1996a; Khan *et al.*, 1995; Wight *et al.*, 1998).

Prospective studies indicate a progressive deterioration in HQoL both following initiation of dialysis and as a function of time on a specific dialysis modality. Again the effect appears to be greater for physical rather than emotional HQoL. For example in the combined Oxford and Manchester study of 159 patients (78 HD and 81 CAPD) a marked deterioration was observed in patients' mobility following commencement of treatment but on various psychological scales (life-stress, happiness and satisfaction), their mean scores proved comparable to a normal population (Auer *et al.*, 1990).

A prospective multicentre study of (incident) HD and PD patients over the first 18 months of treatment also showed that physical HQoL (PCS) decreased over time with the greatest decline being noted for the PD group. Mental HQoL on the other hand appeared to remain stable in both groups (Merkus *et al.*, 1999b). Inspection of individual SF-36 subscales showed that deterioration was concentrated in physical functioning and somewhat less in the general health sub-scale. Another study recruited only PD patients and showed a steady decline in all HQoL dimensions (assessed by generic and renal specific sub-scales) over the two-year study period (Bakewell *et al.*, 2002). Although the patients who completed all five

HQoL assessments were on PD for different periods of time, their decline was uniform. The most significant changes were in PCS, MCS, and three kidney specific sub-scales: patient satisfaction; symptoms; and burden of kidney disease.

Opposite findings have also been reported. Mittal *et al.* (2001a) evaluated HQoL using the SF-36 in a cohort of 134 prevalent HD patients, with assessments taken every three months for 2 years. There was no significant mean change in self-assessed physical (PCS) and mental well being (MCS). Both PCS and MCS tended to decline in the initial months of HD but stabilised over time. Despite not finding statistically significant changes in the mean scores, analysis of individual rate of change indicated that more patients had deterioration in PCS whereas the reverse was true for the MCS with more patients reporting improvement in MCS. These findings of stable physical and emotional well-being over time were replicated in prevalent PD patients (CAPD and APD) (Mittal *et al.*, 2001b). Sesso *et al.*, (2003) found that HQoL in the first 7 months on HD were dependent on patients' socio-economic status (SES). HQoL improved in the high SES group but not in the low and medium SES patients.

2.2. Dialysis treatment HQoL comparisons: HD vs. PD

Inconclusive data exist regarding differences in HQoL between HD and PD patients (see reviews by Gokal *et al.*, 1999; Valderrabano *et al.*, 2001). Evidence is conflicting with studies reporting equal or superior HQoL for either PD or HD treatment.

The vast majority of studies comparing HQoL in hospital HD and CAPD patients report no significant group differences in either physical or mental processes of HQoL after adjusting for case-mix differences such as sociodemographic, clinical, and dialysis characteristics (Bremer *et al.*, 1989; Churchill *et al.*, 1987; Diaz-Buxo *et al.*, 2000; Evans *et al.*, 1985; Harris *et al.*, 2002; De Wit *et al.*, 2002; Hart & Evans, 1987; Julius *et al.*, 1989a; Merkus *et al.*, 1999b; Mingardi *et al.*, 1999; Moreno *et al.*, 1996a; 1996b; Nissenson 1992a; Simmons & Abress, 1990; Tucker *et al.*, 1991; Waiser *et al.*, 1998; Wight *et al.*, 1998) or when dialysis groups were closely matched (Bakewell *et al.*, 2001; Harris *et al.* 2002; Killingworth & Van de Akker, 1996).

The issue of sufficient and appropriate adjustment for casemix differences is critical given the absence of patients' random allocation to treatment. It is further highlighted by several studies comparing HQoL between HD and PD patients before and after case-mix adjustments. Significant group differences in mental HQoL indicators favouring PD patients were found only in case-mix unadjusted comparative analyses. These treatment effects however disappeared after case-mix adjustments (Bremer *et al.*, 1989; Merkus *et al.*, 1999a; 1999b; Simmons & Abress, 1990). These findings include studies highly regarded for their methodological rigour that used large samples, psychometrically sound instruments, and directly compared the issue of case-mix (Bremer *et al.*, 1989; Evans *et al.*, 1985; Merkus *et al.*, 1999a; 1999b).

In the studies where treatment related differences persisted after case-mix adjustments, results could be summarised as follows:

HD patients were found to score higher than PD in measures reflecting physical HQoL (Barrett *et al.*, 1990; Julius *et al.*, 1989b; Diax-Buxo *et al.*, 2000). Prospective studies similarly showed a more favourable effect of HD on physical HQoL over time compared to with PD (Merkus *et al.*, 1999b; Mittal *et al.*, 2001b). The lower physical well-being scores have largely been explained by lower albumin levels in the PD groups (Mittal *et al.*, 2001b) and the continuous physical burden of PD compared with the intermittent character of HD. In addition, peritonitis may explain the higher pain perception in PD patients.

Psychological indicators of HQoL tend to favour PD or CAPD patients (Merkus *et al.*, 1997; Simmons *et al.*, 1990; Wolcott *et al.*, 1988a; Wight *et al.*, 1998). Simmons & Abress (1990) however noted that the advantage of CAPD over HD was no longer significant for patients on treatment for 1 to 3 years, suggesting that it may only become evident only as time on therapy lengthens and/or as patients doing less well switch therapies or die. A meta-analysis by Cameron *et al.* (2000) examined differences among RRTs in two fundamental QoL dimensions: psychological well-being and emotional distress. Their results indicated that CAPD patients reported higher psychological well-being than HD but as stated by the authors this finding is threatened by possible publication bias (i.e. studies not showing statistically significant differences may not have been published).

2.3 Dialysis treatment comparisons: hospital HD vs. home HD

Home HD has been consistently associated with improved HQoL compared with hospital HD (Bremer *et al.*, 1989; Evans *et al.*, 1985; Kutner *et al.*, 1986). A meta-analysis by Cameron *et al.* (2000) also found that patients on hospital HD report significantly more emotional distress than home HD patients. On the other hand, studies that HQoL was assessed using preference based instruments report no significant differences between the two HD groups (Churchill *et al.*, 1987). How home HD compared with the other home based treatment modalities (CAPD; APD) remains to be evaluated.

2.4 Dialysis treatment comparisons: CAPD vs. APD

The HQoL on APD has rarely been studied with only five HQoL studies incorporating APD patients. Three of these studies reported data on the aggregate level (combined sample of CAPD and APD patients) making it impossible to draw conclusions on the relative performance of the APD patients (De Wit *et al.*, 2002; Morton *et al.*, 1996a; 1996b). One study focused on the impact of different types of APD equipment on HQoL (McComb *et al.*, 1997).

Only three studies compared APD and CAPD. Bro *et al.* (1999) in a small randomised trial (n = 25) comparing HQoL in APD and CAPD patients found no significant group differences in physical and emotional well-being. Significantly more time for work, family, and social activities was available to patients on APD compared to those on CAPD. Sleep problems on the other hand tended to be more marked in the APD group. In a most recent investigation (De Wit *et al.*, 2001), APD patients had higher emotional well-being as indexed by the MCS SF-36 scores and were significantly less anxious and depressed than CAPD patients. Physical functioning indicators were however equivalent between the two groups. It is also worth noting the report of McComb *et al.* (1997), who found no significant change in HQoL when a small sample of 26 patients were switched from CAPD to APD.

Diaz-Buxo *et al.* (2000) compared SF-36 scores in hospital HD, CAPD and APD patients. They found that among PD patients, those on APD (n = 532) had worse scores on scales

reflecting physical processes and better scores on scales reflecting mental/emotional processes than CAPD patients (n = 728).

2.5 Dialysis comparisons: Conclusions

The inconsistent results in the literature may in part be explained by cross-sectional designs, and improper or insufficient adjustment for casemix differences that are likely to impinge upon HQoL.

As patients are not randomly assigned to RRT, many key variables relevant to HQoL (such as age or comorbidity) may differ significantly between groups (Cameron *et al.*, 2000). In reviewing the literature, it should be borne in mind that lacking random allocation, it is difficult to ascertain and estimate the effect of different dialysis modalities (HD vs. PD) due to the presence of many confounders (Nissenson, 1994). This presents additional challenges to the synthesis and interpretation of the literature. The observed superiority of one treatment may be attributable not to valid differences in the HQoL afforded by a particular treatment modality but to pre-existing non-renal and/or non-treatment related differences. Research findings are hence ambiguous, when investigators do not take such casemix differences into consideration (Greenfield *et al.*, 1994).
The meta-analysis by Cameron *et al.* (2000) also concluded that although psychological dimensions of HQoL differ systematically across patients receiving alternative RRTs, it is not clear whether this occurs because of valid differences between treatment modalities, pre-existing differences among patients, or a combination of these two alternatives.

Inconsistencies may also relate to the characteristics of the various measurement tools used to assess HQoL. This is illustrated by Deniston *et al.* (1989). HQoL was assessed using 19 different HQoL instruments in a cross sectional sample of 742 ESRD patients. Depending on the choice of instrument, different conclusions were reached about the relationship between demographic characteristics, treatment modality and HQoL. Depending on which of the 19 scales (or a greater number of sub-scales) was examined, either PD or HD was judged to provide better HQoL. To summarise, the impact of dialysis modality on HQoL is uncertain. Overall, the analysis suggests that PD and HD are equivalent therapies when

appropriate correction is made for casemix differences. Comparisons of PD with HD must be treated with considerable caution. The studies that are available, however, suggest both treatments may result in similar HQoL levels.

Another issue particularly pertinent to PD vs. HD comparisons relates to the specific dialysis group being compared. Results are less clear-cut when comparisons also involve home HD or APD patients rather than solely comparisons between hospital HD and CAPD patients.

APD and Home HD appear to be associated with more favourable HQoL relative to hospital HD and CAPD albeit not consistently so. For example, Diaz-Buxo *et al.* (2000) performed a cross-sectional study of HQoL in 16,755 HD and 1,260 PD patients (CAPD and APD) using the SF-36. HD and PD patients scored similarly for scales reflecting physical processes. APD patients scored higher than HD for mental processes, although no differences were found between HD and CAPD. Two earlier studies have also shown that home HD offers patients a better quality of life, a greater independence, and a better rehabilitation opportunity than PD (Bremer *et al.*, 1989; Evans *et al.*, 1985). Evans *et al.* (1985) for instance, found that PD patients had better health status and physical well-being, and greater life satisfaction than hospital HD patients but not as good as home HD or transplant patients.

A reinvestigation of how home HD compares with the other treatment modalities is warranted given that dialysis techniques and practices have changed substantially since 1980's when this question was last addressed. Finally although the question of which dialysis modality imparts the best HQoL is not a new agenda and has indeed been repeatedly investigated none of the previous studies have evaluated and compared HQoL between the four dialysis treatments: Home HD, hospital HD, APD and CAPD.

It is thus important not just to document HQoL in the modern dialysis population but also to evaluate HQoL outcomes of hospital vs. home-based dialysis care.

It is possible and relevant to speculate that home-based dialysis may impair the HQoL to greater extent than hospital based treatment for several reasons: increased demands or responsibility placed upon the patient and his/her family; time requirements performing for instance the CAPD bag exchanges may be greater (Devins *et al.* 1990a) or the presence of dialysis-related equipment (e.g. machines) in patients' homes or personal space may act as

a constant reminder of their condition. Home-based delivered dialysis may also pose more HQoL risks as it allows for less compartmentalisation in different life aspects, requires tremendous motivation and might entail more emotional strain on their partner.
Conversely, one might argue that PD regimens might afford better HQoL as they allow more flexibility in everyday life and impose fewer dietary and social restrictions. It is generally held that the greater patients' involvement in PD regimen and Home HD should discourage learned helplessness and allow the patient to take control of the treatment, hence maximising HQoL (Ronco & LaGreca, 1997). On the other hand PD may be more distressing on a more sustained basis due to the responsibility patients must take for their health and well-being. Investigators (Maiorca & Cancarini, 1996; Maiorca *et al.*, 1995a; 1996b) have also commented that after a number of years there may be burnout of either the CAPD patients or the caregiver. These comparisons are now evaluated.

Section 3: HQoL Research and Transplantation

Because of the high cost, interest in transplantation outcomes is particularly intense (Beidel, 1987; Dew, 1998; Levy 1994). In general, the relative success of transplantation has led to a shift in research agendas beyond the success of the procedure and graft and patient survival, to include an examination of recipients' psychological response to transplantation, and their functioning and HQoL (Hanaeur, 1994). Given that potential recipients of an organ have generally poor functioning it is not surprising that transplantation has been found to lead to HQoL improvements (Bravata *et al.*, 1999; Caine *et al.*, 1996; Dew *et al.*, 1997; Wright-Pinson *et al.*, 2000).

There are many reasons for the improvement in HQoL of dialysis patients after transplantation. On a physical level the correction of anaemia has a definite effect on HQoL leading to improvements in symptoms such as fatigue, sleep, and appetite disorders. There is an improvement in sexual dysfunction – women resume menstruation and recover their fertility while men recover their sexual potency and libido. Fluid intake and diet restrictions are lifted. On a psychological and social level, the physical dependence on the HD

machine, or the rigorous CAPD and APD routine disappear and patients have more freedom to pursue work social and family activities.

3.1 Prospective studies pre- to post-transplantation

Prospective studies that assessed patients prior and post-transplantation uniformly showed substantial improvements in all HQoL dimensions (Christensen *et al.*, 2002; Dew, 1998; Dew *et al.*, 2000a; 2000b; Hathaway *et al.*, 1998; Russell, *et al.*, 1992). In most previous studies the period of assessment ranged from a few months to nine years, but serial sampling has not been performed. Data on the HQoL of TX patients over time are contradictory.

(a) Most studies show an improvement, typically at 12 months post-transplantation. Gains were most consistently noted for physical functioning HQoL and global QoL perceptions. These effects are maintained at longer follow-ups but no further improvements occur (Jofre *et al.*, 1998; Laupacis *et al.*, 1996; Pafrey *et al.*, 1988a; Park *et al.*, 1996; Simmons *et al.*, 1977; 1981).

(b) Some show continuous improvements over time (Hilbrands *et al.*, 1995a) whereas in some cases poorer results were achieved (Jofre *et al.*, 1998; Rebollo *et al.*, 2000)

(c) Factors such as gender, race, previous dialysis experience, diabetes, and creatinine have had an effect on the magnitude of HQoL improvements (Jofre *et al.*, 1998; Johnson *et al.*, 1998b; Wright-Pinson *et al.*, 2000).

Patients pre-transplantation functioning is another important consideration. A study comparing HQoL pre- and after different types of solid organ transplantation (Wright-Pinson *et al.* 2000) showed that the trajectory of HQoL improvement among lung, liver, heart, and kidney TX patients, is different, as patients start at different levels of HQoL prior to TX operation. Renal TX patients who start out the best, mainly because of dialysis, improved the least and retained their functional classification (Karnofsky), and HQoL levels (PCS and MCS) during the first 2 postoperative years.

3.2 HQoL in Transplantation compared to general population

HQoL levels afforded by transplant patients have typically been reported as equivalent or nearly equivalent to that of the general population (Bremer *et al.*, 1989; Dew, 1998; Evans *et al.*, 1985; Gouge *et al.*, 1990; Insense *et al.*, 1999; Littlefield *et al.*, 1996; Painter *et al.*, 1997; Shield *et al.*, 1997).

3.3 HQoL in transplantation compared to dialysis

Findings consistently show that among RRTs, transplantation imparts the best HQoL for ESRD patients (Cameron *et al.*, 2000; Valderabanno *et al.*, 2001). Dew *et al.*, (1997) reviewed 66 studies with more than 6,500 renal transplant recipients and concluded that data were sufficient to confirm that TX produces a significant improvement in both physical (78% of the patients) and psychosocial aspects (70%) of HQoL as well as in global health perceptions (100%). When data were averaged across patients a between treatment HQoL advantage was identified for renal transplantation compared to dialysis. There is indeed ample evidence (from empirical investigations) in support of this conclusion (e.g. Bakewell *et al.*, 2001; Evans *et al.*, 1985, Googe *et al.*, 1990, Hathaway *et al.*, 1998; Jofre *et al.*, 1998; Johnson *et al.*, 1982, Wight *et al.*, 1998).

Cameron and associates (2000) questioned the validity of some of the findings in the previous literature. They warned that publication bias and casemix differences might have biased the results to favour TX over dialysis. The need for consistent documentation and sufficient control of casemix variables in such comparisons becomes clear if the impact of treatments has to be clearly understood.

3.4 HQoL in CAD and LRD transplantation

The majority of previous HQoL studies has been limited to samples of CAD patients or have not specified the transplant donor source (Devins *et al.*, 1990a; Morris & Jones, 1988). Freeman (1985) attributed the findings of enhanced HQoL (Evans *et al.*, 1985) to

the large proportion (50%) of living related transplant recipients recruited in studies. These conclusions have not however been substantiated by empirical evidence. Studies evaluating the effect of transplant source on global QoL and health status (e.g. life satisfaction and functional ability) reported no differences between the two transplant groups. Evans *et al.* (1984) found that the source of transplant did not significantly affect physical and emotional measures of HQoL. Similarly Julius *et al.* (1989b) found no differences between CAD and LRD transplant patients in measures of physical functioning. In the most recent investigation, Christensen *et al.*, (2002) found that the main effect of donor source was unrelated to depression and HQoL.

Section 4: Transplantation specific outcomes

Health care providers and transplant recipients themselves have become increasingly aware that TX may give rise to new set of stressors, psychosocial challenges and adaptive demands (Grady *et al.*, 1996; Hanson, 1987; Hathaway & Strong, 1988; McQuellon *et al.*, 1998; Robertson, 1999; Wainwright *et al.*, 1999).

It may be expected that although the recipients of different transplanted organs will have many similar types of concerns, these may vary in the degree of importance. Commonly reported stressors identified across a range of transplant populations, include the cost and side-effects of immunosuppressive medication, worries about the viability of the transplanted organ, fear of rejection and the need to adhere to a rigorous post-transplant care regime (Fallon *et al.*, 1997; Frey, 1990; Gubby, 1998; Hathaway *et al.*, 1990; Hauser *et al.*, 1991; Hayward *et al.*, 1989; Kong & Molassiotis, 1999; Sutton & Murphy, 1989; White *et al.*, 1990). It has been argued that a viable organ transplantation, albeit a life saving procedure for several end-stage medical conditions, does not cure disease but rather extends life by trading one chronic disease for another (Johnson, 1990). Immunosuppressive therapy continues indefinitely after transplantation and is often accompanied by some dietary restrictions. Transplant recipients are also required to regularly attend outpatient transplant clinic and laboratory appointments and check ups, although their frequency decreases with time. They are also expected to engage in several

preventative or health protective behaviours (e.g. use sun block agents) or monitoring behaviours (e.g. monitor themselves for early signs of rejection). Accumulating evidence suggests that a considerable number of transplant recipients fail to adhere completely to their treatment recommendations (Bunzel & Laederach-Hofmann, 2000; Colon *et al.*, 1991; Hilbrands *et al.*, 1995b; Kiley *et al.*, 1993; Rovelli *et al.*, 1989a; 1989b; Schweizer *et al.*, 1990; Siegal & Greenstein, 1997). This is of particular concern in the light of evidence indicating that poor adherence is a major determinant of graft failure (Burke *et al.*, 1996; Didlake *et al.*, 1988; Dunn *et al.*, 1990; Hilbrands *et al.*, 1995b; Hong *et al.*, 1992; Kalil *et al.*, 1992; Schweizer *et al.*, 1990) and mortality (Rodriguez *et al.*, 1991).

Other areas of concern and potential stress for organ recipients include: impact on family relationships, post-transplant adjustment (e.g. resuming an independent role, change in physical and social activity), integration of the transplanted organ to body image, and emotional responses most notably feelings of gratitude and guilt towards the donor or donor's family as well as feelings of personal inadequacy and/or responsibility for ultimate graft survival (Bosnak, 1996; Bunzel *et al.*, 1992a; 1992b; Bunzel & Wollenek, 1992; Castelnuouvo-Tedesco, 1981; Hathaway *et al.*, 1990; Kimball & Famularo, 1980; Kuhn *et al.*, 1988; Lewino *et al.*, 1996; Mai, 1986; Muslin, 1971; Rauch & Kneen, 1989; Robertson, 1999; Schlebusch, 1986; Schlebusch *et al.*, 1989; Schlebusch & Pillay, 1992; Simmons, 1983; Simmons *et al.*, 1977; Witzke *et al.*, 1997). It is possible that these specific emotional and behavioural responses to transplantation may differ between transplant types (living vs. cadaver), and may in turn impinge upon HQoL.

These issues, though highly relevant remain largely unexplored by HQoL instruments. Although these have provided useful data and offer ready comparisons across studies and patient groups, they fail to capture these specific and often subtle emotional and behavioural concerns of transplant recipients. Measurement specificity is the alternative approach and the value of condition-specific instruments has been widely recognised (Bradley, 1994; Welch, 1994). Specific instruments can be expected to provide more sensitive measurement of processes and responses unique to transplantation but existing transplantation-specific measures have been proven to be relatively unproductive as they are limited both in terms of their content and coverage as well as their psychometric

properties. Transplantation-specific QoL instruments (*Quality of Life Inventory*; Carrington *et al.*, 1996; *Bone Marrow Transplantation Symptoms Checklist*; Fife *et al.*, 2000; *End Stage Renal Disease Symptom Checklist-Transplantation Module*; Franke *et al.*, 1999; *Heart Transplant Symptom checklist*; Grady & Jalowiec 1995; *General Health/QoL rating scale*; Lanuza *et al.*, 2000; *Kidney Transplant Questionnaire*; Laupacis *et al.*, 1993) assess mainly physical functioning usually incorporating some psychosocial functioning items. They thus take little consideration of transplant-specific emotional responses or treatment related issues.

There appear to be no widely used psychometrically sound instruments to assess the specific responses of receiving an organ transplant. A few studies use transplant-specific measures but those that do, tend to employ idiosyncratic instruments and the psychometric properties and development of which are not always described in sufficient detail for research or clinical use (Fife *et al.*, 2000; Kerr *et al.*, 1997; Lanuza *et al.*, 2000; Siegal *et al.*, 1989; Teichman *et al.*, 2000; Witzke *et al.*, 1997; Wolcott *et al.*, 1986). For example Wolcott *et al.* (1986) developed a recipient questionnaire for bone marrow transplant patients but did not report on its psychometric properties nor item content. Other investigators (Bortman *et al.*, 1999; Greenstein *et al.*, 1997; Ostrowski *et al.*, 2000; Schlitt *et al.*, 1999) employed transplantation-specific questionnaires but analysed each item separately reporting the percentages of patients endorsing or not a particular item rather than identifying subscales and establishing or examining the psychometric properties of their measure.

One central problem in the existing questionnaires is their limited scope. Typically the measures are tailored to study particular samples, such as kidney, bone marrow or heart transplant patients (Franke *et al.*, 1999; Grant *et al.*, 1992; Jacobs *et al.*, 1998; Ketefian & Starr, 1990; Laupacis *et al.* 1993; McQuellon *et al.*, 1997; Molassiotis, 1999; Parfrey *et al.*, 1989; Park *et al.*, 1992; Sutton & Murphy, 1989; Wirth & Barton, 1985) or were designed to assess newly transplanted patients (Hayward *et al.*, 1989). This restricts their use with other transplant populations. The transplant-specific questionnaires appear to cover some but not all of the important aspects of post transplant experience identified in the literature. Other transplantation specific measures have specifically been designed to measure a very specific single concept such as body image (*Bone Marrow Transplantation Symptoms*

Checklist; Fife *et al.* 2000; *Body Image Questionnaire*; Schlebusch *et al.*, 1992), symptom experience (*Heart Transplant Symptom Checklist*; Grady & Jalowiec, 1995; Transplant Symptom Frequency and Distress Scale; Lough *et al.*, 1987), treatment (Heart Transplant Regimen; Grady & Jalowiec, 1995), knowledge about transplant regimen (De Geest *et al.*, 1995; Soine *et al.*, 1992) or understanding of self care principles (Wirth & Barton 1985) and thus, albeit of value, they are limited by a narrow focus.

Transplant stressor instruments, on the other hand, are somewhat more comprehensive in their content but have been designed to measure and document the stressors of organ transplantation rather than measuring the effects of these stressors (*Heart Transplant Stressor Scale*; Grady & Jalowiec, 1995; *Recipient Stressor Scale*; Gubby, 1998; *Kidney Transplant Recipient Scale*; Hayward *et al.*, 1989; *Kidney Transplant Questionnaire*; Ketefian & Starr, 1990). Overall, none of the existing measures adequately assessed the emotional and behavioural issues associated with transplantation and this limits our understanding of the psychological processes of organ transplantation.

Section 5: Factors associated with HQoL in ESRD

Table 2.1 lists the different factors reported in the literature to influence HQoL in dialysis and transplant patients.

Table 2.1: Factors associated with HQoL in ESRD

Poorer HQoL	Better HQoL
Comorbidity	Haemoglobin (high)
Diabetes	Socio-economic level (high)
Poor nutritional status (albumin)	Educational level (high)
Poor dialysis adequacy	Race (black)
Rejection episodes	Social support (high)
Low GFR	
Unemployment	
Depression (high)	

5.1 Clinical factors

Clinical factors other than treatment modality have been associated with HQoL in ESRD. These include: comorbidity (Khan, 1998; Khan *et al*, 1995; Merkus *et al.*, 1997; Mingardi, 1998a; 1998b), especially diabetes (Moreno *et al.*, 1996a; 1996b), haemoglobin/anaemia, (Moreno *et al.*, 2000; Valderrabano, 2000) and albumin levels indicative of patients' nutritional status (Mingardi et al., 1999). Several studies have, however, shown that the traditional clinical parameters (such as comorbidity, diabetic status, albumin) that determine outcomes such as mortality, may have a lesser effect in HQoL outcomes (Martin & Thompson, 2000; Merkus *et al.*, 1997; Mozes *et al.*, 1997; Steele *et al.*, 1997).
Time of diagnosis of CRF and pre-dialysis care influence HQoL after dialysis onset, with patients with delayed diagnosis and referral reporting worse physical and emotional well-being in the first two months of dialysis (Sesso & Yoshihiro, 1997).

5.2 Sociodemographic variables

Many factors that affect HQoL in general (such as SES, finances, social deprivation index, living conditions) are expected to exert powerful influences on patients' HQoL but a discussion of each one of these is beyond the scope of this thesis.

The influence of age however, deserves some further mention, as it is likely to differ between dialysis and transplantation, and is also very closely linked to clinical parameters such as comorbidity.
Many authors have indicated that increased age has a negative effect on HQoL of ESRD patients undergoing dialysis (Evans *et al.*, 1985; Merkus *et al.*, 1997). This effect is mainly observed in the physical rather than the psychological dimensions of HQoL (Kutner & Brogan 1992; Lamping *et al.*, 2000; Mingardi *et al.*, 1999; Moreno *et al.*, 1996a; Wight *et al.*, 1998). Age is also important because the impact of ESRD on HQoL appears to be less in elderly patients. In studies comparing different groups of dialysis patients with the healthy population, the groups of elderly patients with ESRD showed fewer differences than the group of younger ESRD patients (Horina *et al.*, 1992; Muthny & Koch, 1991). Elderly patients reported greater satisfaction and accepted the limitations associated with

ESRD better than the younger patients with ESRD. Similar results have also been reported for elderly transplant recipients (Benedetti *et al.*, 1994; Hestin *et al.*, 1994; Rebollo *et al.*, 2001). In the last study the elderly transplant patients had a HQoL even better than that of the general population of the same age and gender.

This selective review illustrates that research so far has placed emphasis on modelling demographic and clinical factors that promote or limit optimal HQoL (Feurer *et al.*, 2002). These sociodemographic and clinical characteristics however explain only a relatively small percentage of HQoL, suggesting that HQoL may be determined by multitude of other factors. Recent work has suggested that psychological factors (such as patients' mood, cognitions, perceptions, beliefs, and attitudes) may also be associated with outcomes such HQoL in ESRD patients. These factors may be either directly related with HQoL or may mediate or moderate the relationship between these sociodemographic and clinical parameters and HQoL. These factors are discussed in the next sections.

Section 6: Depression in ESRD

Another psychosocial outcome that has received considerable attention, much earlier than the explosion of research interest in HQoL, is depression.

Perceptions of HQoL and depressive mood are linked in several ways: Firstly, depression has become an important domain for HQoL researchers (Cagney *et al.*, 2000). Measures of depressive mood are included in many HQoL indices (Edgell *et al.*, 1996).
Depression may also be conceptualised as a predictor of HQoL. For example, it may have a significant impact on perceptions of HQoL in that depressive affect and magnitude of negative outlook may result in a more negative view of patients' functional status, well-being and HQoL. Several studies found that depression and anxiety are strongly associated with HQoL in ESRD (Martin & Thompson, 2000; Steele *et al.*, 1997).

6.1 Depression prevalence

Depression is the most commonly encountered psychological problem in ESRD (Christensen & Moran 1998; Finkelstein & Finkelstein, 1999; 2000; Kimmel, 2000a; 2001; 2002), affecting both HD and PD patients (Wuerth *et al.*, 2001). The prevalence of depression has however varied greatly in different studies (Furr, 1998; Kimmel *et al.*, 1993; Smith *et al.*, 1985; Watnick *et al.*, 2003).

The differences have been attributed principally to the differing criteria and methodology used to diagnose and measure depression. It is important to be clear what is meant by depression, and how it is measured. Depressive affect should not be confused with the clinical diagnosis of depression. Rates of depressive affect based on self-report ratings of symptoms range from 25% (Martin & Thompson, 2000; Rodin & Voshart, 1987) to 50% (Kutner *et al.*, 1985). Estimates of the prevalence of clinical depression (based on psychiatric assessment and diagnostic criteria) range from 12% to 45%, depending on the method and criteria used to define a depressive disorder (Aghanwa & Morakinyo, 1997; Craven *e al.*, 1987; 1988; Hinrichsen *et al.*, 1989; Hong *et al.*, 1987; Lowry & Artcherson, 1980). As is the case with other chronic medical conditions, there is evidence that depression among ESRD patients frequently goes unrecognised and untreated (Smith *et al.*, 1985).

Another reason for the variability of the findings may be due to the difficulty of diagnosing depression in ESRD patients (Kimmel *et al.*, 1993). Symptoms of depression can be divided into somatic and cognitive categories. Typically the somatic aspects of depression are included in diagnostic evaluations but there is an overlap between the somatic symptoms of depression and those of uraemia (Kimmel *et al.* 1993; Smith *et al.*, 1985). Depressive symptoms such as sleep disturbance, appetite disturbances or weight change, and fatigue) are common manifestations of ESRD and associated treatments. Using the cognitive symptoms of depression, such as hopelessness and helplessness, feelings of guilt, worthlessness and self-loathing, loss of interest in life or pleasure, may be critical in separating uraemic symptomatology from depression (Sacks *et al.* 1990)

6.2 Depression comparison between RRTs

Only a few studies have compared depressive affect in patients established on either different dialysis treatments or different RRTs.

Some studies report no differences in depression rates between HD and PD patients (Iacovides *et al.*, 2002; Iordanidis *et al.*, 1995; Killingworth & Van den Akker, 1996; Majkowicz *et al.*, 2000; Mittal *et al.*, 2001b; Zimmermann *et al.*, 2001). Others (Griffin *et al.*, 1994; Oldenburg *et al.*, 1988) found that HD patients showed better psychological adjustment than PD patients (lower anxiety and higher positive mood scores), despite being more severely ill and suffering from physical symptomatology to a greater degree than PD patients. In contrast, Kimmel *et al.* (1998a) found that the adjusted risk of hospitalisation for any mental disorder, depression, and alcohol and drug use was lower in PD compared with HD.

More clear-cut are the findings regarding depression rates between dialysis and transplant patients. Dialysis patients appear to be more depressed (and anxious) than transplant patients (Cameron *et al.*, 2000; Christensen *et al.*, 2000; Gokal, 1993; Waiser *et al.*, 1998; Zimmermann *et al.*, 2001).

6.3. Depression consequences

Whereas clear understanding of the causes of depression remains inconclusive, evidence has accumulated on the consequences of depression in ESRD patients. Depression may detract substantially from the HQoL of ESRD patients and is particularly problematic given that dialysis patients are at increased risk for suicide (Kimmel, 2001). Several studies have noted a strong relationship between depressive symptoms and overall HQoL (Martin & Thomspon, 2000; Steele *et al.*, 1997).

Although the precise relationship between depression and medical outcomes remains unclear (Finkelstein & Finkelstein, 1999), several studies have found that depression has an impact on ESRD patients' morbidity and mortality (Christensen & Moran, 1998;

Finkelstein & Finkelstein, 2000). Higher levels of depression have been found to lead to more hospital admissions (Numan *et al.*, 1981) for renal or psychiatric care. Studies on PD suggested that patients with higher depression scores have greater rates of peritonitis than patients with less severe depressive symptoms (Juergensen *et al.*, 1996; 1997; Troidle *et al.*, 2003; Wuerth *et al.*, 1997). The directionality of these associations remains in question as peritonitis episodes are likely to trigger depressive symptoms.

Findings of the relationship between depression and survival have however been mixed (reviewed by Kimmel, 2001; 2002), with some showing that depression leads to poorer survival rates (Kimmel 1992; 2000a; Kimmel *et al.*, 2000; Lopes *et al.*, 2003; Peterson *et al.*, 1991) and others that depression does not predict survival (Christensen *et al.*, 1994; Devins *et al.*, 1990b). Early studies of the association of depression and mortality in ESRD patients were, however, often poorly controlled for the medical factors that might have affected mortality and also been confounded with depression, such as the symptoms of comorbid renal and systemic diseases. Variable follow-up times also contribute to the conflicting findings. Studies with long follow-up times, i.e. more than 3 years (Devins *et al.*, 1990b; Christensen *et al.*, 1994) failed to find a relationship between depression and mortality. Significant associations between depression and survival have mainly been reported in studies with shorter follow up times (typically 1-2 years) (Peterson *et al.*, 1991; Shulman *et al.*, 1989).

Section 7: Study aims and hypotheses regarding HQoL

(a) To assess and describe levels of HQoL in ESRD patients

(b) To compare HQoL outcomes between patients on different RRTs and to compare these outcomes with norms

(c) To evaluate the effect of transplant type and immunosuppressive regimens on HQoL among transplant recipients

(d) To identify variables that predict HQoL in dialysis and transplantation

(e) To develop a transplant specific instrument to provide a thorough coverage of an individual's emotional and behavioural response to receiving a transplanted organ, and the pressures and stresses that this may cause.

CHAPTER 3: PATIENTS' ILLNESS AND TREATMENT BELIEFS

In part the present study was conducted within a framework of a biopsychosocial model that considers that individuals' cognitive interpretations of illness and treatment, rather than their objective illness severity or treatment burden, are critical in psychosocial adjustment and HQoL. In particular, this research investigated the role of illness and treatment self-schemas: illness representations, and perceived illness and treatment effects (perceptions of illness-related or treatment-related disruption). The basic theoretical framework underlying this research was the self-regulatory framework by Leventhal and colleagues, which is briefly reviewed below.

Section 1: The theoretical framework - the Self-Regulatory Model

During the last decade, in the field of psychological research in chronic illness, considerable attention has been directed to Leventhal's self-regulatory model (SRM; Leventhal *et al.*, 1980; 1984; 1998; Leventhal & Diefenbach 1991). The SRM identifies the factors involved in the processing of information by the patient regarding their illness, how this information is integrated to provide a 'lay' view of the illness and how this 'lay' view guides coping behaviours and outcomes.

Patients' representation of illness, or the manner in which an individual conceptualises and gives meaning to an illness and its consequences, is a key component of the SRM and has been a significant focus of inquiry in the field of Health Psychology (Petrie & Weinman, 1997). Illness representations can be further defined as individual's representations of their disease, including disease-related beliefs, emotions, knowledge, and experiences (Skelton & Croyle, 1991). Understanding such illness representations is important because the responses of patients to their conditions (e.g. seeking medical care, developing self-care behaviours, becoming depressed) are believed to be determined at least partially by these beliefs (Leventhal *et al.*, 1996; Schiaffino, & Cea, 1995).

Although there are differences in methodology and terminology, research into the structure of lay theories about illness has established that the content of an illness representation can be ordered into logical themes or dimensions (Baumann *et al.*, 1989; Lau & Hartman 1983; Lau *et al.*, 1989; Leventhal *et al.*, 1980):

(1) Identity - the label the patient uses to describe the illness, and the signs and the symptoms the patient views as being part of the illness

(2) Cause - personal ideas about the cause of the illness for example as a consequence of genetic factors or of external agents such as viruses or germs.

(3) Timeline - expectations about the duration of the disease and its characteristic course, perceptions about whether the illness is expected to be acute, episodic or chronic,

(4) Consequences – personal ideas about short and long term effects and outcomes of the disease; the perceived physical social and economic consequences of the illness

(5) Control or cure - beliefs about the extent to which the illness is amenable to control or cure.

Leventhal *et al.* (1980) proposed that the SRM is a parallel-processing model in that people typically make simultaneous cognitive and emotional representation of their illness. Thus an illness representation may not only comprise the dimensions outlined previously, but also emotional representations (see Figure 3.1.).

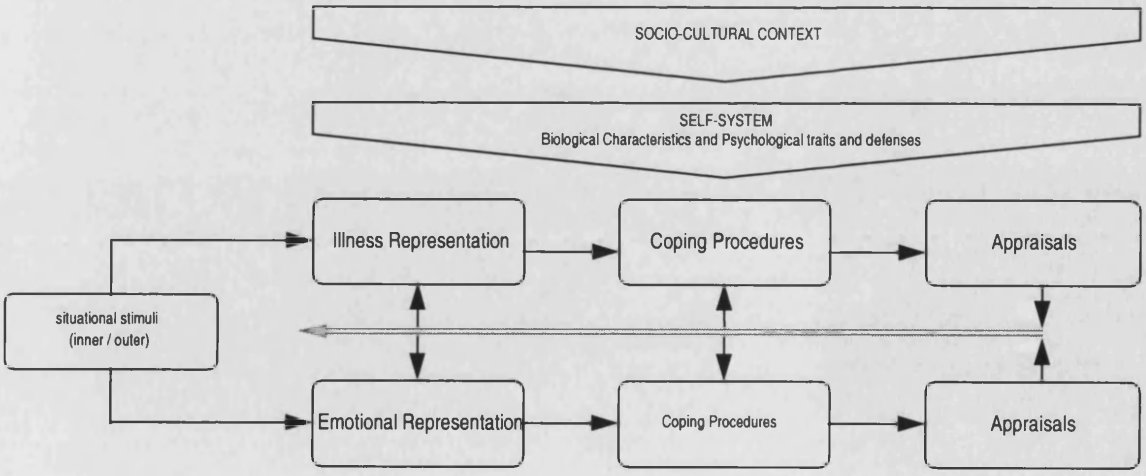


Figure 3.1: The Self Regulatory Model

Illness representations are guided by three basic sources of information: (a) personal experience with an illness (including symptomatic information), (b) information from the external social environment, from perceived significant others or authoritative sources such as doctors or parents and (c) the general pool of 'lay' information assimilated by the individual for previous social communication and cultural knowledge of the illness.

A major tenet of the SRM is that a causal relationship exists between illness representations and illness outcomes such as psychological and physical adjustment, which is mediated by coping responses. SRM postulates dynamic interactions between illness representations, coping and outcomes through stages of appraisal and feedback processes.

Numerous studies have examined illness representation in various patient groups and provided empirical support for the theoretical premises (Hagger & Orbell, 2003). Components of illness have been found to be associated with functional status (Scharloo *et al.*, 1998), psychosocial adjustment (Moss-Morris *et al.*, 1996; Schiaffino *et al.*, 1998), depression (Edwards *et al.*, 2001; Rutter & Rutter, 2002), and treatment adherence (Griva *et al.*, 2000; Hampson *et al.*, 1995; Meyer *et al.*, 1985; Skinner *et al.*, 2002). In addition preliminary evidence suggest that interventions designed to alter patients' illness representation can improve their adaptive outcome (Petrie *et al.*, 2002). It is beyond the scope of this thesis to document the numerous studies of illness representations in patients other than ESRD. The interested reader is directed to the work of Petrie & Weinman (1997) and Cameron & Leventhal (2003) for more detailed reviews of previous research.

Despite a cogently argued rationale and the ample empirical evidence on illness representations determining a range of physical and psychological outcomes, the application of this framework in ESRD has been limited. No studies have been published which assessed the five components of illness representations in ESRD explicitly using the SRM. This does not mean that patients' perspective has been completely overlooked. ESRD research has examined patients' beliefs and cognitions but not strictly from a self-regulatory perspective and without explicitly adopting the SRM model. The constructs assessed bear a strong conceptual resemblance to SRM components and can be mapped onto one of the five illness representation components.

A selective overview of this line of research and its conceptual background will be presented and the conceptual links of these concepts to the self-regulatory framework will be discussed.

Section 2: Illness Intrusiveness

The bulk of ESRD research has focused on perceptions of illness intrusiveness or disruption.

2.1 The conceptual background of illness intrusiveness

The concept of 'illness intrusiveness' refers to illness induced lifestyle disruptions to valued activities and interests that limit the personally rewarding experience and compromise HQoL (Devins *et al.*, 1983).

The notion of intrusiveness is relevant in all chronic illnesses and in ESRD in particular since it introduces significant psychosocial challenges and adaptive demands and involves considerable illness and treatment-related constraints. Despite safe and effective long-term treatments, individuals with ESRD experience threat of death, loss of physical strength and stamina, economic hardships, dietary and fluid restrictions, and dependency on medical technology and personnel, which may interfere substantially with important facets of a person's life (Devins *et al.*, 1990a; 1990c; 1991).

Direct intrusiveness may be introduced through the physiological effect of irreversible renal failure such as reduced physical strength and stamina or increased uraemic symptoms. Treatment-related symptoms are also thought to contribute to the overall perceptions of illness-related disruption. These physical aspects may limit patients' ability to perform social, family, or self-care behaviours or to maintain active participation in vocational and leisure activities and other life domains.

Such effects are usually augmented by the presence of non-renal comorbid conditions and renal complications such as diabetes, renal bone disease or cardiovascular problems. Direct interference may also be caused by the treatment when it often comes into conflict with patients' lifestyle. Hospital-based dialysis for example may require that a person dialyses during working hours, thus making difficult or preventing maintenance of full-time employment.

Devins *et al.* (1990b) argued that indirect interference might also be introduced to the extent that family relationships and friendship patterns change. Following the onset of ESRD and the need for RRT, family members' perception of their relative may change dramatically. The person may be seen as chronically sick, dependent and 'helpless', whereas she/he may have previously been considered very independent and capable. Family roles and responsibilities may therefore begin to shift with the result that ESRD patient's autonomy and independence are eroded significantly.

Perceived illness intrusiveness cannot be fully explained by the objective features of an illness or a treatment. Patients with the same medical diagnoses and treatments may have quite different perceptions of the burdensome aspects of their illness. Faced with the objective constraints of their illness, patients make their own evaluation and subjective appraisal of the effect of their disease on their lives (Devins *et al.*, 1990b; Kimmel *et al.*, 1998b; Greenberg & Peterson, 1997a). Perceptions of illness intrusiveness are conceptually linked or similar to the 'consequences' beliefs from the SRM. Both constructs measure patients' appraisal of the short or long term physical psychosocial and financial impact/burden associated with their disease.

2.2 Factors associated with illness intrusiveness in ESRD

A wide range of factors may influence perceptions of illness intrusiveness such as age, disability, social support (family environment), personality and cultural factors (Devins *et al.*, 1997a; 1997b). The effect of cultural factors was demonstrated by Kutner & Devins (1998) who showed that elderly white dialysis patients experienced more symptoms, had

higher levels of illness intrusiveness, greater dissatisfaction with their health and more global life dissatisfaction than did elderly African-American patients.

2.3 Illness intrusiveness and outcomes in ESRD

This subjective appraisal of illness burden is thought to be central in determining patients' response to illness. Illness intrusiveness is thought to mediate the relationship between outcomes such as HQoL/psychosocial adjustment and the objective circumstances of disease (e.g., pain, fatigue, and disability) or associated-treatments (e.g., side-effects, complications, and disruptive treatment schedules). Models such as the SRM also postulate that perception of illness may be as or more important to adjustment and coping with illness, than medical severity and the objective features of an illness (Greenberg & Peterson, 1997a; Weinman & Petrie, 1997).

Illness intrusiveness is hypothesised to influence psychosocial outcomes among people affected by chronic disease such as ESRD through at least two complementary mechanisms:

- directly, as a result of reduced positive experience when the condition interferes with continued participation in valued activities and interests
- indirectly, due to reduced expectations of personal control.

A growing body of evidence supports the claim that illness intrusiveness mediates the psychosocial impact of ESRD (Devins *et al.*, 1983). Illness intrusiveness has been found to be negatively associated with HQoL (Devins, 1991; 1994; Devins *et al.*, 1990a; 1990c; 1990d; Patel *et al.*, 2002) and depression (Devins *et al.*, 1993a; 1997a; 1997b; Eitel *et al.*, 1995; Kimmel *et al.*, 1995a; 1996; Sacks *et al.*, 1990). Factors such as age and self-concept have been demonstrated to moderate the association between illness intrusiveness and emotional distress (Devins *et al.* 1997a).

Higher illness intrusiveness was associated with poorer survival despite being dissociated with clinical indicators of illness severity (Kimmel *et al.*, 1998b; Shulman *et al.*, 1989). Although the mechanisms underlying such associations are unclear, neurohumoral and

behavioural pathways, as well as the effects of adherence and social support may be involved (Kimmel, 2001; 2000a; 2000b Kimmel *et al.*, 1998a; 1998b; 1998c).

2.4 Illness perceptions as an outcome in ESRD

Perceived illness intrusiveness/burden may also be considered as an important outcome in and of itself rather than as a determinant of other outcomes. One way of assessing the impact of RRT is to assess the illness and treatment intrusiveness, which measures the degree to which the illness interferes with lifestyle, activities and interests (Devins, 1994).

It has been suggested that illness intrusiveness may be greatest for CAPD or home HD patients who must administer their treatment daily while continuing with their everyday activities and work. These patients may be less able to separate their treatment from their non-treatment activities (cf. Lewin, 1951). In contrast, because HD patients typically receive treatment within distinctive blocks each week, they may be better able to separate their treatment from other daily activities. In contrast to the rigorous schedule of HD and the regular dialysate exchanges of PD, renal transplantation would appear to be relatively the most non-intrusive ESRD treatment insofar as the treatment regimen after transplantation typically entails little more that the daily immunosuppressive medication. Research has indeed indicated that relative to chronic dialysis, successful renal transplantation is associated with lower perceived illness and treatment intrusiveness. Systematic differences however have failed to emerge in comparisons involving the various dialysis modalities (Devins *et al.*, 1983; 1990a; Devins, 1994; Sacks *et al.*, 1990).

Importantly, research to date has focused predominantly on illness-related beliefs or implicitly collapsed illness and treatment perceptions. Illness burden was seen as directly related to the exigencies of treatment. It is instructive to consider in more detail what aspects of treatment may be considered as stressful or the extent to which treatment disrupts life and personal and social behaviours. Treatment-related beliefs may be distinct from views and beliefs regarding illness and these are considered below as a separate category called treatment perceptions.

Section 3: Treatment Perceptions in ESRD

3.1 Conceptual background

In contrast to patients' beliefs about their illness the investigation of treatment beliefs has been less far reaching (Horne, 1997; 2003a; 2003b; Horne & Weinman, 1999).
The SRM does consider the importance of treatments for the illness through the cure/control component of illness representations and some researchers (e.g. Hampson *et al.*, 2000) have explicitly labelled this component as *treatment effectiveness.* However, it does not examine in detail the perceptions of the treatment, and how these may vary in the same underlying condition.

Treatment representations are clearly qualitatively different from illness representations albeit possibly related to patients' implicit model of illness. It is feasible that the self-regulatory patient will not just have their own ideas about their illness but also about treatment being offered. Treatment constitutes a major part of the experience of any chronic illness (in this case, ESRD) so it should be anticipated that patients develop their views and beliefs regarding treatment issues or engage in treatment appraisals and evaluations that complement illness representations.

Horne and colleagues have produced valuable work in the area of medication beliefs that emphasised the importance of patients' beliefs about treatment in general. In a series of studies Horne, Weinman *et al.* (1999; 2002; Cooper *et al.*, 2002) have demonstrated that the concrete experience of different illnesses and their treatments lead to different illness and treatment representations, which in turn are associated with particular patterns of coping and medication adherence.
Although this line of research has focused on beliefs regarding medication, it highlighted the value of treatment beliefs and their relationship to health related behaviours and outcomes.

3.2 ESRD and treatment perceptions

Patients' subjective appraisal of treatments (re: side-effects and intrusiveness) is a key to understanding the balance between benefit and burden of different ESRD treatments. Some aspects of the treatment or side-effects of treatment (e.g. impotence, muscular weakness) have little or no direct effect on morbidity and mortality, yet can be perceived by renal patients as extremely disturbing and may influence broader outcomes such as HQoL. This issue is clearly highlighted in the early literature on treatment stressors.

All individuals with ESRD face a variety of acute and chronic stressors and implicit in many of these stressors is the concept of perceived intrusiveness described earlier. The constraints that ESRD treatments impose can be extensive ranging from the dialysis procedural details through to the dietary and fluid intake restrictions and medication regime. The treatment is also thought to raise issues of independence especially in dialysis as individuals are totally dependent on artificial means of survival (such as the PD machine or PD exchange procedure), on medical professionals (Levy, 2000; 2003), and have little or no hope of recovery of adequate renal function.

There is consensus about which aspects of dialysis treatment are viewed as stressful; for example, activity limitations, fluid limitations and fatigue are frequently reported stressors in HD (Baldree *et al.*, 1982; Gurklis & Menke, 1995; Lok, 1996; Welch & Austin, 1999; 2001) although their ranking may vary from study to study. Welch & Austin (1999) found a consistent trend for HD stressors to become more intense over time. Stressors in HD may be different to those associated with PD. Bihl *et al.* (1988) found that stressors reported by CAPD patients were related to uncertainty of future, limits on vacation and frequent hospitalisation, while in HD patients perceived stressors were as described above, i.e. fatigue and boredom, limitation of fluid intake and length of treatment. Similar findings have been reported in other studies (Eichel, 1986; Fuchs & Schreiber, 1988).

Overall there is some suggestion that PD is less stressful than HD. Wolcott & Nissenson (1988) found that CAPD patients perceived less illness- and treatment-related stress compared to pair-matched HD patients, although Maiorca *et al.* (1995; 1996c) commented that after a number of years there may be burnout of either the PD patient or their caregiver.

As patients age, there may come a point in time when he or she is no longer able to maintain PD.

This work has been useful in identifying the stressful aspects of dialysis however it is limited in several ways: Small samples sizes; recruitment of only hospital HD and CAPD patients such that we know nothing as to how other treatment options such as APD or transplantation are perceived. Most importantly, a number of key questions remained unanswered. The narrow focus of previous work on procedural treatment stress does not allow us to gauge and compare the overall appraisals of treatment impact across the different RRT groups and how these perceptions may be associated with both illness perceptions and broader outcomes such as HQoL.

The different natures of the treatments for ESRD provide an opportunity to investigate in a systematic manner treatment and illness perceptions in the same underlying condition. A better understanding of the interplay between illness and treatment beliefs might not only contribute further to the development of the Leventhal's SRM but also explain better the impact of ESRD.

Beliefs regarding the treatment are likely to be of particular relevance/importance in ESRD since available treatments differ significantly not only technically but also in the intrusion and demands imposed upon patients. It is possible that even though all ESRD patients have the same underlying condition, the experience of different treatment might differentially affect beliefs, perceptions and adjustment. Some patients may conduct a disease vs. treatment effects comparison and this may occasionally influence treatment adherence. A study of 47 hospital HD patients showed significant associations between medication beliefs and medication adherence (Horne, 1997). There have been no studies examining the relationship between treatment perceptions and HQoL in ESRD. The effect of treatment beliefs on outcome may be negative as well as positive. This is illustrated by a recent study in which breast cancer patients who, prior to treatment had strong concerns about the potential adverse effects of their treatment (chemotherapy or radiation), were subsequently more likely to experience adverse emotional and physical consequences (Buick, 1997). An awareness of patients' perception of treatment offers the potential for a better understanding of patients' response to illness and treatment with major implications for research and practice.

Section 4: Symptoms in ESRD

Although the majority of ESRD research conducted in this area has been atheoretical 'symptom' perceptions are in essence fundamental cognitive variables just like illness intrusiveness or the IPQ components discussed earlier. Symptoms are not just the mere manifestation of pathology but reflect individuals' perception, interpretation and processing of physical signs. The quote below clearly illustrates this:

Symptoms belong to the lived experience of the illness rather than being a precise map of the underlying disease' (Benner & Wrubel, 1989).

It is important that studies have also failed to show a substantial impact of demographic, clinical and dialysis related variables on symptom reporting and symptom burden (Barrett *et al.*, 1990; Merkus *et al.*, 1999a). The SRM identity component is perceived to reflect symptom experience. According to the SRM, symptom experience is guiding self-regulation. Symptoms are key factors in the cognitive representation of disease, they are targets for coping and treatment. Symptom amelioration is critical for the appraisal of progress in mitigating the health threat.

The previous literature indicates marked symptom burden in both dialysis and TX patients (Weisborg *et al.*, 2003) Despite advances in the medical management of ESRD, many of the symptoms of renal failure continue to occur in a substantial number of ESRD patients (Killingworth & Van de Akker, 1996). Symptoms related to dialysis procedures or immunosuppressive medication complete the picture of renal symptomatology in ESRD.

A host of physical and psychological symptoms occur in patients on chronic dialysis (Merkus *et al.* 1999a), with considerable variation in their frequency and in the severity with which the symptoms affect the individuals concerned (Brunier, & Graydon, 1993; Curtin *et al.*, 2002; Devins *et al.*, 1993; McCann & Boore, 2000; Parfrey *et al.*, 1988b; 1989; Thomas-Hawkins, 2000).

Fatigue and reduced energy are customarily ranked as the most important and prevalent symptoms for dialysis patients (Barrett *et al.*, 1990; Cardenas & Kutner, 1982; Laupacis *et al.*, 1992; Merkus *et al.*, 1999a; Parfrey *et al.*, 1988b; Srivastava, 1989).
Post-dialysis fatigue is a common and often incapacitating symptom in HD. Interestingly, no routinely measured parameter of clinical or dialytic function appears to predict post-dialysis fatigue. In addition, painful nocturnal cramps (painful involuntary muscular contractions, typically in the lower extremities) interfering with normal life still remain a common complication of HD (Chou *et al.*, 1985; De Vecchi *et al.*, 1994; Lok, 1996; McGee, 1990; Riley & Antony, 1995; Romagnoli *et al.*,. 1998).

Treatment differences in symptom experience are not consistent with some studies reporting either more symptoms in HD compared to CAPD patients (Simmons *et al.*, 1984) or no group differences (De Vecchi *et al.*, 2000; Merkus *et al.*, 1999a; Waiser *et al.*, 1998).
Transplant patients also experience a range of symptoms, mainly resulting from the immunosuppressive medication although some of the renal specific symptoms may still persist (Barbosa *et al.*, 1995; De Geest & Philip, 2000; Forsberg *et al.*, 1999; Franke *et al.*, 1999; Winsett *et al.*, 2001)

The potential impact of these symptoms, particularly occurring in this cumulative manner on other aspects of the individual's life and HQoL is enormous. Symptom experience has been shown to be associated with sleep difficulties, and with mood problems, in particular depression and anxiety (Barrett *et al.*, 1990; Killingworth & Van de Akker, 1996; Sklar *et al.*, 1996; 1999) and to adversely affect physical functioning and HQoL (Curtin *et al.*, 2002; DeGeest & Philip 2000; Hathaway *et al.*, 2003; Kimmel *et al.*, 2003; Laupacis *et al.*, 1992; McCann & Boore, 2000; Merkus *et al.*, 1999a). Determining the causal direction of these associations is problematic as mood difficulties may be driving symptom reporting or vice versa, the experience of symptoms affecting HQoL and physical functioning.

Section 5: Study Aims and Hypotheses in relation to patients' beliefs

This selective literature overview emphasised the importance of patients' beliefs and perceptions but also highlights the need for further research. Several key theoretical and empirical questions have not been addressed.

Little is known about the precise nature of the illness representations components in ESRD patients on different RRTs, their interrelations, their relationship to treatment beliefs and the role and relative importance of these beliefs in predicting various outcomes (i.e. HQoL) in ESRD patients. No studies have examined the dynamic nature of illness and treatment representation formation and changes in these cognitions over the course of ESRD.

It is reasonable to assume that illness representations develop and change over the course of ESRD and that the match or mismatch, at any point in time, between personal experience and personal beliefs could contribute to emotional distress or adversely affect HQoL. In some quarters, this type of distress has been referred to as dissonance (Festinger, 1964).

On the more theoretical angle, the role of treatment beliefs in the SRM model warrants further investigation.

The present study was thus designed to examine some of these issues

a. To assess whether individuals with ESRD develop systematic and coherent cognitive representations of their illness and treatment.

No specific hypotheses were formulated regarding the association between these two sets of beliefs.

b. To investigate whether the different forms of dialysis treatments (HD vs. PD) lead to differences in these illness and treatment beliefs.

c. To compare illness and treatment beliefs between dialysis and transplant patients.

d. To investigate the associations between these illness and treatment beliefs and HQoL.

CHAPTER 4: NEUROPSYCHOLOGY AND ESRD

ESRD and the uraemic state that results from renal failure are known to have a variety of systemic effects including influences on the central nervous system (Fraser & Arieff, 1988). Advanced uraemia and its clinical manifestations believed to be caused by the accumulation of neurotoxins, results in abnormalities in clinical and mental status and neuropsychological performance. The neurobehavioral syndrome in untreated uraemia or chronic renal failure (CRF) is characterised by confusion, inability to concentrate, decreased mental alertness, impaired memory and occasionally in some patients with severe untreated uraemia, hallucinations, tremors, myoclonous, and generalised non-specific complaints progressing to frank encephalopathy with asterixis and seizures. There are characteristic electroencephalographic (EEG) findings, principally loss of alpha rhythm, shift of power spectrum to slow wave activity, and impairment of evoked potential responses. These are non specific findings typical of a toxic metabolic encephalopathy (Cooper *et al.*, 1978; Markland, 1984), but many of these complaints appear to be related to secondary anaemia as they improve with anaemia treatment (Eschbach, 1989).

With the improvements of RRT (dialysis and transplantation) the incidence and severity of these disturbances have declined such that the gross manifestations of advanced uraemia have largely disappeared (Pliskin *et al.*, 2001). Consequently, studies of the dialysis-related epiphenomena such as dialysis encephalopathy and dialysis disequilibrium have drastically declined in recent years (Arieff, 1994; Brown & Brown, 1995).

Current dialysis treatments, PD or HD do not however fully restore normal renal function. Dialysis of either modality rarely replaces more than 5-15% of normal Glomerular Filtration Rate. Consequently patients are restored from a lethal renal failure to one of severe renal insufficiency albeit without the grossly symptomatic uraemia. Even perfectly dialysed patients remain chronically ill as the level of renal function achieved is low compared to normal though adequate to avoid uraemia.

Section 1. Neuropsychology and ESRD - Research findings

Our understanding of neuropsychological (NP) function in ESRD has evolved a great deal in the past 30 years. Early studies in the 1960's and 1970's documented the NP effects of uraemia and CRF, while investigations in the 1970's and 1980's focused on the NP outcomes following initiation of dialysis, the cognitive functioning of HD and PD patients, and correction of anaemia and aluminium toxicity. Recent investigations quantifying dialysis delivery have provided new insights into the NP effects of dialysis and several investigations into the effects of renal transplantation have also appeared.

In order to examine the literature on NP functioning in ESRD, a literature search was performed focusing on studies in which NP testing of ESRD patients was reported. Papers were identified for the present review through electronic databases (MedLine, PsychLit 1960-2000) using a combination of relevant keywords ('*cognitive*'; '*neuropsychological*'; '*deficit*'; '*impairment*'; '*functioning*'; '*dysfunction*'; '*processing*'; '*brain*'; '*norms*'; '*memory*'; '*attention*'; '*concentration*'; '*psychomotor*'; '*language*'; '*verbal*'; '*visual*'; '*speed*'; '*response*'; '*intelligence*'; '*IQ*'; '*abilities*'; '*ESRD*'; '*dialysis*'; '*renal*'; '*failure*'; '*transplantation*') and by manually searching the references of identified papers and other reviews. Single case studies and papers published in languages other than English were excluded.

Seventy-nine studies on the topic of NP functioning in ESRD were identified. Details of the characteristics of the studies are given in Table 4.1 .

Table 4.1: Authors, patient groups, number and list of neuropsychological tests

First author	Year	Design	N	Sample	No Tests	NP tests used†
Blatt	1966	Cross sectional	17	CRF	1	1
Schupak	1967	Cross sectional	25	HD	1	1
Trieschmann	1971	Cross sectional	83	CRF	1	1
Fishman	1972	Prospective	12	HHD	1	4
Gentry	1972	Cross sectional	21	HD	1	2
Greenberg	1973	Cross sectional	24	ESRD	1	1
Winokur	1973	Cross sectional	38	HD	1	1
Hagberg	1974	Prospective	23	HD	9	6, 7, 26, 59, 93, 94, 95, 102
Teschan	1974a	Prospective	44	CRF HD	4	16, 55, 58, 98

First author	Year	Design	N	Sample	No Tests	NP tests used†
Teschan	1974b	Prospective	n/s	HD CRF		16, 55, 98
English	1975	Cross sectional	29	HHD	3	1, 28, 102
Ginn	1975a	Cross sectional	n/s	CRF HD	5	16, 55, 58, 65, 98
Ginn	1975b	Cross sectional	n/s	CRF HD	3	16, 55, 98
Heilman	1975	Cross sectional	24 12	CRF CTL	10	14, 18, 20, 31, 32, 35, 39, 76, 77, 93, 97
Murawski	1975	Cross sectional	39 63 24	HD CRF CTL	1	65
Teschan	1975	Experimental	4	HD	2	58, 98
Teschan	1976	Prospective	n/s	CRF HD TX	3	29, 58, 65
Spehr	1977	Prospective	20	HD	3	30, 74, 89
Kaplan deNour	1977-78	Cross sectional	47	CRF	1	3
Rabinowitz	1978	Cross sectional	17 11	HD CRF	2	3, 92
Ginn	1978	Experimental	19	HD	2	29, 58
Teschan	1979	Prospective	72 70 18 45	CRF HD TX CTL	5	16, 29, 55, 58, 65
Alexander	1980	Cross sectional	28 28	HD CTL	2	65, 66
Freeman	1980	Cross sectional	107 30	HD CTL	1	1
Gilli	1980	Cross sectional	42 8	HD CRF	2	1, 5
Lewis	1980	Prospective	6	HD	5	20, 26, 62, 72, 73
Ryan	1980	Cross sectional	72	CRF	1	
Ziesat	1980	cross sectional	28	HD	1	5
Kenny	1981	Prospective	50	HD	6	20, 55, 62, 85, 86
Ryan	1981	Cross sectional	16 16 16	HD CRF CTL	1	110
Teschan	1981	Experimental	10	HD	2	58, 65
McKee	1982	Prospective	34	mixed CRF HD	3	5, 20, 62
Souheaver	1982	Cross sectional	24 48	CRF CTL (x2)	2	1, 110
Gilli	1983	Cross sectional	54	HD	2	1, 5
Hart	1983	Cross sectional	24 18 20	HD CRF CTL	12	12, 14, 17, 18, 20 24, 57, 62, 67, 84
Ratner	1983	Prospective	20	HD	15	2, 11, 20, 43, 46, 49, 54, 55, 58, 62, 80,

First author	Year	Design	N	Sample	No Tests	NP tests used†
						82, 85, 86, 90
Teschan	1983	Experimental	n/s	HD	1	58
Tennyson	1985	Prospective	10	HD	1	56
Conrad	1987	Prospective	16	HD	1	25
			10	CTL		
Gottlieb	1987	Prospective	9	HD	1	108
Jackson	1987	Cross sectional	57	HD	4	1, 33, 42, 92, 96
Rovelli	1988	Cross sectional	47	HD	4	19, 20, 22, 92
Spargue	1988	Cross sectional	10	HD	5	23, 36, 37, 38, 108
			6	CAPD		
Wolcott	1988a	Cross sectional	17	HD	5	21, 54, 55, 56, 61
			17	CAPD		
Altmann	1989	Cross sectional	27	HD	7	33, 112
Baker	1989	Cross sectional	25	HD	2	1, 3
			9	CAPD		
			10	CRF		
Bolla Wilson	1989	Cross sectional	10	HD	5	12, 48, 54, 55, 62
			10	CAPD		
			8	CRF		
Grimm	1989	Pr- EPO	15	HD	1	54
Wolcott	1989	Pr-EPO	15	HD	8	21, 38, 54, 55, 56, 60, 97, 102
Grimm	1990	Pr-EPO	15	HD-EPO	2	54, 108
			6	HD CTL		
Smith	1990	Prospective	29	HD	1	54
Ventura	1990	Cross sectional	62	HD	2	3, 11
			33	CTL		
Bolla	1991	Cross sectional	21	HD	5	54, 55, 59, 62, 108
Bosch	1991	Cross sectional	5	CRF	1	109
Brown	1991	Pr-EPO	14	HD	8	21, 38, 54, 55, 56, 60, 97, 102
Churchill	1991	Prospective	47	HD	>17	15, 30, 40, 51, 52, 54, 55, 69, 70, 71, 74, 78, 92, 101, 104, 105, 106
Garcia-Maldonado	1991	Cross sectional	28	HD	1	54
			11	CAPD		
			n/s	CTL		
Horina	1991	Pr-EPO	11	HD	3	20, 62, 108
Marsh	1991	Pr-EPO	24	HD	4	21, 38, 55, 56
Bolla	1992	Cross sectional	35	HD	20	8, 12, 21, 31, 40, 45, 48, 50, 54, 55, 57, 62, 79, 81, 82, 86, 87, 102, 107
Buoncristiani	1992	Cross sectional	22	HD	2	20, 54, 108
			15	CAPD		
Churchill	1992	Experimental	22	HD	18	1, 8, 10, 11, 19, 20, 38, 41, 53, 54, 55, 61, 62, 65, 85, 92, 93, 102

First author	Year	Design	N	Sample	No Tests	NP tests used†
Musolino	1992	Cross sectional	26	HD	8	5, 21, 47, 61, 65, 68, 81, 108
Rozeman	1992	Cross sectional	22	CRF	3	54, 55, 111
			74	CAPD		
			25	HD		
Temple	1992	Pr-EPO	9	HD EPO	5	1, 21, 33,44, 63
			9	HD CTL		
Fox	1993	Cross sectional	30	mixed	2	1, 5
				HD		
				CAPD		
Sagales	1993	Pr-EPO	43	HD	1	1
Fazekas	1995	Prospective	30	HD	2	108, 109
Temple	1995	Pr-EPO	9	CAPD	6	21, 33, 54, 62, 63, 100
				EPO		
			8	CAPD		
				CTL		
Brickman	1996	Cross sectional	426	HD	8	5, 20, 27, 31, 53, 55, 65
Fazekas	1996	Cross sectional	20	HD	2	107, 108
			20	CTL		
Kramer	1996	Prospective	15	HD-TX	2	54, 108
			45	CTL		
Pliskin	1996	cross sectional	16	HD	13	1, 5, 13, 20, 31, 39, 43, 48, 53, 55, 62, 82, 86, 91
			12	CTL		
Bremer	1997	Cross sectional	12	HD	3	54, 55, 91
			12	CAPD		
			20	CTL		
Sehgal	1997	Cross sectional	336	HD	1	108
Umans	1998	Cross sectional	10	HD	7	20, 53, 54, 55, 61, 64, 65
			10	CTL		
Yount	1998	Cross sectional	554	mixed	5	27, 53, 55, 62, 65, 69
				HD PD		
				CRF		
Yavuz	2000	Cross sectional	112	HD	1	108
Kutlay	2001	Cross sectional	84	HD	1	108
Groothoff	2002	Cross sectional	98	TX	1	1
			16	HD		
			12	PD		

† See appendix A for NP tests used in the studies

Note: CRF = chronic renal failure; HD = haemodialysis; CAPD = continuous ambulatory peritoneal dialysis; CTL = healthy controls; TX = transplant patients; Pr-EPO = prospective before and after erythropoietin treatment; ns = not stated

This chapter considers the NP impairments associated with ESRD treatments. It is organised into sections on (a) chronic renal failure, (b) haemodialysis, (c) peritoneal dialysis, (d) anaemia corrective treatment and (e) renal transplantation.

Section 2: Chronic Renal Failure and NP functioning

CRF has been found to be associated with NP impairments (see reviews by Hart & Kreutzer, 1988; Osberg *et al.*, 1982; Pliskin *et al.*, 2001). Intellectual deterioration, impaired memory, and reduced mental efficiency, psychomotor speed and attention have been found on neuropsychological testing in CRF patients (Bosch & Schlebusch, 1991; Ryan *et al.*, 1980; 1981; Souheaver *et al.*, 1982).

Results from early studies, conducted in the late 1970's should be treated cautiously given their shortcomings related to insufficient methodological documentation of assessments, sample and methods, and the inclusion of patients with much more advanced uraemia than more recent studies (Blatt & Tsusima, 1966; Compty *et al.*, 1974; Fishman & Scheider, 1972, Greenberg *et al.*, 1973; Kaplan De Nour *et al.*, 1977; Malmquist *et al.*, 1972; Rabinowitz, & van de Spuy, 1978; Sand *et al.*, 1966, Trieschmann & Sand 1971). Those early studies are thoroughly reviewed by Hart & Kreutzer (1988) and Osberg *et al.* (1982) and to whom the reader is directed for more detail of this work.

Section 3: Dialysis and NP functioning

Studies of the NP performance of dialysis patients have involved comparisons with pre-dialysis CRF patients, healthy controls and existing test norms.

Dialysis patients have generally been found to perform better that non-dialysed CRF patients (Baker *et al.*, 1989; Hart *et al.*, 1983; Ryan *et al.*, 1981) albeit not consistently so (Rozeman *et al.*, 1992; Yount *et al.*, 1999).

The level of severity of renal failure is a critical confounding factor in evaluating these studies. Teschan *et al.*, (1979) reported that haemodialysis patients performed significantly better than pre-dialysis patients with high creatinine levels on memory and attention tasks but their performance fell significantly short of that of pre-dialysis patients with low creatinine concentrations. Similarly, Gilli *et al.*, (1980) found that pre-

dialysis patients with residual renal function (5.9 ml/min creatinine clearance) had higher memory, full scale IQ and Performance IQ scores than dialysis patients with absolutely no residual renal function. One may speculate that unless creatinine clearance falls below a certain level indicating severe or near-terminal renal failure, the NP performance of pre-dialysis patients might not necessarily be inferior to that of dialysis patients. The lack of sufficient biochemical data in these studies prevents further examination of this hypothesis. In addition these studies should be viewed with caution due to their small sample sizes and multiple statistical comparisons with no apparent adjustments of significance levels.

3.1 HD and cognitive functioning

Prospective studies indicate that patients' NP status improves with the initiation of HD (Gilli & DeBastiani, 1983; Hagberg, 1974; McKee *et al.*, 1982; Teschan *et al.*, 1974a). The improvement does not fully restore cognitive functioning to pre-morbid levels, and some reports indicate that cognitive dysfunction persists after the initiation of HD, in comparison to normative data or controls. In order to examine the impact of HD on different NP domains, the NP performance of individuals on HD is discussed according to NP domain examined.

Studies are summarised in terms of (a) measures of general intelligence (b) memory, (c) attentional processes and (d) other cognitive abilities and (e) generalised rating scales.

3.1.a Measures of General Intelligence

On intelligence tests, such as the Weschler's Adult Intelligence Scale, HD patients show a deterioration of the total Intelligence Quotient although mean scores are still close to norms and fall in the range of low average IQ (Baker *et al.*, 1989; Davis & Masey, 1973; Fishman & Schneider, 1972; Gilli & De Bastianni, 1983; Greenberg. 1973; Horina *et al.*, 1991; Jackson *et al.*, 1987; Maher *et al.*, 1983; Pliskin *et al.*, 1996; Schupak *et al.*, 1967; Temple *et al.*, 1992; Ventura *et al.*, 1990; Winokur *et al.*, 1972).

The decline in IQ scores is largely due to slowness in executing the performance tasks, which are timed. Verbal tests, requiring (well)-learned knowledge do not tend to show any decline. Given this tendency it is not surprising that some studies have reported a large discrepancy between Verbal and Performance IQ (English *et al.*, 1978; Temple *et*

al., 1995; Ventura *et al.*, 1990), a pattern reflective of cortical dysfunction (Nissenson, 1992b), and dementing illnesses.

Deterioration indices based on WAIS scores have also been used. English *et al.* (1978) reported the mean Weschler deterioration quotient of HD patients was outside the normal range. Baker *et al.* (1989) and Jackson *et al.* (1987) used a deterioration index based on reading scores as a marker of pre-morbid intellectual level and both concluded that there is a slightly higher incidence of deterioration in long-term HD and CAPD patients than would be expected in a random sample of the population.

Studies, which included control groups rather than norms, have produced mixed findings. No significant WAIS differences between HD patients and matched controls were reported by some investigators (Freeman *et al.*, 1980; Pliskin *et al.*, 1996) while others found that HD patients had significantly lower scores in WAIS tasks in particular with respect to performance tasks (Groothoff *et al.*, 2002; Ventura *et al.*, 1990).

3.1.b Memory

- Verbal memory

A large number of studies using a variety of tests assessed verbal memory function in HD patients. Test procedures have included standardised measures of verbal memory (e.g. Rey Auditory Verbal Learning Test) requiring immediate and delayed recall of words, digits, sentences or stories. On the whole, study findings suggest that verbal memory function is diminished particularly in registration, learning, and reproduction of recently acquired data, the 'working' memory being more vulnerable than information retrieval from long term memory.

Studies using control groups showed that HD patients perform less well than controls in verbal memory tasks (Altmann *et al.*, 1989; Buoncristiani *et al.*, 1993; Fazekas *et al.*, 1996; Musolino *et al.*, 1992; Rozeman *et al.*, 1992; Teschan *et al.*, 1979; Wolcott *et al.*, 1988a), although observed mean scores for HD patients do not always indicate deficits relative to norms (Brown *et al.*, 1991; Churchill *et al.*, 1992; Hagberg, 1974; Wolcott *et al.*, 1989).

The literature is however by no means consistent. Contrary findings of uncompromised verbal memory function have also been reported (Hart *et al.*, 1983; Marsh *et al.*, 1991; Pliskin *et al.*, 1996; Ryan *et al.*, 1981).

- Non-verbal memory

A number of studies have evaluated non-verbal memory in HD patients (see Table 4.1). Various visual memory tests have been used typically involving the reproduction of designs and figures (e.g. Benton Visual Retention test) and/or recognition of designs and figures.

Performance in visual memory tasks appears to be compromised in HD patients, particularly with regard to reproduction tasks (Altmann *et al.*, 1989; Bolla *et al.*, 1992; Fazekas *et al.*, 1996; Hart *et al.*, 1983; Musolino *et al.*, 1992; Ratner *et al.*, 1983; Rozeman *et al.*, 1992; Ventura 1990; Ziesat *et al.*, 1980). No deficits have been found in visual recognition tasks (Hart *et al.*, 1983) while others found equivalent visual memory abilities in HD and control participants (Pliskin *et al.*, 1996).

There are important methodological issues, which may in part account for inconsistencies in the findings. In the majority of the studies reporting memory deficits, NP assessments were taken at variable times mainly either prior to a dialysis run when uraemia is most severe, to immediately after when adverse physical states such as fatigue, nausea are frequently documented. This issue is particularly important as different results have been found depending on the timing of NP assessment relative to the dialysis cycle. Studies in which assessments were taken at 24-hours post-dialysis tend to show no memory deficits (Marsh *et al.*, 1991; Pliskin *et al.*, 1996; Wolcott *et al.*, 1989). For example, Pliskin *et al.*, (1996) found no significant difference between adequately dialysed HD patients (assessed at 24-hours post-dialysis) and matched controls in neither verbal nor visual memory tasks for immediate and delayed conditions, as well as percent of information retained. Exceptions are four studies (Fazekas *et al.*, 1996; Hart *et al.*, 1983; Ratner *et al.*, 1983; Rozeman *et al.*, 1992) in which memory impairments, particularly pronounced in visual memory tasks were evident in HD patients at 24 hours post dialysis. Hart *et al.* (1983) found a significant impairment only in one of the five memory tests administered (visual memory task), with a tendency for impairment in a second.

Other methodological differences in HD patients' clinical characteristics, such as time on dialysis or adequacy of dialysis delivery are also likely to explain the different findings reported. For example, in the study by Hagberg (1974) HD patients were on treatment for less time (12 months) than participants in the previously referenced studies. Ventura *et al.* (1991) who compared memory functioning in HD patients who had been on treatment for either more or less than four years, reported significant better memory functioning for the group who had been on dialysis for less time. Pliskin *et al.* (1996) attributed the lack of significant NP differences between adequately dialysed HD patients and controls to adequate dialysis delivery. As however sample sizes of HD and control groups assessed in all these studies were very small (ranging from 10 to 16), it also plausible that studies were under-powered to detect significant differences.

Longitudinal studies do not indicate memory deterioration in HD patients although methodological qualifications such as the lack of comparison groups and small sample sizes make these findings difficult to interpret. Gilli & Bastianni (1983) reported a decline in memory quotient over periods of at least 1 year but McKee *et al.* (1982) and Hagberg (1974) found no evidence of deterioration in memory over period of 22 months and 6 months respectively. Patients on dialysis for 6 months versus 4.3 years performed similarly, although the latter group did tend to score lower on recall tasks (McKee *et al.*, 1982).

3.1.c Attention - Concentration

A wide range of NP tests measuring attention, concentration, and psychomotor speed has been used. A basic distinction can be drawn between simple tests of attention (e.g. Trailmaking part A) and more difficult or complex tests of attention such as Trailmaking part B. Study findings differ according to the specific NP tests used, and the point of reference on which comparisons were made, i.e. normative data or healthy controls.

Attention impairments have been noted mainly in the performance of more complex attention tests rather than the more simple tasks. Earlier research (Alexander *et al.*, 1980;Ginn, 1975; Ginn *et al.*, 1975; Murawski *et al.*, 1975; Teschan *et al.*, 1979) and several recent studies have shown that dialysis patients perform significantly worse than control groups on tasks of complex attention and mental tracking such as Trailmaking B

or Stroop test (Altmann *et al.*, 1989; Bremer et al., 1997; Brown *et al.*, 1991; Churchill *et al.*, 1992; Fazekas *et al.*, 1996; Grimm *et al.*, 1990; Krammer *et al.*, 1996; Marsh *et al.*, 1991; Musolino *et al.*, 1992; Pliskin *et al.*, 1996; Ryan *et al.*, 1981; Rozeman *et al.*, 1992; Wolcott *et al.*, 1988a, Yount *et al.*, 1999). However, some other measures of complex attention such as the Category test or the WAIS digit symbol test do not show deficits (Bremer *et al.*, 1997, Hart *et al.*, 1983, Pliskin *et al.*, 1996, Umans & Pliskin, 1998). These inconsistencies may partly be attributed to small sample sizes assessed.

Findings on HD patients' performance in relation to existing norms are mixed with some studies showing clear deficits (Ratner *et al.*, 1983; Rozeman *et al.*, 1992) and others not, with the observed mean scores falling in average or low average range (Brown *et al.*, 1991; Krammer *et al.*, 1996; Pliskin *et al.*, 1996; Umans & Pliskin, 1998; Wolcott *et al.*, 1989).

Evidence regarding less complex attention tasks is equivocal. Some studies recorded no deficits in simple attention or vigilance tasks such as Trail Making Part A for HD patients relative to healthy controls (Buoncristiani *et al.*, 1993; Hart *et al.*, 1983; Pliskin *et al.*, 1997; Ryan *et al.*, 1981; Umans & Pliskin, 1998; Wolcott *et al.*, 1989). Opposite findings have also been reported (Garcia-Maldonado *et al.*, 1991; Krammer *et al.*, 1996; Rozeman *et al.*, 1992).

Results of studies that employed normative comparisons to evaluate the performance of HD patients in simple tasks of attentional processes are conflicting. Deficits were documented only when patients were assessed prior to their dialysis session or at unspecified times (Churchill *et al.*, 1992; Garcia-Maldonado *et al.*, 1991; Smith *et al.*, 1990; Wolcott *et al.*, 1988a). Mean scores were within normal range when assessments were taken at 24-hours post-dialysis and after anaemia corrective treatment (Brown *et al.*, 1991; Grimm *et al.*, 1990; Wolcott *et al.*, 1989).

3.1.d Other cognitive abilities

Language and selective verbal functions, orientation, and constructional abilities (e.g. fluency, conceptual reasoning) appear to show no impairments as a result of HD (Altmann *et al.*, 1989; Bremer *et al.*, 1997; Brown *et al.*, 1991; Churchill *et al.*, 1990;

1992; Fazekas *et al.*, 1996; Jackson *et al.*, 1987; Marsh *et al.*, 1991; Wolcott *et al.* 1989; Ratner *et al.*, 1983; Pliskin *et al.*, 1996; Wolcott *et al.*, 1989).

Findings regarding motor abilities appear to vary according to the specific tasks examined. Some studies reported bilateral impairments in tasks of gross motor strength such as grip strength (Pliskin *et al.*, 1996; Ratner *et al.*, 1983) and tasks of visual motor co-ordination requiring fine motor movement, i.e. grooved pegboard (Churchill *et al.*, 1992; Ratner *et al.*, 1983). In contrast, findings of intact performance or comparable to that of controls were found in manual dexterity tasks such the finger tapping and the purdue pegboard test (Churchill *et al.*, 1991; Hart *et al.*, 1983; Pliskin *et al.*, 1997; Ryan *et al.*, 1981).

3.1.e General rating scales and inventories

This section considers findings on generalised rating scales used to form gross diagnostic impressions. These are included even though such measures should not be regarded as NP tests. They provide crude estimation of general cognitive function and given their low sensitivity (Anthony *et al.*, 1982) they are more suited as screening instruments (e.g. to exclude patients with dementia) rather than measures of cognitive abilities.

Contradictory findings have been reported for measures of general cognitive functioning such as Minimental State Examination (MMSE) with some studies reporting normal mean scores for HD patients and other studies documenting cognitive deficits (Gottlieb *et al.*, 1987; Krammer *et al.*, 1996; Kutlay *et al.*, 2001; Sehgal *et al.*, 1997).

The timing of test administration in relation to the dialysis cycle appears to be critical factor that differs between studies. Findings of 'normal' MMSE scores have been reported when HD patients when assessed either immediately after a dialysis session (Musolino *et al.*, 1992) or at 120 minutes after a dialysis session (Buoncristiani *et al.*, 1993), and at 24 hours post-dialysis (Grimm *et al.*, 1990) albeit not consistently so (Fazekas *et al.*, 1995; 1996). In contrast, MMSE scores indicative of cognitive impairment were found when HD patients were assessed prior their dialysis session (Gottlieb *et al.*, 1987; Sehgal *et al.*, 1997). For example, Sehgal *et al.* (1997) assessed a large sample of 336 HD patients during dialysis and noted that the prevalence of

cognitive impairment is markedly higher than that of the general population after controlling for age and education. They found that 30% of patients scored in the range of mild to moderate impairment.

Studies that used a control group reported significantly lower mean MMSE scores for HD patients assessed at 24-hours post-dialysis (Fazekas *et al.*, 1995; 1996, Krammer *et al.*, 1996).

3.2 Acute NP changes in HD patients

HD is an intermittent treatment with the result that renal clearance changes greatly from pre- to post-dialysis. This is reflected in significant physiological and biochemical changes occurring during haemodialysis (Lewis *et al.*, 1980; Ratner *et al.*, 1983; Spehr *et al.*, 1977). It is logical to assume that the patients' ability to perceive, process, and organise information could fluctuate across the dialysis cycle.

The subsidiary question is whether any observed cognitive changes are correlated with specific components of the physiological changes such as the decrease of blood urea nitrogen, creatinine and potassium following this general line of reasoning. One would hence expect that in HD patients NP performance would be optimal on a midweek non-dialysis day to avoid acute effects of dialysis or of its lack during the long weekend, and then worst on the first dialysis day of the week.

The data reviewed above tends to support this contention, with NP differences between HD and controls tending to occur prior to dialysis and no longer been apparent 24-hours after the completion of dialysis. Such fluctuations should not apply to (nearly continuously dialysed) PD patients for whom their nearly stable biochemical profile would predict no temporal changes in their cognitive functioning.

There is indeed some evidence that NP performance in HD patients parallels the treatment biochemical profile with systematic differences through the dialysis cycle (Osberg *et al.*, 1982). Acute changes in cognition have been reported from immediately pre- to 24-hours post-dialysis (Buoncristiani *et al.*, 1993; Ginn *et al.*, 1975a; Lewis *et al.*, 1980; Spehr *et al.*, 1977; Teschan *et al.*, 1974a). The evidence seems to suggest that 24-hours post-dialysis is a time when cognitive function is optimal during the interdialytic interval. Little variation has been found over shorter time intervals through the dialysis cycle (Conrad *et al.*, 1987; Tennyson *et al.*, 1985). NP improvements have

been noted mainly in tasks of attention concentration and psychomotor abilities. In contrast, Ratner *et al.* (1983) found improvements in some but not all NP tests used (7 out of 14) from before dialysis to 20-hours post-dialysis. As these changes in NP tests did not relate to changes in serum biochemistry levels the authors attributed the improvements to learning effects.

According to the early work of Teschan and co-workers, the adequacy of dialysis may be monitored by repeated NP measurements. NP scores have been found to vary directly with degree of uraemia with choice reaction time and continuous performance tests being sensitive indices in CRF patients not yet on dialysis (Teschan *et al.*, 1979). Evidence on dialysed patients is unfortunately conflicting and inconsistent. Study findings are consistent in noting the lack of one-to-one correspondence between NP improvements and biochemical/physiological changes across dialysis (Ratner *et al.* 1983). Observed correlations were found to be generally small and non significant, perhaps due to the relatively small number of patients studied.

All above studies are limited by two main methodological flaws that constrain the generalisability and validity of their findings. Some relate to issues raised earlier, i.e. small sample sizes that undermine their power to detect significant effects, and insufficient control for salient clinical factors such as dialysis adequacy.
Most importantly though, their methodological limitations relate to study design, in that these investigations have failed to rule out factors other than treatment that might be driving the acute NP changes. It is also not possible to rule out the competing hypothesis that the observed acute NP improvements are due to learning or practice effects, by not having a concurrently assessed control group. The retest effect, defined as an improvement in performance after repeated presentation of a test, is a general problem for longitudinal NP studies (McCaffrey & Westervelt, 1995; Mitrushina & Satz, 1991). Effects of implicit or explicit learning, as well as of anxiety reduction are always an issue when the same task is repeated more than once. The sole use of parallel forms for the NP tests, employed by most of the previous research is not considered an adequate manipulation of test retest effects, as it cannot take account of strategy changes (McCaffrey & Westervelt, 1995).

Another competing hypothesis would be that factors other than biochemical changes might be driving the observed changes in cognitive functioning across the dialysis

cycle. Mood may influence motivation to perform tasks, and stress, or fatigue may transiently influence NP performance. Subjective reports of the physical state appear to echo their biochemical profile with patients often reporting that they feel tired and lethargic the day of hemodialysis and best the day after haemodialysis. It would therefore be valuable to compare cognitive functioning in these two days (Smith & Winslow, 1990).

The need to control for intra-individual variability with regard to factors such as fatigue and mood becomes imperative if we are to understand NP functioning in dialysis. Such measures have not been included in the studies reviewed here and hence the extent to which they might have influenced the observed findings is unclear.

In view of these methodological shortcomings it is appropriate to conclude that evidence on acute NP changes is inconclusive and appears to raise more questions regarding the temporal course of cognitive abilities through the dialysis cycle.

3.3 PD and cognitive functioning

There have been few studies on the cognitive functioning of patients on PD. Most previous studies have recruited only CAPD patients, hence there is a complete paucity of data on the NP functioning of patients on APD.

Study findings for CAPD patients indicate that compared to norms, CAPD patients present with mild NP impairments in attention, concentration, and verbal memory (Baker *et al.*, 1989; Kenny *et al.*, 1981; Rozeman *et al.*, 1992; Temple *et al.*, 1995; Wolcott *et al.*, 1988a). Mean performance in most of the NP tests used fell within or borderlined low average range.

Findings of studies using control groups are conflicting with one report of equivalent cognitive functioning (Buoncristiani *et al.*, 1993) between groups and two reports of inferior NP performance in the CAPD group mainly in tests of attention and concentration (Bremer *et al.*, 1997; Rozeman *et al.*, 1992). There is only one longitudinal NP evaluation of PD patients. Kenny *et al.* (1981) repeatedly assessed patients while on intermittent PD and after 2, 12, 18 and 24 months on CAPD. Significant NP improvements in attention and concentration were found at 6 and 12

months for the group as a whole, although NP impairments relative to norms were still evident for approximately 1/3 of patients. The validity of these findings is questionable as the study was conducted in the early days of CAPD and since then substantial technical improvements have been achieved and the findings could reflect learning the tests with repeat performance

Other inconsistencies in findings are likely to be largely due to studies' methodological qualifications, the most important being the small sample sizes recruited. Data interpretation is further constrained by the inclusion of both HD and CAPD patients in some reports (Bremer *et al.*, 1997) and the lack of documentation of relevant clinical parameters such as dialysis adequacy delivery and comorbidities, in the recruited samples. Lastly, research has overlooked certain areas of cognitive functioning such as non-verbal (visual) memory or psychomotor abilities. The assessment of these cognitive abilities in this population is hence a question for future research.

3.4 HD and PD comparisons

Comparing the NP impact of the alternative dialysis modalities is important as they have different physiological and biochemical processes. PD as described earlier is a continuous therapy in that it clears wastes to a variable degree whenever PD fluid is dwelling in the abdomen. By contrast, HD is an intermittent therapy, which provides no replacement for lost renal function between treatments but can provide above normal levels of clearance during dialysis; in other words biochemical indices vary greatly from immediately before to during and after dialysis. The two treatments also differ in their efficacy to remove specific molecules as discussed earlier (see Chapter 1; section 2.3). Thus if NP functioning depends differently on the peak concentration of toxins, on their rates of change over time or their time-averaged concentration, one might expect differences between HD and PD (Pliskin *et al.*, 2001).

There have been few comparative NP evaluations of HD and PD patients. In addition, in all previous investigations only hospital HD and CAPD patients were recruited so there is no data on how other treatment modalities such as home HD and APD fare in relation to the hospital HD and CAPD.

Studies comparing cognitive functioning between patients on hospital HD and CAPD have produced inconsistent and contradictory findings. Some studies have shown more efficient cognitive functioning in CAPD patients compared to hospital HD (Buoncristiani *et al.*, 1993; Garcia-Maldonado *et al.*, 1991; Wolcott *et al.*, 1988a; Yount *et al.*, 1998) and others have reported no significant differences between groups (Rozeman *et al.*, 1992).

Procedural differences in the timing of the NP assessment relative to the cycle of dialysis appear to account for these contradictory findings. This point is particularly important because as described above systematic behavioural and electrophysiological differences accompany alterations in uraemic status over the period of days between HD sessions. Differences in NP performance favouring PD patients were found only when HD patients were assessed immediately prior to their dialysis. No systematic differences were evident when NP assessments were scheduled on a non-dialysis day (24-36 hours post-dialysis). The following studies illustrate this point.

The first comparative study was conducted by Wolcott *et al.* (1988a). Results indicated that there are detectable differences in performance on NP tests of verbal memory and attention/concentration between HD and matched CAPD patients. Even though the sample was small, CAPD patients had better NP scores than HD patients albeit their mean performance was still impaired compared to norms. The authors concluded that CAPD might be more efficient in reversing the cognitive deficits associated with uraemia. However HD patients were assessed thirty-to-sixty minutes before beginning a dialysis treatment. As discussed earlier this is probably a time when HD patients are at their worst.

Rozeman *et al.* (1992) who assessed pre-dialysis, CAPD and HD patients 24-40 hours after their dialysis session by means of neurophysiological and NP measures, failed to demonstrate a better cognitive performance for CAPD. All groups differed significantly from controls but there were no significant differences between groups. A minor trend toward better cognitive performance of CAPD patients relative to HD patients on the Colour Vigilance test, an index of attention and response speed, was found but it did not reach statistical difference.

In studies comparing NP performance of CAPD patients to that of HD patients assessed both prior and shortly after dialysis, reported significant differences in favour of the CAPD group only in relation to the pre-dialysis NP scores of HD patients (Buoncristiani *et al.*, 1993). The authors of this study conclude that CAPD is better than HD since patients are able to steadily maintain normal or within normal limits cognitive function, whereas in hemodialysis, cognitive functioning is restored only transiently, in the post-dialysis phase. Caution is however warranted in interpreting these findings, as practice effects have not been ruled out.

Yount *et al.* (1998), in the most recently published study, reported that CAPD patients performed significantly better on measures of focused attention than HD patients. Performance of memory tasks and tests of sustained attention was equivalent in both dialysis groups. Treatment modality was found to be a significant predictor of attention (favouring PD over HD) but as it accounted for only 1% increase in the explained variance, the authors concluded that this was not clinically significant. Although the study benefits from an exceptionally large sample of CRF, PD, and HD patients, the lack of specification of NP test administration for the HD group constrains data interpretation.

The possibility of pre-dialysis differences in cognitive function of patients chosen or opting for hospital HD and CAPD should be considered when evaluating treatment-modality differences. The modality selection process or assignment method may contribute to this potential source of bias. One might speculate that patients with higher cognitive function may opt for, or may be chosen for a home dialysis modality (such as CAPD), though there is presently no evidence to support this contention.

Moreover in general, studies comparing HD and PD are difficult to interpret because of the small sample sizes used, the absence or insufficient adjustment for casemix, and other confounding factors likely to impinge upon NP performance. Sociodemographic and clinical factors such as age, education, adequacy of dialysis, comorbidities, which have been shown to impact heavily on NP performance have not always been adequately examined (Hart & Kreutzer, 1988; Pliskin *et al.*, 1996; 2001). Given the methodological shortcomings of previous research, it remains unclear whether there are general differences in cognitive functioning between well dialysed HD and PD patients. It is difficult to identify the NP processes which are likely to be implicated in the

cognitive dysfunction seen in dialysis patients, and reliably ascertain the presence or not of modality induced cognitive deficits, as well as the merits of different dialysis treatments.

3.5 Anaemia and cognitive functioning

The possible cognitive deficits associated with ESRD may not be explained solely by uraemia but also by anaemia, that almost invariably accompanies ESRD (Nissenson, 1989). Anaemia is generally severe and can be detected in over 90% of patients with ESRD. It is caused by a relative deficiency of erythropoietin. Severe anaemia has been shown to be directly associated with cognitive dysfunction, mood disturbances and reduced energy. Anaemia corrective treatments, such as the use of androgens and blood transfusions, are problematic in many patients and rarely completely correct anaemia. Furthermore the risks associated with transfusions, including the development of cytotoxic antibodies and transmission of infection (hepatitis, human immunodeficiency syndrome) are substantial. The development of recombinant human erythropoietin (rHuEPO) has however provided an effective treatment to reverse anaemia in most ESRD patients (Eschbach *et al.*, 1989) and thereby possibly improving attention, mental processing speed, learning, memory, energy and mood.

Studies that have used neurophysiological and NP tests in dialysis patients to measure the effect of increasing haematocrit through rHuEPO (thus improving cerebral oxygen delivery) on cognitive function are summarised in Appendix B.
In most of these studies cognitive function was assessed in patients after haematocrit was increased to 30 – 36%, indicating partial correction of anaemia as haematocrit levels are not completely normalised. Even though achieved haematocrit targets were similar, study follow-up times ranged from 2 to 12 months. This may be an important methodological consideration for the detection of NP improvements after haematocrit stabilisation.

Studies have shown that relative to normative data, dialysis patients' NP scores are in the low average or below average range at baseline, i.e. before rHuEPO treatment but after anaemia correction normal NP functioning results (Brown *et al.*, 1991; Wolcott *et al.*, 1989). Significant NP improvements were found in general intelligence measures (Temple *et al.*, 1992; 1995) and tests of attention, concentration and psychomotor speed

such as the Symbol Digit Modality Test, Trail Making Test (Brown *et al.*, 1991; Horina *et al.*, 1991; Marsh *et al.*, 1991; Temple *et al.*, 1992; Wolcott *et al.*, 1989) at 3 and 12 months follow-up. Verbal learning, fluency and memory followed a similar pattern of improvement but changes have not always reached significance (Brown *et al.*, 1991; Horina *et al.*, 1991; Marsh *et al.*, 1991; Temple *et al.*, 1992; Wolcott *et al.*, 1989).

Several explanations can be brought forward to account for these findings. First, it is plausible that the observed trends for language and learning may be due to improved attention capacity. Also, methodological issues related to small sample sizes also need to be considered, as studies might have been under-powered to detect significant changes. Moreover, the absence of control group in most of these studies further constrains data interpretation as observed improvements could be explained as learning or practice effects.

Section 4: Cognitive functioning in Transplantation

Most of the existing research on the NP aspects of kidney function has focused on the effects of dialysis treatment (Pliskin *et al.*, 2001) or the cognitive functioning in paediatric transplant populations (Fennell *et al.*, 1984; Lawry *et al.*, 1994; Mendley & Zelko, 1999). There have been only a few studies that have examined NP aspects of kidney transplantation in adults (Farmer, 1994).

Teschan *et al.* (1976) studied 8 patients repeatedly during dialysis treatment and during 4 -23 months following kidney transplantation. They found a significant improvement in EEG, choice reaction times and memory test scores following kidney transplantation. Teschan *et al.* (1979) compared CRF, dialysis and transplant patients to normal controls and found transplant patients to perform at levels comparable to those of normal controls on the attention and memory NP tasks. However the authors did not present comparisons between the dialysis and transplant groups.

Kramer *et al.* (1996) reported improved cognitive functioning as measured by the Trailmaking test and MMSE in a group of 16 HD patients before and after transplantation as compared to age-matched healthy subjects. Prior to transplantation,

HD patients performed significantly worse than controls on both NP tests, but performance between groups did not significantly differ following transplantation.
There are methodological weaknesses in previous studies that limit interpretation and generalisability of findings. These relate to the small sample sizes, the NP tests used and insufficient adjustment for casemix and other confounding factors likely to impinge upon NP performance. Measures used did not assess cognitive domains found to be particularly impaired in ESRD patients (Pliskin *et al.*, 2001) such as complex attention and mental processing or are not considered to be sensitive enough to subtle cognitive deficits, i.e. MMSE (Anthony *et al.*, 1982).

Given these shortcomings a reinvestigation of this area with improved methodology is warranted to ascertain how the NP performance of TX patients compares to that of patients still on dialysis and to verify whether TX restores NP performance relative to normative data.

In addition, there are several empirical questions that have not been addressed in previous research. These included a comparison of the NP functioning between cadaver (CAD) transplant recipients and living related donor (LRD) transplant patients. It has been demonstrated that these two types of transplant show different clinical outcomes regarding patients and graft survival (see Chapter 1; section 2.4.b). One question addressed in this study was whether these differences are reflected in NP performance.

Another pertinent question in TX relates to the NP consequences of anti-rejection medication. The clinical benefits of transplantation are achieved at the cost of lifelong therapy with immunosuppressive drugs such as glucocorticoids and cyclosporin or Tacrolimus, resulting in CNS side-effects. These may range in severity and may include symptoms such as involuntary fine tremor, headache, insomnia, ataxia, parasthesias, impaired visual acuity and profound disturbances in mental status and focal neurologic deficits. Neurocognitive dysfunction such as delirium, dementia and deficits in memory and attention has been documented in organ transplant recipients receiving cyclosporin or tacrolimus (Christe, 1994; Craven, 1991; Trzepacz & Dimartini, 2000). While the neurological complications of these treatments are well-documented (Burke *et al.*, 1994; Cohen & Raps, 1995; Craven, 1991) and there is evidence on neurotoxic effects and brain imaging changes with both Cyclosporin and Tacrolimus (Bartynski *et al.*, 2001), no studies have examined their impact on NP functioning.

Section 5: Limitations of previous research

The published literature in this field is beset with significant methodological and conceptual limitations.

1. Extremely low sample sizes.

2. Sociodemographic variables (such as patient age, education) have not been controlled for.

3. Disease factors (e.g. comorbidities; disease and treatment duration) have not been accounted for.

These issues have been highlighted by Pliskin *et al.* (1996; 2001). Pliskin attributed the NP deficits reported in previous research to lower and inadequate levels of dialysis delivery, uncorrected anaemia, unrecognised comorbidities and inadequate methodological control rather than ESRD per se.

The effects of anaemia on cognitive functioning have been discussed earlier. Furthermore many comorbid conditions, which are now common in ESRD patients (e.g. coronary artery disease, diabetes, uncontrolled hypertension), also contribute to NP dysfunction,

4. Dialysis adequacy delivery is another particularly important consideration overlooked in previous research.

Medical standards of dialysis adequacy for example have changed dramatically (Pliskin *et al.*, 2001). Thus many patients studied earlier may have been relatively underdialysed at the time of assessment compared to current standards for dialysis prescription (Gotch & Sargent, 1985; Lowrie *et al.*, 1981). Adequacy of dialysis remains an elusive term yet to be defined. Adequate dialysis refers to the "minimal effective dose" of dialysis that achieves stated clinical goals and standards regarding clearance of uraemic toxins. The vast majority of previous studies have failed to quantify or to report dialysis delivery, thus allowing for the possibility that patients might have been underdialysed at the time of assessment. The deficits reported in some studies may hence reflect an inadequate dialysis delivery. This is particularly the case for the older studies conducted before the establishment of minimal dialysis prescription suggested by the results of National Co-operative Dialysis Study (NCDS; Gotch & Sargent, 1985). This issue is made more

complex because dialysis standards have since crept upwards with more recent evidence in support for increased HD dose and PD dose prescriptions (CANADA-USA Peritoneal Dialysis Study Group, 1996; Port *et al.*, 1998; Szczech *et al.*, 2001). Indeed, no studies on PD patients recorded PD adequacy levels and only a few of the studies on HD patients reported dialysis prescription based on urea kinetic modelling (Churchill *et al.*, 1991; Churchill *et al.*, 1992; Kramer *et al.*, 1996; Pliskin *et al.*, 1996; Umans & Pliskin, 1998; Wolcott *et al.*, 1988a). Their findings seem to suggest well dialysed HD patients manifest little evidence of clinically significant NP impairments. Recent research found that ESRD patients receiving dialysis treatment at levels consistent with current NCDS standards and verified by urea kinetic modelling (KT/V = 1.1 or greater), did not have NP dysfunction when compared to well matched controls (Pliskin *et al.*, 1996). Unfortunately the small sample sizes and other specific characteristics (e.g. lower educational status) of HD responders hinders drawing firm conclusions about the presence of NP deficits in well dialysed patients based on these otherwise methodologically sound studies.

5. The clinical management of renal patients today bears little resemblance to that of renal patients in the 70's and 80's when the vast majority of NP studies were conducted. The current ESRD population is now quite different than their counterparts 10 or 20 years ago. Current dialysis patients are older, often less educated, and of lower socio-economic status, more chronically ill, more apt to have had dialysis instituted earlier in the course of renal failure and more apt to receive adjunctive treatment to control secondary conditions such as hyperparathyroidism and anaemia.

6. The time of the NP assessments relative to the cycle of dialysis in the case of HD has not been controlled.

Section 6: The effect of NP functioning on other outcomes

Studies have reported significant associations between NP performance and HQoL outcomes (Bremer *et al.*, 1997; Fox *et al.*, 1993; McSweeny *et al.*, 1985; Tarter & Switala, 2000; Yavuz *et al.*, 2000). Bremer *et al.* (1997) found that NP impairments are not only predictive of emotional wellbeing and unemployment but play a mediating role between ESRD and vocational rehabilitation.

Despite these findings, evaluation of the NP implications of ESRD and associated treatments, once a popular research agenda, has been overlooked in recent literature and has rarely been integrated into renal treatment outcome research.

Section 8: Subjective Cognition

The study of NP outcomes in ESRD patients would not be complete without considering patients' appraisal of their cognitive abilities. This area has been termed subjective cognition, and it is by definition more closely related to patients' experience.

It is not uncommon for dialysis patients to report cognitive complaints particularly with memory and concentration (Brickman *et al.*, 1996). These complaints are often anecdotally quoted in the renal literature (Pfettscher *et al.*, 1995; Smith & Winslow, 1990).

This is an important area of study as perceptions of cognitive functioning may have broader consequences on patients' well-being. Subjective cognition being part of patients' experience may be more strongly associated with outcomes such as emotional distress and HQoL. They could adversely affect their morale, discourage efforts to adhere to rigorous treatment regimen and impede their adjustment to ESRD.

A systematic evaluation of subjective cognition in patients on different dialysis treatment (HD and PD) and patients with a kidney transplant is still lacking.

The extent to which these subjective cognitive complaints are related to objective indices of cognitive performance is not known. One study (Brickman et al. 1996) reported that NP scores in WAIS digit symbol were significant predictors of memory and attention complaints in dialysis patients, contributing a significant albeit very modest percentage (1.4%) of the total variance.

Research in different areas showed no association between subjective cognition and NP scores in patients following cardiac surgery (Khatri *et al.*, 1999; Newman *et al.*, 1989) or in elderly populations (Ponds *et al.*, 2000). As to whether these findings will be replicated in the renal population remains open to investigation.

The lack of significant association however does not necessarily suggest that either patients' perceptions or reports are not valid or that NP tests are not sensitive enough to capture subjective experience. These findings highlight the conceptual distinction and independence between objective and subjective phenomena. Both have their place in evaluating the outcomes associated with ESRD and associated treatments.

Section 9: Study aims and hypotheses regarding NP functioning

The present study was designed as a prospective investigation of a large cohort of patients on HD and PD as well as renal transplant patients to assess acute cognitive changes in the dialysis groups and to evaluate differences in cognitive functioning across the different renal replacement treatment modalities (i.e. HD, PD and TX).
The aims of the study were as follows:

(a) To examine NP changes in HD and PD patients, specifically any improvement within the cycle of dialysis, from immediately before HD and again at 24 hours post HD.

NP improvements were predicted for both groups but we anticipated that the magnitude of NP change would be greater for the HD group. Given the methodological limitations of previous research, formulating specific predictions regarding which of the specific cognitive abilities will change from pre- to post- dialysis was in our view unwarranted, so no a priori hypotheses were made. Greater NP improvements were predicted mainly for the HD group for which both learning and biochemical changes were expected across the two assessments.

(b) to compare NP performance of HD patients and PD patients over the same time period

Following this line of reasoning regarding the acute NP changes across the two dialysis groups, it was further hypothesised that group differences, if any, in NP functioning between HD and PD groups would be evident at the pre-dialysis (T1) assessment when the HD group would be at their worst physiological state. These differences should be reduced or neutralised at the post-dialysis (T2) assessment when the HD group would have improved physiological functioning.

(c) To compare NP functioning between transplant and dialysis patients

It was hypothesised that TX patients should present with more efficient cognitive functioning compared to dialysis patients (irrespective of specific dialysis modality), as TX provides more efficient renal clearance/restores renal function. No a priori

hypothesis was made regarding the association between transplant type, immunosuppressive medication and NP performance.

(d) To explore the relationship between NP functioning in ESRD patients (dialysis, transplantation) and biochemical measures.

This is a two-fold question:

- How do absolute levels of biochemistry relate to cognitive functioning in dialysis and TX patients?

No specific predictions regarding the relationship of specific biochemical assays and specific NP scores were made.

- Do any observed NP changes in the dialysis correspond with the biochemical and physiological changes that take place across the dialysis cycle?

We expected significant biochemistry changes from T1 to T2 assessment only for the HD patients and not for the PD group. We hypothesised that NP improvements in the HD group, if any, should parallel biochemical changes but no specific hypotheses, in terms of identifying particular biochemical predictors were formulated.

(e) To examine the relationship between objective and subjective cognitive functioning. This entailed:

- examining the associations between acute changes in objective NP functioning and perceived ratings of acute cognitive changes over time in HD and PD
- evaluating the association between objective NP scores and retrospective subjective evaluations of cognitive decline or amelioration since dialysis onset or receipt of a kidney transplant.

(f) to examine the association between objective NP functioning and HQoL

It was expected that absolute NP functioning will be associated with HQoL and it might possibly mediate the relationship between ESRD and HQoL. We were anticipating that these associations would be stronger for emotional well-being or aspects of HQoL. This expectation was based on the assumption that NP impairments could lead to frustration and feelings of emotional distress but should not impact on physiological function. Thus it was deemed unlikely that NP performance would be strongly associated with physical functioning and physical well-being.

CHAPTER 5: METHODS

Section 1: Participants

The intention was to perform a robust study sufficiently powered to compare the three main treatment modalities for ESRD, namely HD, PD and transplantation. Initial a priori power calculations (Gpower version 2.1) using a power of .80 with a likelihood of type error set to .05 and the probability of type II error at .20 determined that a target sample of 159 patients would be necessary to detect a medium effect size (0.25) in three groups ANOVAs. No power calculations were made for the secondary comparative analyses between other sub-groups in the study.

The overall study population consisted of chronic dialysis and kidney transplant patients treated in two urban renal units. Patient recruitment began in October 1997 and was concluded in October 1999.

Patients were approached if they met the following inclusion criteria: (a) aged 18 years or more, (b) no history or clinical evidence of cerebrovascular disease as reflected by new, transient, or fixed neurological deficits, (c) no major visual or hearing impairments, or other sensory or motor impairments that prohibit them from completing the scheduled assessments, (d) absence of acute or chronic psychosis, evident depression, severe learning disabilities, and/or dementia, (e) currently stable, defined as not being acutely ill or hospitalised at the time of the assessments (patients hospitalised during the last 3 months for intercurrent problem or problems related to dialysis or TX were not eligible), (f) be fluent in written and spoken English, and (g) a minimum of 3 months on their respective mode of treatment and dialysis techniques (e.g. the same dialysate or dialyser if on HD). This criterion was necessary since in several cases initial dialysis treatment modality is often provided on an urgent basis and is not always the treatment that the physician or the patient would select for long-term therapy.

Additionally patients with severe refractory anaemia (Hb < 8 g/dl) despite erythropoietin therapy, blood transfusions and supplemental iron, and patients with evidence of protein malnutrition as marked by serum albumin < 35 U/L or protein catabolic rates < .08 (in the last three consecutive assessments) were also excluded. Finally patients using medication with known NP effects during the previous 3 months were not eligible for participation. The different study samples are described below.

1.1 Transplantation Sample: Middlesex Hospital (MIDDX-TX)

Renal transplant recipients were recruited from the Middlesex Hospital, London, UK Transplant Unit. This sample completed the full study protocol and participants satisfied the inclusion criteria described above. Eligible TX patients were opportunistically recruited into the study based on their clinic attendance during the study window. One hundred and eighty one patients of the 288 registered MDDX-TX patients had scheduled appointments but 155 actually attended the transplant clinic. Thirty-three of them had to be excluded mainly due to their failure to speak the language of the tests and/or illiteracy. The remaining 123 eligible TX patients were sequentially approached to participate and 117 consented to the full protocol (response rate = 95.1%).

Table 5.1: Sociodemographic and clinical characteristics of the MIDDX-TX sample.

	All TX (n = 117)		**CAD TX** (n = 92)		**LRD TX** (n = 25)	
	M (Sd)	***%(n)***	***M (Sd)***	***%(n)***	***M (Sd)***	***%(n)***
Age (years)	50.26 (12.33)		52.43 (12.11)		41.91 (9.41)	
Gender						
% male		59.8% (70)		62% (57)		52% (13)
% female		40.2% (47)		38% (35)		48% (12)
Ethnicity						
% white		83.8% (98)		85.9% (79)		84% (21)
% black-all		9.4% (11)		8.7% (8)		12% (3)
% indian/pakistani		1.71% (2)		1.08% (1)		4% (1)
% asian-all		5.13% (6)		6.53% (6)		
% other						
Education (years)	11.19 (3.84)		10.7 (3.86)		13.04% (3.20)	
Educational level						
% no formal qualification		23.1% (27)		28.7% (25)		8.3% (2)
% vocational qualification		2.6% (3)		3.4% (3)		
% GCSE/O-Level		28.2% (33)		31% (27)		25% (6)
% A-Level/HND		23.1 (27)		22.8% (21)		20.9% (5)
% graduate/postgraduate		18.9% (22)		12% (11)		45.9% (11)
Relationship						
% married		65% (76)		65.9% (60)		66.7% (16)
% in cohab relationship		1.7% (2)		1.1% (1)		4.2% (1)
% divorced/separated		3.4% (4)		4.4% (4)		
% widowed		5.1% (6)		6.6% (6)		
% single		23.1% (27)		22% (20)		29.2% (7)
Able to work						
% able to work f/t p/t		71.1% (81)		66.7% (60)		87.5% (21)
% not able		28.2% (33)		33.3% (30)		12.5% (3)

Employment (post-TX)			
% working f/t or p/t	49.1% (56)	42.2% (38)	75% (18)
% retired	21.9% (25)	26.7% (24)	4.2% (1)
% unemployed	8.5% (10)	10% (9)	4.2% (1)
% other	20.2% (23)	5.5% (5)	16.7% (4)
Employment (pre-TX)			
% working f/t or p/t	68.4% (65)	65.6% (59)	79.2% (19)
% retired	6.1% (7)	6.7% (6)	4.2% (1)
% unemployed	6.1% (7)	5.6% (5)	8.3% (2)
% other	18.8% (22)	22.2% (20)	8.4% (2)
Income			
% 0 – £10,000	23.4% (25)	28.2% (24)	4.5% (1)
% £10,001 – 20,000	21.5% (23)	24.7% (21)	9.1% (2)
% £20,001 – 30,000	19.6% (21)	18.8% (16)	22.7% (5)
% above £30,001	27.1% (29)	18.8% (16)	61.9% (13)
% do not wish to answer	8.4% (9)	9.4% (8)	4% (1)
Living arrangements			
% rent	22.6% (26)	24.2% (22)	16.7% (4)
% own home	68.7% (79)	67% (61)	75% (18)
% live with parents	7.8% (9)	7.7% (7)	8.3% (2)
% other	.9 (1)	1.1% (1)	
Time TX (months)	70.70 (62.47)	59.08 (53.08)	113.46 (75.87)
Time RRT (months)	110.89 (77.37)	104.38 (70.66)	134.86 (96.11)
Time DL (months)	31.67 (31.89)	36.67 (33.24)	12.75 (15.67)
ESRD-SI	7.94 (8.06)	9.21 (8.51)	3.29 (3.25)
Glumerofiltration rate	40.32 (17.92)	38.96 (17.59)	45.16 (18.62)
Comorbidity	3.20 (1.78)	3.34 (1.77)	2.64 (1.70)
% diabetes	5.1% (6)	6.5% (6)	
% hypertension	11.1% (13)	92.4% (85)	76% (19)
% heart disease	26.5% (31)	30.4% (28)	12% (3)
Primary Kidney Disease Diagnosis			
% GN	17.1% (20)	31% (12)	32% (8)
% APKD	12% (14)	15.2% (14)	
% Reflux	12% (14)	14.1% (13)	4% (1)
% Diabetes	4.3% (5)	5.4% (5)	
% Hypertension	8.5% (10)	10.9% (10)	
% Other	54.71% (64)	34.3% (38)	64% (16)
Immunosuppression			
% on Cyclosporin	59.8 (70)	57.6% (53)	68% (17)
% Tacrolimus	36.4 (40)	38% (35)	20% (5)
% Prednisolone and other	6% (7)	4.3% (4)	12% (3)
TX			
% had previous TX	6.9% (8)	3.3% (3)	4% (1)
% past rejection (yes)	54.4% (64)	54.6% (50)	77.3% (19)
Haemoglobin	12.88 (1.70)	12.91 (1.76)	12.80 (1.47)
Albumin	43.68 (5.27)	43.71 (5.74)	43.54 (2.93)

Note. TX = transplant; CAD = cadaver; LRD = living related donor; RRT = renal replacement therapy; DL = dialysis; ESRD = ESRD = End Stage Renal Disease; GFR = glomerular filtration rate; GN = Glumeronephritis; APKD = Adult Polycystic Kidney Disease;
$_1$ = values reported are Pearson's chi-square with yate's correction

All transplant recipients were on triple immunosuppressive therapy consisting of either cyclosporin or tacrolimus, steroids (prednisolone) and mycophenolic acid which was prescribed only for highly sensitised patients and/or in the event of delayed function for the first 6 months post-transplant operation.

1.2 Dialysis

The dialysis sample consisted of patients receiving different forms of dialysis at the renal units of the Middlesex and Royal Free Hospitals in London, UK. Of the total number of dialysis patients (n = 236) treated in the participating units, sixty-nine patients had to be excluded because they did not meet one or more of the inclusion criteria. The most common reason for excluding patients was their non-English speaking status (n = 42) and consequent inability to perform the NP tests and complete the research questionnaires.
Patients (eligible) on hospital HD and CAPD were systematically sampled with a random start from a list provided by the respective HD and PD nursing sister. An attempt was made to include patients of various age, ethnic groups and equivalent number of male and female patients as well as haemodialysis patients on different dialysis rota (i.e. morning, afternoon and evening) to achieve the widest possible distributions and to maximise representativeness of the sample. In contrast, all (eligible) patients established on APD (n = 31) and home HD (n = 29) were consecutively contacted to participate because of the substantially smaller number of patients established on these two dialysis treatments compared to the hospital HD and CAPD programme supported by the participating renal units.

Of the eligible 167 patients who were approached, a total of 145 agreed to the full research protocol (response rate = 88.4%). Among those who declined initial participation (n = 22) at baseline, reasons for non response included: time constraints (n

= 6), lack of interest and motivation (n = 5), poor health (n = 7), concerns about confidentiality (n = 1), reluctance to talk about self (n = 1) and reluctance to give requested blood samples (n = 2).

The resulting dialysis study sample included patients established on four different dialysis modalities: Hospital HD (n = 52), Home HD (n = 25), CAPD (n = 45), and APD (n = 23). The details of these four dialysis groups are summarised in the Table 5.2.

Table 5.2: Sociodemographic and clinical characteristics of the four dialysis groups

	Hospital HD	**Home HD**	**CAPD**	**APD**
	M (Sd) %(n)	***M (Sd) %(n)***	***M (Sd) %(n)***	***M (Sd) %(n)***
Age (years)	46.85 (16.02)	51.08 (12.11)	53.84 (14.58)	49.17 (9.74)
Gender				
% male	57.5% (30)	56% (14)	26.7% (12)	73.9% (17)
% female	42.3% (22)	44% (11)	73.3% (33)	26.1% (6)
Ethnicity				
% white	63.5% (33)	80% (20)	57.8% (26)	60.9% (14)
% black-all	15.3% (8)	12% (3)	20% (9)	21.7% (5)
% indian/pakistani	5.8% (3)	4% (1)	13.3% (6)	8.6% (2)
% asian-all	5.8% (3)		4.4% (2)	4.3% (1)
% other	9.6% (5)	4% (1)	4.4% (20	4.3% (1)
Education (years)	12.5 (6.34)	11.76 (4.13)	12.27 (5.32)	12.94 (4.76)
Educational level				
% no formal qualification	17.3% (9)	8% (2)	20% (9)	13% (3)
% vocational qualification	3.8% (2)		6.7% (3)	8.7% (2)
% GCSE/O-Level	25% (13)	28% (7)	28.9% (13)	17.4% (4)
% A-Level/HND	26.9% (14)	32% (9)	26.7%(12)	43.5% (10)
% graduate/postgraduate	25% (13)	24% (6)	11.1% (5)	17.3% (4)
Relationship				
% married	44.2% (23)	68% (17)	71.1% (32)	65.2% (15)
% in a relationship	5.8% (3)	4% (1)	2.2% (1)	
% divorced/separated	5.8% (3)	4% (1)	8.9% (4)	13% (3)
% widowed	9.6% (5)			
% single	34.6% (18)	24% (6)	17.8% (8)	21.7% (5)
Employment				
% working f/t or p/t	32.7% (17.7)	44% (11)	20% (9)	65.2% (15)
% retired	34.6% (18)	28% (7)	42.2% (19)	21.7% (5)
% unemployed	21.2% (11)	8% (2)	11.1% (5)	8.7% (2)
% other		20% (5)	26.6% (12)	4.3% (1)
Work change since DL				
% no change	46.2% (24)	56% (14)	64.7% (44)	72.7% (16)
% increase			1.5% (1)	
% decrease	23.1% (12)	8% (2)	11.8% (8	13.6% (3)
% had to leave work	30.8% (16)	32% (8)	22.1% (15)	13.6% (3)

% change career		4% (1)		
Able to work				
% able to work f/t p/t	48.1% (15)	48% (12)	38.2% (26)	69.6% (16)
% not able	51.9% (27)	52% (13)	61.8% (42)	30.4% (7)
Income				
% 0 – £10,000	67.3% (35)	40% (10)	71.1% (32)	34.8% (8)
% £10,001 – 20,000	17.3% (19)	48% (12)	22.2% (10)	21.7% (5)
% £20,001 – 30,000	7.7% (4)	8% (2)	4.4% (2)	26.1% (6)
% above £30,001	7.7% (4)	4% (1)	2.2% (1)	17.4% (4)
Income change since DL				
% none	34.6% (18)	36% (9)	48.9% (22)	69.6% (16)
% increase	13.5% (7)	8% (1)	46.7% (21)	4.3% (1)
% decrease	51.9% (27)	56% (14)	4.4% (2)	26.1% (6)
Living arrangements				
% rent	42.3% (22)	24% (6)	44.5 (20)	30.4% (7)
% own home	36.5% (19)	68% (17)	48.9% (22)	65.2% (15)
% live with parents	17.3% (9)	8% (2)	4.4% (2)	4.3% (1)
% other	3.8% (2)		2.2% (1)	
Time DL (months)	38.94 (39.64)	88.44 (71.2)	21.56 (23.15)	12.94 (4.76)
Time RRT (months)	64 (60.45)	163.6 (84.26)	26.83 (36.59)	37 (48.34)
ESRD-SI	9.19 (8.58)	13.48 (9.72)	12.47 (9.68)	10.52 (10.33)
Kt/V	1.65 (.258)	1.75 (.195)	1.82 (.358)	
URR	.651 (.078)	.659 (.058)		
Comorbidity				
% diabetes	11.5% (6)	100% (25)	31.3% (14)	21.7% (5)
% hypertension	11.5% (6)	44% (11)	86.7% (39)	91.3% (21)
% heart disease	36.5% (19)		44.4% (20)	34.8% (8)
Primary Kidney Disease Diagnosis				
% GN	25% (13)	20% (5)	2.2% (1)	4.3% (1)
% APKD	9.6% (5)	20% (5)	8.9% (4)	26.1% (6)
% Reflux	5.8% (3)	16% (4)	6.7% (3)	17.4% (4)
% Diabetes	9.6% (5)		17.8% (8)	13% (3)
% Hypertension	7.7% (4)		22.2% (10)	13% (3)
% Other				
TX				
% had previous TX	42.3% (23)	64% (16)	8.9% (4)	4.3% (1)
% on TX list	86.5% (45)	96% (24)	86.7% (39)	95.&% (22)
Haemoglobin	10.59 (1.38)	11.42 (1.66)	11.24 (1.46)	11.21 (1.23)
Albumin	39.67 (3.49)	40.12 (3.41)	34.68 (3.84)	37.48 (3.99)

Note: HD = haemodialysis; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; DL = dialysis; f/t = full time; p/t = part time; RRT = renal replacement therapies; ESRD-SI = end-stage renal disease severity index; Kt/V = K is defined as the total urea clearance rate, t represents the number of minutes of dialysis and V is the urea distribution within the patient (dialysis adequacy); URR = urea reduction ratio; GN = glumeronephritis; APKD = Adult Polycystic Kidney Disease; TX = transplant.

1.2.a Hospital HD

The hospital HD sample (n = 52; response rate = 92.85%) was predominantly male (n = 30, 57.7%) and Caucasian (n = 34, 65.4%). Their average age was 46.85 years (SD = 16.023, range = 19-77) and at the time of entry into the study all consenting hospital HD patients had been receiving high-flux haemodialysis for at least 3 months duration (*mean* = 38.942, SD = 39.46, range = 3–228 months).

They all had negligible residual renal function as determined by (endogenous) urea clearance and minimal (< 200ml) to no daily urine output. Haemodialysis was performed with cellulose acetate (Althin) or hemophane (gambro) membranes and volume controlled equipment. Dialysate was bicarbonate buffered and dialysis flow/dialysate flow rate was set at 500 to 600 ml/min. Blood flow rate was equal or greater than 200 ml/min (range = 200-300ml/min). Duration of individual dialysis sessions was equal or greater than 3 hours. The average treatment time per dialysis session was 3.96 hours typically three times a week. In both HD units, haemodialysis was offered at three shifts: morning, afternoon and evening to accommodate a large number of patients and individual needs. Out of the recruited HD participants, eighteen patients (34.6%) were dialysed in the morning (08:30 a.m.–12:00 a.m.), twenty patients (20.5%) in the afternoon (13:00 p.m.–17:00 p.m.), and fourteen (26.9%) in the evening (21:00pm-01:00 am hours).

1.2.b Home HD

Eligible home HD participants were recruited from only one renal unit (Royal Free Hospital) in which such a programme was in effect (Middlesex hospital did not run a Home HD programme). Of the 29 patients established on home HD, 25 patients consented to the study protocol (86.2% response rate).

Home HD participants, of whom n = 14 were male (68%) had a mean age of 51.08 years (SD = .351, range = 30-69) and have been on the home HD programme for an average of 80.44 months (SD = 12.11, range = 9-312). Their home HD regime consisted of three four- to six-hour-long haemodialysis sessions a week (*mean* = 4.98 hours, SD = .51). Haemodialysis was performed using a bicarbonate dialyser with a dialysate flow rate of 250 to 500 ml/min and a blood flow rate equal or greater than 200 ml/min (range = 200-450ml/min).

1.2.c CAPD

A total n = 45 CAPD patients (response rate = 88.23%) of whom 73.3% (n = 33) were male and predominantly of Caucasian race (n = 26, 57.8%) were recruited onto the study. They had a mean age of 53.84 years (SD = 14.59, range = 24–83) and had been on CAPD for an average of 21.56 months (SD = 23.15, range = 3–87).

All of the recruited participants had a double-cuffed silastic Tecknoff catheter positioned with the standard medical procedure approximately a week prior initiation of treatment. The daily exchange procedure was four- or five-times per day depending on clinical assessment. The daytime exchanges consisted of 2.27% glucose in all patients, with volumes of 1.5 L and/or 2 L. At the time of first assessment 35.6% of the participants (n = 16) were using 1 strong (2 L) and 3 weak bags (1.5 L) during a day, 26.7% (n = 12) were performing 4 weak bags with a strong bag every other day and the remainder of the sample were on various other PD regimens. The prescribed bag strength regime and their recommended combination, however was varied depending on the patients clinical profile and needs (such as diabetic status or fluid overload) throughout the study period.

1.2.d APD

Of the total 31 of patients registered on the APD programme, twenty-three agreed to participate in this study (response rate = 71.87%). Patient selection for APD in the participating unit (MIDDX) was not elective but based on clinical criteria (such as peritoneal membrane function, residual renal function) and in some cases special social considerations (e.g. housing, work). Data from PET tests indicated that in our recruited APD sample five APD patients (21.7%) had low to average peritoneal transport, three (13%) patients had high peritoneal transport, whereas the majority of the APD participants (n = 15, 65.2%) were classified as high to average peritoneal transporters. Mean age was 49.17 years (SD = 9.745, range = 29 - 65).

APD was performed with the Homechoice cycler (Baxter) in all APD participants. The exchange procedure was once overnight using multiple hourly cycles in which spent dialysis solution was completely drained with each cycle. Night-time exchange volumes were 10L in eight patients (34.8%), 12L in thirteen patients (56.5%) and 15L in two

patients (8.7%). APD participants received a total of 15 L of PD solution over a 8 - 9.5 hours overnight (*mean* = 8.74, *SD* = .44) session with 5-10 exchanges using 1.5L to 2.0L instilled volume and a dwell time of 45-75 minutes each time.

Appropriate PD regimens prescribed at study entry, were adjusted throughout the study period so as to ensure adequate dialysis delivery as indexed by a Kt/v of 2.0 or a total clearance of 70L week per 1.73 m^2 as concluded in the CANUSA study (Canada USA Peritoneal Study Group, 1996) and the UK renal association guidelines (1997).

1.2.e Representativeness of dialysis sample

To evaluate whether the recruited dialysis sample was representative of the dialysis population treated in the participating renal units, demographic (age, gender, employment status) clinical and dialysis characteristics were collected for all dialysis patients that did not participate in our study protocol. The groups of non-participants (*n* = 132) included non-responders (*n* = 22) and non-eligible patients (*n* = 69) or patients who could not be contacted during the duration of the study (*n* = 41).

Comparisons between dialysis participants and non-participants (including non-eligible patients and patients who declined participation) were performed only for Hospital HD and CAPD patients as the number of non-responders on APD (*n* = 8) and home HD (*n* = 4) was extremely small.

Independent samples *t*-tests, revealed only two statistically significant group differences. Hospital HD non-responders were significantly older (*mean* = 58.57, *SD* = 16.93; t(116) = -3.823, *p* <.000) and had significantly higher albumin values (*mean* = 38.29, *SD* = 3.63; t(105) = 3.508, *p* = .001) compared to hospital HD study participants. It should however be noted that mean albumin levels for both HD responders and non-responders were considered adequate as they met clinical benchmarks (≤35g/dL). No significant differences were found between CAPD participants and non-participants. A tendency was noted for CAPD participants to have a lower Kt/V (*mean* = 1.81, *SD* = .402) relative to non-participants (*mean* = 2.00, *SD* = .46) but it did not reach significance (t (79) = -1.879, p = .064).

Section 2. Beliefs and HQoL

2.1 Participants

Dialysis patients and transplant recipients took part in this study (see sections 1.1 - 1.2)

2.2 Procedure

2.2.a Ethical Approval

Ethical approval for the study protocol was sought and successfully granted by the participating Hospital Ethics Committees.

2.2.b Recruitment

Recruitment procedures for both dialysis and transplant patients were identical. Opportunistic sequential recruitment of dialysis and transplant patients that met the pre-stated inclusion criteria was undertaken. An invitation letter signed by a Nephrology consultant and an information sheet detailing the aims and procedures of the protocol were posted to all patients scheduled to attend the outpatient clinics or dialysis units for either one of their regular check ups or one of their dialysis sessions.

Approximately a week before patients' pre-scheduled clinic appointments, the head researcher contacted the identified patients by telephone and individually invited them to take part in this research. Each of the potential participants was told that the research was being conducted to get a better understanding of their experience with their treatment (transplantation or dialysis) and that if they agreed to participate a researcher would administer a number of questionnaires and some tests of memory and concentration. Appointments were then made with consenting patients and further confirmed a few days prior to the respective interviews.

2.2.c Data collection

After obtaining written consent from all patients, study questionnaires were presented and administered by the researcher.

All assessment sessions for transplant patients commenced with the collection of background information and proceeded with the administration of part 1 of the study questionnaire (see Appendix C) followed by the NP assessment (described in more detail in subsequent section 4.2). After an optional break, the assessment session was resumed and concluded with the administration of part 2 of the questionnaire (see Appendix C).

There was no theoretical reason that an order effect would be present in relation to the completion of questionnaires. The assessment was hence conducted to help the participants focus and think back about their perceptions and feelings about their treatment and illness experience. It was therefore decided to present the questionnaires in an order that began with most relevant to their ESRD experience (part 1) and finally ended with the more general ones (part 2).

Participants were asked to complete the questionnaire in the presence of the researcher, available at all times to clarify queries regarding the self-report measures used. Upon patients' request however, the interviewer offered her assistance (e.g. reading out the questionnaire) to those patients.

In TX patients all measures were taken on one assessment session. In the dialysis patients study questionnaire was completed over two sessions scheduled to coincide with the repeated NP assessments. Part 1 was completed at the first assessment and part 2 was administered the following day (second assessment) after repeated NP evaluation.

Most assessments were conducted in a specially designated assessment room in Health Psychology Research Unit by the same researcher. The room was made available for the duration of the study to enable participants to complete the questionnaire and NP tests in privacy and without being disturbed by the dialysis ward and outpatients clinic activity. Given the complexity and time demands of this research protocol, patients' comfort and convenience was a priority when arranging assessments. Upon patients expressed preference, therefore, home visits for the assessments were also arranged at times most convenient to research participants.

Each assessment required approximately 2 hours to complete. Assessment times varied depending on the patient.

2.3 Measures

2.3.a Psychological measures

Questionnaires were selected to measure variables identified by the researchers as part of the model for this research. Important selection criteria were primarily the measures' psychometric properties and its use and applicability with ESRD patients.

i. *Sociodemographic Questionnaire*

Demographic information including age, gender, ethnicity, education, marital and employment status, perceived work ability, housing/living arrangements and household income was collected by questionnaire (see Appendix C).

ii. *Fatigue Rating Scale*

The visual analogue scale (Brunier & Graydon, 1996) was used to measure fatigue.
The scale (100mm line) was anchored at either end by 'no tiredness at all' at the left end and 'complete exhaustion' at the other end. Participants were shown the scale and were asked to place a mark on the line that best described how tired they have been feeling right now, generally first thing in the morning, in the middle of the day and before they go to bed. The intensity of fatigue was scored by measuring from the low end (left side) of the scale to the subjects' mark in millimetres. A higher score indicated lower levels of fatigue.

The scale has been used with ESRD patients (Brunier & Graydon, 1996; McCann & Boore, 2000) and is significantly associated with more elaborate multi-item fatigue measures (Brunier & Graydon, 1996; McCann & Boore, 2000). The reliability and validity of VAS to measure subjective feelings has been demonstrated in various studies (e.g. Gift, 1989).

iii. *Illness Perception Questionnaire* (IPQ)

The IPQ (Weinman *et al.*, 1996) was used to assess causes, identity, timeline, consequences and control/cure dimensions that underline patients' representation of illness (Leventhal *et al.*, 1984; Lau *et al.*, 1989).

The IPQ hence comprises 5 sub-scales and provides a quantitative assessment of the nature and strength of participants' beliefs about each of the components of their illness representations. Designed specifically for use in the context of chronic illness, it has also been suggested that the IPQ should be used as a tool for assessing psychological needs of an individual 'prior to renal transplantation' (Wright, 1994). In this study a modified version of the questionnaire was used in that the IPQ has been adapted for use with dialysis and TX patients in accordance with the authors' instructions.

The first part of the IPQ measures illness identity with a list of generic and condition-specific symptoms. To make this sub-scale more appropriate for ESRD patients, the core items of the IPQ (n = 12) were supplemented with items about ESRD and RRT specific symptoms. These were chosen for a number of reasons: (a) they had been reported by patients to be important (in the pilot stage of the study), (b) a review of these by a panel of renal clinicians involved in patient care approved their inclusion, and (c) finally because they had been incorporated by others in disease-specific questionnaires (Hays *et al.*, 1994; 1996; Laupacis *et al.*, 1992; Parfrey *et al.*, 1989).

The modified dialysis version of the identity IPQ sub-scale therefore consisted of a total of 19 symptoms: the 12 core IPQ items and 7 renal-specific ones. The additional dialysis symptoms used for the assessment of dialysis patients were: hair loss, muscle spasms or stiffness (leg cramps), restless legs, itching, fatigue, and nausea.

The transplantation-specific version of the identify IPQ sub-scale contained all these 19 items (core and renal items; n = 19) and an additional 22 items referring to potential side-effects associated with immunosuppressive medication. Examples of these additional items included weight gain, hair growth, gum problems, tremor, acne, impaired visual acuity, bruises, and weak muscles.

These transplant-specific adaptations were based on a comprehensive review of relevant research (De Geest *et al.*, 1995), and recommendations made by transplant health care professionals.

Patients were asked if they thought the symptom was part of their renal disease and to rate how often they experience the listed symptoms. The items measuring symptom occurrence are scored on a 4-point rating Likert scale ranging from 1 (*'never experienced'*) to 4 (*'occurring all the time'*). There are several ways to score the identity sub-scale. Authors suggest the illness identity scores can be classified as present and given a score of '1' or absent and given a score of '0'. These individual item scores may then be aggregated to a total score with high higher scores indicating more symptoms. Alternatively, the scores (ranging from 0 to 3) can be summed to give a weighted illness identity, with higher scores indicating a higher level of symptom burden. For the purposes of this study the former scoring method (i.e. symptom count) was chosen as it the most widely used procedure in previous research.

The second part of the questionnaire consists of 28 statements using a 5-point Likert scale (*'strongly agree'*-*'agree'*-*'uncertain'*-*'disagree'*-*'strongly disagree'*) and provides separate scores for causes, consequences, timeline and control/cure.
The items of the causal sub-scale are scored individually as 'each item represents a specific causal belief' (Weinman *et al.*, 1996). They are treated as stand-alone items and thus individual scores are obtained for the following: germ or virus, diet, pollution, heredity, chance, stress, own behaviour, other people, poor medical care in the past, and state of mind.

For the remaining three IPQ sub-scales (timeline; consequences; control/cure) item scores are summed and divided by the number of items in the sub-scale in question. The timeline sub-scale contains four items with scores ranging from 1 to 5 and higher scores representing a belief that the illness is going to last for a longer time. The consequences sub-scale contains seven items and scores ranged from 1 to 5 with higher scores representing a stronger belief that the illness has had serious consequences.

The cure/control sub-scale contains eight items. The original IPQ control item 'what I do determines whether my illness gets better or worse' was rephrased to form two separate ones (i.e. 'what I do determines whether my illness gets better' and 'what I do determines whether my illness gets worse') as patients in the pilot phase expressed distinct views regarding control expectancies with regard to clinical improvement or

deterioration. Scores ranged from 1 to 5, with higher scores indicating a higher level of belief in control or potential for cure of the illness.

The IPQ has been used extensively in different illness populations including patients suffering from arthritis, diabetes, chronic fatigue or myocardial infarction, a thorough description of which is beyond the scope of this work (see review by Hagger & Orbell, 2003).

Fairly extensive psychometric data have been published for all sub-scales. The psychometric properties of the IPQ have been evaluated in seven illness groups including individuals with asthma and diabetes, and renal dialysis patients. The internal reliability for each sub-scale is satisfactory, with Cronbach alpha coefficients .73 to .82. Similarly good test-retest data for each sub-scale have been obtained in patients with chronic illnesses and a range of concurrent, discriminant and predictive validity data have been published for different chronic illness groups (Weinman *et al.*, 1996).

iv. *Illness Effects Questionnaire* (IEQ)

The IEQ (Greenberg & Peterson, 1997a; 1997b) has been used to measure illness intrusiveness. This 20-item scale assesses individuals' perceptions about how illness interferes with or affects personal, social behaviours, and life in general. Questions range from perceived family and personal disruption to physical problems and fears about illness effects, e.g. "my illness creates problems between myself and my family", "my illness disrupts my appetite", "my illness prevents me from enjoying myself".

The scale uses an eight-point ordinal response scale (each item is scored between 0 and 7) where 0 represents no illness intrusiveness or the absence of a problem and values greater than 0 represent the severity of the problem of interference/disruptiveness. A total score is obtained by summing across individual ratings. Scores range from 0 to 140 with scores between 56 and 88 indicating average distress/disruptiveness and scores above 89 indicating moderate to extreme distress (Greenberg & Peterson, 1997b). McGee *et al.* (1998) based on a HD sample, reported slightly different norms with scores between 47 and 74 indicating average distress/disruptiveness and those above 74 indicating moderate to severe distress/disruptiveness.

The IEQ has been found to be a very reliable instrument with internal reliability of alpha = .93 and test retest reliability of .99 (Greenberg & Peterson, 1997a; 1997b). Its validity

has also been supported through correlations with measures including the illness behaviour questionnaire (IBQ; Pilowski & Spence, 1975) (Wise *et al.*, 1994), measures of psychosocial impairment (Mancini *et al.*, 1986; Wise *et al.*, 1994), and depression in various medical populations (Rosenberg *et al.*, 1988), including ESRD patients (Eitel *et al.*, 1995; Kimmel *et al.*, 1996; Sacks *et al.*, 1990).

IEQ scores have also been found to be associated with other outcomes in ESRD such as vocational, sexual and social adjustment, and life and marital satisfaction in dialysis patients (Kimmel *et al.*, 1995a; 1995b; 2000; 2003), and significant associations have also been shown with survival in HD (Kimmel *et al.*, 1998b; 2000). Finally, its sensitivity and responsiveness to treatment effects and interventions (e.g. pain management programme) has also been demonstrated (Stevens *et al.*, 1988, Stratton, 1989). Kimmel (2000b; 2001) has stated that the instrument's reported associations with clinical and psychological outcomes as well as its intercorrelations and lack of correlations with severity of illness makes the IEQ 'a potential prime psychosocial measure for use with ESRD patients treated with HD'.

v. *Treatment Effects Questionnaire* (TEQ)

The TEQ (Greenberg & Peterson 1997b) assesses patients' perceptions of the physical and psychosocial impact associated with their treatment rather than their illness. It includes the evaluation of issues such as treatment impact, side-effects (e.g. appetite/sleep disturbance), treatment-associated distress (e.g. helplessness, preoccupation, anxiety), treatment effectiveness and dependency that are likely to impact heavily on adherence and quality of life

The TEQ contains 20 items and has the same administration and scoring format as the IEQ. Ratings are made along an 8-point ordinal scale ranging from 0 (strongly disagree) to 7 (strongly agree). A total score is obtained by summing across individual ratings with higher scores indicating greater disruption from the treatment. Authors attempted to have as much of the TEQ's items content as similar to the IEQ's as possible but since treatment yields its own issues, some dissimilar items were developed. The TEQ therefore shares 75% of the IEQ content (items: 1; 3; 4; 5; 7; 8; 10; 12; 13; 14; 15; 16; 17; 18; 20 see appendix C).

There is empirical support for TEQ's psychometric properties. Its internal consistency is high (Greenberg & Petterson, 1997b). Significant associations ($r = .66$, $p < .001$) between TEQ total score and depressive symptoms from the Beck Depression Inventory have been reported in support of its construct validity and changes in TEQ scores at an intervention study demonstrate its clinical responsiveness and sensitivity to treatment changes (Heilbronner *et al.*, 1989).

As suggested by the authors, TEQ may be particularly useful in treatment comparisons and it was in this respect that it was chosen for this study. Besides normative comparisons TEQ can be useful as a measure of effects of different treatments for the same disease as with different forms of dialysis (haemodialysis vs. peritoneal dialysis); for evaluating new or modified treatment to established treatments; or for obtaining a patients' serial appraisal and adaptation to a treatment such as dialysis or moving from dialysis to having a kidney transplant (Greenberg & Peterson, 1997b). When different treatments, such dialysis modalities deliver essentially similar medical benefit, it may be that the patient's appraisal of how acceptable a treatment is in terms of its general biopsychosocial consequences will influence the best individual treatment approach.
It was considered useful to use particularly in conjunction with the illness effects questionnaire (IEQ) as recommended by the authors (Greenberg & Peterson, 1997b). A comparison of the two relative scores may aid in understanding why adjustment or adherence problems exist for some patients in a way that would not be possible if the instruments were used separately/in isolation.

vi. *Beliefs about your medicines Questionnaire* (BMQ)

The BMQ (Horne & Weinman, 1999) was used to assess patients' representations of their prescribed medication. The questionnaire was administered only to transplant patients, as this was the group for whom medication (a regime of immunosuppressive agents) is the core treatment component. It was not used for the assessment of dialysis participants mainly to avoid burdening patients with too many questionnaires in addition to extra NP assessment session and because medication, albeit essential to dialysis patients management was seen as secondary to dialysis treatment itself.

The BMQ consists of two sections: the BMQ specific which assesses representation for medications prescribed for personal use and BMQ – general which assesses beliefs about medication in general. These two sections of the BMQ can be used in combination or separately.

For the purposes of this study the BMQ specific section was used. This comprises two 5-item sub-scales assessing beliefs about the necessity of prescribed medication (specific necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication (specific concerns). Examples of items from the necessity sub-scale include: "My health, at present, depends on my medicines" and "My medicines protect me from becoming worse." Examples of items from the 'concerns' sub-scale include: "I sometimes worry about the long term effects of my medicines" and "I sometimes worry about becoming too dependent on my medicines".
Respondents indicate their degree of agreement with each individual statement about medicines on a five-point Likert scale, ranging from 1=strongly disagree to 5=strongly agree. Scores obtained for the individual items within each sub-scale are summed to give a sub-scale score. Thus, total scores for the necessity and concerns sub-scales range from 5 to 25. In order to facilitate comparisons between sub-scales, a mean item score was computed by dividing each scale score by the number of items, giving a range of 1 to 5. Scores can be interpreted in two ways: as a continuous scale where higher scores indicate stronger beliefs in the concepts represented by the scale or by dichotomising at the scale midpoint. The continuous scale is used in statistical analyses as this provides richer information that is lost when the scale is dichotomised (Oppenheim, 1992).

The BMQ has satisfactory internal consistency and test-retest reliability. Concurrent and discriminant validity has also been established. Beliefs about medication have been found to be strongly associated with medication adherence (Horne, 1997; 2003a; 2003b Horne & Weinman, 1999; 2002; Byer & Myers, 2000).

vii. *Spielberger State Anxiety Inventory* (STAI)

Anxiety was measured using a short version of the STAI (Marteau & Bekker, 1997). The STAI (Spielberger *et al.*, 1983) is designed to measure anxiety as a 'state like' or

situationally determined condition; the scale has been used to measure the type of anxiety induced by stress associated with a medical condition or its treatment. The short version was preferred due its brevity. It contains 6 self-report items rated on a 4-point Likert scale ranging from 'not at all' to 'very much so'. Higher scores signify greater anxiety. The scale has a satisfactory concurrent and construct validity and acceptable levels of internal consistency and is advocated as an alternative when the time demand and length of assessments is a consideration.

viii. *Positive and Negative Affect Schedule, expanded-form* (PANAS-X)

The expanded form of the positive and negative affect scale (Watson *et al.*, 1988; Watson & Clark, 1994) was used as a measure of current affect. This scale was used to assess the independent dimensions of positive and negative affect which have reliable emerged as the dominant dimensions in the emotional experience (Almagoroth & Ben-Porathe, 1989; Meyer & Shack, 1989).

The PANAS-X comprises 60 adjectives describing positive and negative mood states. Items are grouped to form positive and negative affect summary scores and separate affective states. In addition to the general dimensions of positive and negative affect, the expanded form assesses 10 specific affects: fear, sadness, guilt, hostility, shyness, fatigue, joviality, self-assurance, attentiveness and serenity. The respondents rate the extent the have felt each of the affective states during their designated time frame, using a 5-point scale ranging from *'very slightly or not at all'* to *'extremely'*. The scale can be used with various time frame instructions. For the purposes of this study participants were asked to rate the adjectives according to the way they have felt at that particular moment in time, in other words 'right now'.

The 10 PANAS items assessing positive mood (interested, excited, strong enthusiastic, proud, alert, inspired, determined, attentive, and active) and the 10 items assessing negative mood (distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid) were each summed to yield separate Positive Affect (PA) and Negative Affect (NA) scores for each participant.

Internal consistency reliabilities have ranged from .86 to .90 for PA and from .84 to .87 for NA and internal consistency is reported to be unaffected by the time frames used (Watson, 1988a; 1988b).

From the other specific affect sub-scales, scores were computed for guilt, fear, shyness, serenity sub-scales by adding relevant items. As with the general PA and NA dimensions, their psychometric properties have been thoroughly investigated and their merit in terms of normative, internal consistency, construct validity is clearly established (Bagozzi, 1993; Watson & Clark, 1991; 1992a)

In addition to the instrument's extensive psychometric development and wide use in psychological research (Henson & Chang, 1998) there is also support for its responsiveness and sensitivity to change. Research also indicates that when used with short-term instructions (i.e. 'moment' or 'today'), the PANAS-X sub-scales (including PA and NA) are sensitive to changing internal or external circumstances (Clark *et al.*, 1989; McIntyre *et al.*, 1990; Watson, 1988a; Watson & Clark, 1992b), which made it the ideal instrument to assess mood variation over 24-hours as was the case with the dialysis participants in this study.

ix. *Beck Depression Inventory* (BDI)

The BDI (Beck *et al.*, 1961) was used to assess the presence and severity of depression in dialysis and transplant patients. The BDI is composed of 21 items. Each category describes a specific behavioural manifestation of depression and consists of a graded series of four evaluative statements. Integer values of 0 to 3 are assigned to each statement to indicate the degree of severity where '0' stands for the absence of a problem whereas '3' represents an extreme problem. An advantage of the BDI is that it places the subject within a range of depression (none, mild, moderate, severe) rather than merely identifying whether a person meets the diagnostic criteria. Scores of 0 to 10 indicate no depression, 11 to 18 signify mild depression, 19-25 moderate depression and 26 or more indicate severe depression (Beck *et al.*, 1961).

According to Gotlib & Cane (1987), the BDI is the preferred self-report questionnaire for measuring the intensity of depressive symptoms. Although the BDI does not provide a psychiatric diagnosis of depression nor does it provide information about periods of

major depression that may have occurred in the past, it is a well-validated index of depression, correlating with diagnostic criteria for depression (Stehouer, 1987). Craven *et al.* (1988) assessed the validity of the BDI by determining the relationship between diagnosis of depression with the DSM-III and the BDI in a sample of renal dialysis patients. A threshold of 15 on the BDI produced optimal sensitivity (0.92), negative predictive value (0.99) and maximised Youden's index of validity (0.72) for the use of BDI as a screening device for depressive symptoms in renal patients.

The BDI has been used extensively to assess depression in ESRD patients (Craven *et al.*, 1988; Edgell *et al.*, 1996, Kimmel *et al.*, 1993; 1995; 1998a; 2000c; Peterson *et al.*, 1991; Shulman *et al.*, 1989). It has been found to be responsive over time in this context (Christensen *et al.*, 2000; 2002).

For the analyses presented here, a subset of 15 cognitive depression items, comprising the Cognitive Depression Index (CDI) were selected to control for the confounding contribution of somatic symptoms of physical illness (Sacks *et al.*, 1990).
The CDI focuses on thoughts and feelings related to the diagnosis of depression, such as guilt, disappointment, and failure, excluding its somatic items and hence can be used to reduce the possible confound between symptoms of medical illness and the somatic components of depression measured in the BDI (Beck et al 1988; Kimmel *et al.*, 1993, Sacks *et al.*, 1990). This subset was used because somatic effects of ESRD and associated treatment such as decreased sexual drive and loss of appetite are also symptoms of depression and thus their inclusion could result in misleading/falsely elevated scores of depression scores. The 15 CDI items as with all BDI items are answered on the same 4-point scale with a total score of 0 to 45. Examples of cognitive feelings surveyed include sadness, guilt, disappointment, failure and decision making.

The cognitive subset of items have been previously used in research on adjustment in ESRD (Brickman *et al.*, 1996; Eitel *et al.*, 1995; Kimmel *et al.*, 1995a; 1995b; Peterson *et al.*, 1991; Sacks *et al.*, 1990; Schneider *et al.*, 1991). The CDI has been found to have a standardised internal consistency of .74 and has been shown to discriminate depressed from non depressed ESRD patients (Hinrichsen *et al.*, 1989). The CDI has previously been highly correlated with the BDI in ESRD patients (Kimmel *et al.*, 1993; 1995a; 1995b; 1996; Peterson *et al.*, 1991), but unlike the BDI was not associated with

measures of severity of illness, nutrition, renal function, and delivery of dialysis (Sacks *et al.*, 1990).

x. *The Medical Outcomes Study 36-item Short-Form Health Survey*

HQoL was measured with the MOS SF-36 (Ware & Sherbourne, 1992; Ware *et al.*, 1993; Ware & Koshinski, 1996)–UK version (Jenkinson *et al.*, 1993; 1996). The SF-36 UK version 2 (Jenkinson *et al.*, 1999), not yet published when dialysis patients' recruitment and data collection commenced, was subsequently used with transplant participants (see Appendix C).

The SF-36 is a generic multidimensional measure of HQoL designed for use in clinical practice and research, health policy evaluation and general population surveys. It comprises eight multi-item sub-scales that represent physical and mental health status: physical functioning (PF; 10 items), social functioning (SF; 2 items), role limitations due to physical health problems (RPh; 4 items), role limitations due to emotional problems (REm; 3 items), mental health (MH; 5 items), vitality (VT; 4 items), bodily pain (BP; 2 items) and general health perceptions (GH; 5 items). There is a further unscaled item asking respondents about perceived health change over the last year.

The SF-36 was developed and extensively evaluated as part of the Medical Outcomes Study, and contains essential psychometric criteria that have been shown to be both reliable and valid and responsive in various clinical and demographic populations (Beaton *et al.*, 1997; Hays *et al.*, 1993a; Keller *et al.*, 1998; Lowrie *et al.*, 2000; McHorney *et al.*, 1993; 1994; Ware *et al.*, 1998). Normative data exist for the general English population (Brazier *et al.*, 1992; Jenkinson *et al.*, 1996; 1999).

It has been extensively used as an outcome measure in ESRD research (Cagney *et al.*, 2000) and is also incorporated into renal-specific HQoL questionnaires, namely the CHOICE (Wu *et al.*, 2001) and KDQoL (Hays, *et al.*, 1994). It has been proven to be both reliable and valid in both dialysis and transplant populations (Edgell *et al.*, 1996; Garratt *et al.*, 1993; Khan *et al.*, 1995; Rettig *et al.*, 1997; Wight *et al.*, 1998). Data in support of its responsiveness in ESRD have also been published (Meyer *et al.*, 1994).

SF-36 has also been shown to be acceptable by renal patients (Kurtin *et al.*, 1992) and its brevity and comprehensiveness provides a distinct advantage over other HQoL measures. It takes approximately 5-10 minutes to complete, a factor, which is important, when one considers the practicalities of the use of an instrument in a large-scale study of patients in a clinical environment. We therefore chose to use this tool because of an ample literature supporting its validity, and its ease of administration and interpretation

There are several scoring systems as described in the RAND 36-Item Health Survey or MOS SF-36™. These are reviewed by Hays *et al.*, (1993b). For the purposes of this study the scoring instructions described in the UK SF-36 manual, which are based on the standard MOS system, were applied (Jenkinson *et al.*, 1996). This is performed as follows: Sub-scale scores were transformed to 0-100 scales with higher scores indicating better HQoL (Ware & Sherbourne, 1992). Scores represent the percentage of total possible score achieved. Subsequently the scales scores were standardised to the scale scores of a general UK population sample (N =8889, age range = 18-64 years, male = 43.4 %) by subtracting the general population mean from the individual mean and dividing by the corresponding scale *SD* from the general population. The resulting *z*-scores indicate how many *SD*s the observed SF-36 scores of dialysis or transplant patients fall below or above the scores of the reference population when the scores of the reference population are set to 0.

To facilitate interpretation and direct comparisons between scores from the original version of SF-36 and version 2 normative based scoring was used (NBS; Ware, 2000; Ware & Kosinski, 2001). NBS involves a linear t-transformation to ensure that in all SF 36 sub-scales the general population mean is 50 with a *SD* of 10. NBS hence puts the sub-scales' scores in both versions on the same metric making comparisons and their joint display meaningful. Without referring to tables of norms it is clear with the NBS method that scores above or below 50 can be interpreted as above or below the general population norm. And, because *SD*s for each scale are standardised at 10, it is easier to see exactly how far above (or below) the mean a score is in *SD* units.

The eight sub-scales were combined into a physical and a mental component score (PCS; MCS) (Ware *et al.*, 1994; 1995). The PCS primarily reflects the dimensions of physical functioning, role limitation caused by physical health problems, pain, and

general health perceptions. The MCS reflects primarily mental health, role limitations caused by emotional problems, social functioning and vitality. For the purpose of research, utilising the summary scores in contrast to using the eight individual SF-36 measures, makes it possible to reduce the number of statistical comparisons and thereby the role of chance in testing hypotheses. Validation studies make it clear that little information is lost when aggregating the eight sub-scale scores into PCS and MCS (Ware *et al.*, 1994; 1995).

2.3.b Medical measures

Patients' medical notes were reviewed to extract relevant medical information (see Appendix D).

i. *Dialysis adequacy measures*

Dialysis adequacy was assessed by a calculated kinetic transfer/volume urea measurement (Kt/V) in both HD and PD patients. Only measurements of adequacy made within six months of the study assessment were used for analysis purposes. The average of the adequacy value was used for those patients who had more than one measure during the six-month period. Treatment was considered adequate when Kt/V met or exceeded the UK Renal Association Guidelines (1997) as follows: for CAPD, a Kt/V of 1.70; for APD (without a daytime dwell) a Kt/V of 2.0; for HD, a Kt/V of 1.20. Absolute scores for Kt/V on HD and PD are not directly comparable (Mallick *et al.*, 1998); consequently for analysis purposes these were converted to standard z-scores.
PD and HD adequacy measures are based on urea clearance but are routinely used as a proxy for measurement of the clearance of small solutes in general. They are described separately in the following sections, as the methods used for calculation are different between HD and PD patients.

(a) HD adequacy

Dialysis delivery in HD was assessed using two related methods: urea reduction ratio (URR) and a single pool of a variable volume urea kinetic determination of Kt/V (Gotch, 1995; Sargent & Gotch, 1975; 1989).

URR (Idem, 1991; Lowrie & Lew, 1991) reflects the fractional reduction in the blood urea nitrogen concentration during a haemodialysis session (Basile *et al.*, 1990; Daugirdas, 1989; 1993; Gotch *et al.*, 2000). URR is calculated with the formula 100 x $(1-[C_t/C_0]$, in which C_t is the post-dialysis blood urea nitrogen (BUN) and C_0 is the predialysis BUN.

For the present study, when and where available Kt/V indices were documented in addition to URR as its use is recommended over that of URR on the premise that it offers enhanced accuracy for calculating total clearance scores (Li *et al.*, 2000).
The Kt/V formula is a dimensionless urea kinetic parameter related to URR. The predialysis and postdialysis BUN concentrations, from which URR is calculated, and body weight are used in practice to estimate Kt/V. It is expressed as the ratio of total urea clearance (K in millimeters per minute) by the length of individual treatment (t: hours) product to the volume of urea distribution in a particular patient (V in millimeters). V stands as a proxy for body mass/size and therefore nutritional status.

Many formulae have been proposed to calculate Kt/V. In the present study the formula used in the participating renal units was applied. Kt/V was hence calculated by the second-generation Ln formula of Daugirdas (1993) as follows: $Kt/V = -Ln(R - 0.008 \times t)+(4 - 3.5 \times R) \times UF/W$ in which Ln is the natural logarithm; R is the postdialysis BUN , predialysis BUN; t is the dialysis session length in hours; UF is the ultrafiltration volume in liters; and W is the patient's postdialysis weight in kilograms.

Concerns and criticisms regarding limitations and inadequacies of both URR and Kt/V have been raised (Gotch, 2001; Lowrie *et al.*, 1998) but a full discussion of these are beyond the scope of this study.
Both methods are widely accepted, compound measures of HD dose (National Kidney Foundation Dialysis Outcome Quality Initiative: NKF-DOQI 1997b), the routine use of which is recommended (NKF-DOQI 2000 website; www. kidney.org/ professionals/ kdoqi/guidelines) when formal urea modelling is not practised.

(b) Peritoneal dialysis adequacy.

Several methods of quantifying the PD dose have been described but no standard accepted method exists (Kopple *et al.*, 1995, Robertson *et al.*, 1995). Total weekly Kt/Vurea and total creatinine clearance normalised to 1.73 m2 Body Surface Area (CL_{CR}) are considered to be among the best options (Selgas *et al.*, 1993) because they are most strongly associated with mortality and morbidity (Churchill, 1994; Churchill *et al.*, 1996; Diaz-Buxo *et al.*, 1999; Keshaviah et al. 2002; Rocco *et al.*, 2000; Szeto *et al.*, 2001; Teehan *et al.*, 1994).

Both indices were recorded (if available) for the purposes of this study. The urea-based measure, Kt/Vurea, measures removal of the direct product of protein catabolism. The creatinine clearance (CL_{CR}) measures removal of a product of muscle metabolism, which provides insight into lean (i.e., fat-free, oedema-free) body mass and possibly into adherence. The calculation of weekly Kt/V and CrCl was performed by standard methods, using data from 24-hour dialysate urea excretion and urine collections/and the serum urea concentration (NKF-DOQI 1997b). Peritoneal CL_{CR}. urea Kt/V were calculated using the computer based kinetic modelling program PD Adequest™ version 1.4 (Vonesh, & Keshaviah, 1997; Vonesh *et al.*, 1991).

ii. *End-Stage Renal Disease Severity Index* (ESRD-SI)

The ESRD-SI (Craven *et al.*, 1991) was used as a measure of co-morbid illnesses and other ESRD complications. As implied by its name, it is a ESRD-specific comorbidity measure that assesses severity of illness (ESRD) as a function of 11 organic conditions: heart disease, cerebral vascular disease, peripheral vascular disease, peripheral neuropathy, bone disease, respiratory disease, visual impairment, access and dialysis events, autonomic neuropathy gastrointestinal disease and diabetes. For use with the transplant patients the item referring to 'access or dialysis events' was replaced with 'transplantation events' (such as infection or rejection episodes) as the former was clearly inappropriate for patients with a functioning kidney transplant.

The index is designed for use by either an independent clinician investigator with full access to medical information, or the patients' own physician. In this study a

Nephrologist familiar with the patient completed the ESRD-SI on the basis of her knowledge of the patient's condition and their medical record. The severity of each condition is scored on a Likert-type scale ('absent', 'very mild', 'mild', 'moderate', 'severe', 'very severe'). Each of these rating points corresponds to descriptions, which are provided for each ESRD-SI category. These examples are provided to guide the raters and to correspond to scores which are defined in the following ranges: 1-3 for biochemical or mild indication of disease; 4-6 for moderately severe physical signs, handicap or prognosis; 7-8 for severe physical handicap or prognosis; and 9-10 for an imminently lethal condition. The scoring system gives a different range of scores for each disease item and the additive sum of item scores provides the total severity index.

The inter-rater reliability of ESRD-SI has been reported at r = .92 with a test retest correlation of r = .92 over one-week period (Craven *et al.*, 1991). The ESRD-SI has been shown to be significantly related to age (Eitel *et al.*, 1995), functional ability (Griffin *et al.*, 1991) and physiological measures of severity of illness such as serum albumin and creatinine levels (Griffin *et al.*, 1995), i.e. blood serum levels that have been found to predict mortality risk in ESRD patients (Lowrie & Lew, 1990, Owen *et al.*, 1993).

Section 3: NP outcomes in ESRD

3.1 Participants

Transplant and dialysis patients participated in this study (see sub-sections 1.1 - 1.2) Recruitment methods (for this sub-study) were therefore identical to those described in section 2.2.a.

3.2 NP Measures

NP tests were selected on the basis of previous reports of their sensitivity and their acceptance and extensive use in the general medical and renal literature (Lezak, 1995; Reitan, & Wolfson, 1993). As this study was designed as an exploratory investigation, a wide range of NP tests assessing various cognitive abilities (attention concentration, psychomotor speed, verbal memory, learning, visual memory, motor functioning) was used. Among those emphasis was given to tests of cognitive functions known to be impaired in renal patients, i.e. attention tasks (Hart & Kreutzer 1988; Pliskin *et al.*, 2001).

i. *Trailmaking test - Forms A and B* (TMT)

TMT (Reitan & Wolfson, 1993) is a two part measure of attention, visual scanning, motor speed and planning ability. Part A (TMT-A) requires participants to connect 25 randomly arranged numbers in the right order. Part B (TMT-B) requires participants to connect a series of numbers and letters in sequence (i.e., 1-A-2-B-3-C.....13) as quickly as possible. Both parts of the tests are timed (number of seconds) to completion with lower scores indicating better cognitive function. Slow scores on either part A or part B have been used as an indication of a likelihood of diffuse brain damage. A slow score on the part B in particular may indicate difficulties in conceptual motor tracking (Bremer *et al.*, 1997). TMT is considered to be one of the best measures of generalised brain functioning (Reitan & Wolfson, 1993). Three parallel forms of Part B which have

satisfactory comparability (Lezak, 1995) were used in order to keep practice effects at a minimum.

ii. *Symbol Digit Modalities Test* (SDMT)

SDMT (Smith, 1968; 1973) assesses a variety of cognitive functions, including immediate visual memory, learning, hand-eye co-ordination, and reading-writing ability. It is very sensitive for detection of an acquired acute or chronic cerebral deficit but is no specific for localisation of such a deficit (Smith, 1973).

It consists of rows containing 110 blank squares each paired with a randomly assigned abstract symbol. Above these rows there is a printed key that pairs each symbol with a number from one to nine. Following a practice run on the first ten, participants are requested to match the printed abstract symbols with the specific number identified in the key as quickly as possible within a specific time frame (90 seconds). The score is the number correct so that higher scores signify a better performance. The test lends itself to a written and oral administration form to allow comparisons between visuomotor and oral responses. The written administration was given first in accordance with the instructions (Lezak, 1995), followed by the oral administration.

iii. Rey *Auditory Verbal Learning Test* (RAVLT)

This is an auditory verbal memory task that assesses immediate memory as well as retrieval from short-term memory storage. RAVLT (Rey, 1964) also provides a learning curve, reveals learning strategies or their absence, elicits retroactive and proactive interference tendencies to confusion or confabulation of memory task and allows for a comparison between retrieval efficiency and learning.

It consists of five presentations with a recall of a list of 15 words, the one presentation of a second 15-word list and finally a sixth recall trial of the original word list. In the first 5 attempts, participants are asked to recall as many of the words as possible after each reading of the list by the examiner whereas for the last attempt word retrieval form short term memory is assessed as participants are requested to repeat as many words as

they can but without the examiners reading them out. Alternative forms were used for the repeat assessments (Crawford *et al.*, 1989; Lezak, 1995).
Two scores were obtained: total verbal recall from trials 1 to 5 (RAVLT-T) and drop in retention from trial 5 to 7 (RAVLT-D).

iv. *Benton Visual Retention Test* (BVRT)

BVRT (Benton, 1974) is a measure of visual perception, visual memory and visuoconstructive abilities.
Ten cards featuring 1 to 3 designs are sequentially presented to participants for 5 - 10 seconds after which time participants are requested to reproduce or copy depending on the administration method employed. For this study, administration A was used which allows 10 seconds exposure to each of the 10 cards with immediate recall by drawing. Administration A was preferred primarily to ensure continuity and comparability with previous studies and also to minimise time costs and strain on the participants associated with the more lengthy administration forms (i.e. administration D). The BVRT has three equivalent forms which were used in this study in counterbalanced order.
The number of correct reproductions (BVRT-C) and number of errors (BVRT-E) were recorded. Six types of errors are recognised: omissions, distortions, preservations, misplacements and errors in size. Thus there can be, and not infrequently are, more than one error to a card. Tabulation of errors by type allows the examiner to determine the nature of patient's problems on this test.

The BVRT is very stable and has a high reliability on repeated administrations (Lezak, 1995). Since this test involves so many different capacities it is considered to be very sensitive to brain damage and it also appears to be sensitive to cognitive alterations that accompany normal ageing (Lezak, 1995). This test was not used in TX assessment due to some logistical constraints.

v. *Grooved Pegboard* (GP)

GP (Klove, 1963, Matthews & Klove 1964) is a test of fine motor co-ordination and manual dexterity. It is known to be sensitive to both focal and diffuse cerebral

impairment and may aid in the detection of lateralised disability or motor dysfunction that can occur despite intact capacity for normal movement.

It involves placing 25 pegs as rapidly as possible into an equivalent number of similarly shaped holes, but whose orientation to the vertical varies to so that the test requires frequent turning and fitting of the pegs. The GP is a timed test so the score is timed to completion with higher scores demonstrating a slower and thus worse performance. Both dominant (GP-DOM) and non-dominant hands (GP-NDOM) were tested so that right to left hand score comparisons (indicative of right and left hemisphere disease) could be made. Hand dominance was determined as the hand used for signing the consent form.

vi. *Subjective Cognition Scale* (SCS)

A subjective cognition scale (Newman *et al.*, 1989) was included in this study to determine if participants perceived any acute and long-term changes in their cognitive function as a result of their treatment (dialysis and transplantation).

The scale administered as a semi-structured interview includes nine questions. The questions look at nine areas of cognitive function and patients are asked to indicate whether each particular aspect had improved, deteriorated, or shown no change (a) since onset of treatment (dialysis or transplantation) and (b) compared to 24-hours previously.

The semi-structured interview on cognitive complaints was hence given twice to the dialysis groups, each time prior to each of the scheduled neuropsychological assessments. Appropriate amendments in the time frame of the scale (as mentioned above) were introduced so as to capture acute and long-term subjective cognitive complaints. At the time of the first NP assessment the long term perceived cognitive changes were assessed. Patients were asked to indicate cognitive amelioration or deterioration since their respective treatment was introduced (i.e. since dialysis onset or since transplantation).
During the second NP assessment (dialysis only), questions related to acute cognitive changes experienced over the 24-36 hour time interval were asked.

The nine cognitive domains addressed include: memory, problem solving, clarity of thinking, concentration, making mistakes, attention, clumsiness, decision making and speed of response. Five of these questions related to the objective NP tests used whereas the questions on problem solving activity, clarity of thinking and making mistakes are either too broad or were not specifically addressed in the neuropsychological tests described above.

These domains concern patients' perspective on their cognitive functioning and can be compared to the formal objective neuropsychological evaluation using the NP tests described above. Previous studies using similar cognitive complaints self reported scale have highlighted the lack of one to one correspondence between self-report cognitive functioning and objective NP scores (Brickman *et al.*, 1996).

3.3 Procedure

3.3.a NP Data Collection

TX patients completed only one assessment while both HD and PD patients completed two NP assessments over a 24 hours interval so as to evaluate acute NP changes over the dialysis cycle.

HD patients were assessed 2 hours prior to their regularly scheduled dialysis session (T1) and at approximately 24 hours after the end of their last dialysis session (non dialysis day; T2). This interval, in accordance with previous research protocols (Lewis *et al.*, 1980; Ratner *et al.*, 1983) was chosen to allow time for the observed dialysis-related disequilibrium effects to wear off and to provide participants with a time of relative convenience for testing. It is to be noted that study participation for hospital HD patients necessitated an additional hospital visit to the three scheduled dialysis sessions. This posed problems for some patients and may explain some of the refusals to participate.

An identical protocol was followed for home HD with one unavoidable difference: T1 assessment had to take place at the patients' home rather than the hospital as travelling to hospital for the purposes for the study and then back home for dialysis would be severely disruptive. Home HD patients on their dialysis days are expected be at their

home to set up HD machine and initiate dialysis session on time. The researcher therefore visited them at home to administer the NP tests.

Assessment time intervals for the PD group mirrored those of the HD group as these patients were in effect used as a control group. In order to reduce inconvenience, the first assessment was strategically planned to coincide with patients' regular monthly check up at the PD Unit while the second assessment took place approximately 24 hours following their clinic visit. Each participant was tested at approximately the same time every day (± 3 hours) on the two assessments to control for variations in performance due to possible diurnal effects (Kraemer *et al.*, 2000).

Every NP assessment session was structured as follows. After the completion of part 1 of the study questionnaire and self-report cognition scale the researcher proceeded with the administration of neuropsychological tests. All participants were however given an option to have a break beforehand and resume in 10 minutes.
NP tests were administered in the order as listed above. This was determined primarily by their cognitive domain focus with all attention or memory tasks administered together, and secondarily by their degree of difficulty, with the relatively easier tasks within each cognitive domain preceding the more difficult ones so as to optimise patients co-operation, boost motivation and foster a sense of achievement, and thus optimise patients' performance.
Parallel forms of the tests, where available, were used for the majority of the instruments in order to limit the effects of learning across the two assessments. The order of parallel form administration was counterbalanced. Practice trials were also administered, as per standard instructions for many of the tests (TMT-A; TMT-B, SDMT-W; SDMT-O; BVRT; GP-D; GP-ND) to ensure that the first testing did not reflect either the subjects' lack of familiarity with the task or a less than stable threshold.

The neuropsychological testing situation was designed to elicit maximum performance from all participants with testing being discontinued if a patient became fatigued, nauseated or unable to perform at an optimal level. NP testing took approximately 30 - 45 minutes. All assessments, with the exception of Home HD patients (T1 assessment) took place in the same specially designated room in the research unit.

To reduce within individual variability due to external confounding variables the two NP assessments of dialysis patients were conducted under similar environmental conditions. This included keeping the same examiner for all assessments, using the same apparatus (e.g. pen) and conducting the tests as much as possible at the same time of the day, and in the same context (home visit or outpatient clinic) (Moffoot *et al.*, 1994; Porterfield *et al.*, 1997).

Training of the examiner in NP assessment had also been undertaken prior to study recruitment. This included: NP test presentation (e.g. general principles, NP instructions, frequently encountered problems), attending sessions of NP assessment led by the NP instructor, and conducting supervised NP assessment of healthy volunteers, followed by 2 sessions of supervised assessment of clinical patients.

3.3.b Collection of blood samples

In order to relate NP functioning to biochemical variables, blood samples were taken **after** the completion of each NP testing session so as to avoid interference of possible venopuncture pain with participants' NP performance. An experienced HD, PD or transplant sister was responsible for taking the blood samples. All blood samples were delivered to respective laboratories ideally within 2 hours of collection.
Laboratory analyses consisted of the measurements of blood concentration of urea (BUN), creatinine (Cr), sodium (NA^+), potassium (K^+), phosphate (PO_4), calcium (Ca^{2+}), alkaline phosphatase (Alk-P-Tase), haemoglobin (Hb) and albumin (Alb). The most recent aluminium values (if within 3 months) were also recorded.

In HD patients on their dialysis day assessment (first NP test administration), blood samples were drawn immediately after the study assessment while patients were being set up on the HD machine.
For the patients on home HD programme, however, blood sampling immediately prior to their dialysis session was not feasible because no medically trained staff was available to take the blood samples (Hospital regulations disallowed blood taking procedures by any person other than the ones appointed and officially (NHS) employed for patients' health care and management).

Section 4: The Development of the Transplant Effects Questionnaire (TxEQ)

In the absence of the availability of a psychometrically sound transplantation specific instrument, which examined the impact of transplantation, a questionnaire was developed to cover this aspect of the study. TxEQ was developed to assess additional domains not covered in traditional generic HQoL measures. The questionnaire was intended to elicit recipients' emotional and cognitive responses to transplantation.

This section outlines the work on the development and psychometric evaluation of the Transplant Effects Questionnaire (TxEQ), which was subsequently used for the assessment of TX recipients.

Phase I describes the preliminary work conducted leading to the development of the initial TxEQ items.

Phase II consisted of two studies conducted to test the acceptability of the new instrument and to examine its psychometric properties:

- Study 1a was the piloting of the initial questionnaire and the evaluation of the internal structure of TxEQ leading to the development of the final TxEQ items
- Study 1b involved the confirmation of the internal structure of the new measure and validation analysis

4.1 Phase I: development of the initial TxEQ

To identify the issues facing transplant recipients, an extensive literature review, and field-testing based on focus group, in-depth interviews, pilot testing with transplant patients and expert panel review were used. The triangulation of such quantitative and qualitative methodologies was thought to be the best method to capture transplant patients' perspective and experience.

4.1.a Literature review

The published literature was examined by means of a computer-based search using the MedLine (1966-1999) and PsychLit databases (1966-1999). Combinations of the following key words were used: '*transplantation*'; '*transplant*'; '*cadaver*'; '*living related*'; '*donor*'; '*quality of life*'; '*health status*'; '*renal*'; '*stressors*'; '*adherence*'; '*compliance*'; '*immunosuppressive*'; '*medication*'; '*side-effects*'; '*donation*'; '*emotional*'; '*adjustment*'; '*well-being*'; '*functioning*'. Additional papers were identified by reviewing/manually searching reference lists of the obtained articles.
In each case note was made of the transplant group studied, the source of the transplant (cadaver or form a living donor), and the measures used (generic or transplant-specific).

Based on the review of literature a list of relevant open-ended questions was then constructed for use in a focus group and individual interviews with kidney transplant recipients. The questions covered the following issues and themes that had all emerged from the literature:

- impact of transplantation on patients and their families (e.g. What are the most important effects of having a transplant?)')
- contrast between life prior and post-transplant (e.g. 'Does life after transplantation meet your expectations?')
- concerns related to and side effects of anti-rejection medication (e.g. 'Were there any problems you have experienced in relation to your treatment or to your recovery?')
- interpersonal attitudes towards donor or donor family (e.g. 'What do you know about the donor?'; 'Do you ever wonder about the characteristics of the donor?')
- feelings of indebtedness gratitude and guilt towards the donor or donor family (e.g. 'How would you describe your feelings toward the donor/donor family?'; 'Do you feel obliged to pay back the donor for the gift of donated organ?')

4.1.b Field testing (Focus Group - Interviews)

A focus group and three semi-structured interviews with transplant recipients were conducted to explore issues of particular relevance and importance to transplant recipients.

Patient input in the development process in particular might be critical to the success of an instrument in obtaining relevant data (Bergner *et al.*, 1981; Hays *et al.*, 1994). It was also thought that the first hand contact and discussion with the recipients themselves, in these early stages of the study would familiarise the researcher with the vocabulary and thinking pattern of patients with a kidney transplant and hence inform the phrasing and wording of the questionnaire items.

The focus group included one female and two male patients with a functioning cadaver kidney transplant (one female patient failed to attend due to some unexpected family illness). Three in depth interviews were subsequently undertaken with three male LRD TX recipients.

Both the focus group discussion and the interviews were run using a standardised protocol with open-ended questions as described above and discussion. Although the list of open-ended questions (see Appendix E) provided the basis of the discussion, when necessary researchers elaborated on issues raised by the participants and probed them to ensure that any subject of importance to the participants was adequately addressed.

The facilitators aimed not to take anything for granted and to be as 'naive' as possible. A non-judgmental approach in relation to the content of the interviews and a confirmative approach to the participants were the guidelines for the conversation. The interviews were conducted as informal conversation and allowed participants to put their reactions into words and test their opinions in a dialogue with the interviewer (Kvale, 1994). Discussions were audiotaped, transcribed (verbatim) and reviewed to identify themes and group distinct thoughts into related categories (Bass *et al.*, 1999).

Comments from focus group participants and interviewees indicated that many were concerned about the side-effects of immunosuppressive medication, but despite these concerns, self-reported adherence rates were very high.

Several participants raised concerns about the viability of their kidney and about resuming and engaging to physical and social activities that could potential threat their health or put their transplant at risk. Comments such as '*the freedom was replaced by a fear of transplant failure*', '*I am still apprehensive about rejection 4 years after operation*' highlight these issues.

All of the participants unanimously indicated that transplantation had met their pre-transplant expectations about how they would feel. They had all anticipated that the receipt of a new kidney would release them from the constraints associated with dialysis and that it would facilitate and mark the return and resumption of normal living and activities. Quotes made by the participants include '*I hated dialysis*'; '*I felt a lot better instantly after the operation*'; '*The kidney is freedom*'; '*it is worthwhile going for a transplant no matter what the circumstances are*'.
It is also of interest that they no longer feel themselves to be patients despite fully acknowledging the vital importance of the treatment they continue to receive.

A common theme among participants, primarily living related transplant recipients that had not emerged in the literature review, related to issues 'disclosure' with regard to their transplant. The term 'disclosure' was used to describe:

(a) individuals' difficulty in talking about or expressing feelings about the donor or the act of donation

(b) recipients' readiness or reluctance to communicate to others that they have a transplant

The issues to do with transplantation identified in this two-stage procedure were combined into items and refined by two raters. The resulting 315 items were subsequently assessed for comprehensibility and redundancy by two raters.
This process resulted in 51 items that represented nine key themes relating to receiving a transplanted organ: outcome of transplantation, fear of rejection, self-care principles, adherence, feelings of guilt, feelings of indebtedness, having a foreign body part, interpersonal relationships (i.e. with family and friends), and emotions.
The relevance, clarity and conciseness of the reduced pool of 51 were then subjected to expert panel review (transplant professionals including two renal consultants and two transplant nurses).

4.1.c Field testing - Pilot study

Lastly the resulting scale was successfully piloted with a small group (n = 7) of first time renal transplant recipients of whom four had received their transplant from a living related donor.

The pilot sample consisting of 4 male and 3 female transplant recipients that had a mean age of 46.2 years (*SD* = 6.83) and who had their transplant an average of 7.66 years (*SD* = 4.95) prior to the pilot. Overall, patients reported the items to be clear. All participants in the pilot study reported no difficulties understanding the wording of the items and completing the new measure. The layout of the questionnaire was slightly modified as a result of patients' feedback and specific recommendations.

4.2 Phase II: TxEQ application - Study 1a and Study 1b

In Phase 2, two studies were sequentially conducted to examine the psychometric properties and structure of this final pool of 51 items of the Transplant Effects Questionnaire (TxEQ).

Data collected in postal survey of a second transplant sample (study 1a) was used to explore the internal structure of the new measure (TxEQ). Data collected from the MIDDX transplant patients (see section 1.1) in a 'face to face format' (study 1b) were then used to confirm the observed (in postal survey; study 1a) internal structure, and to examine test-retest reliability and criterion validity.

4.3 Postal Survey- Study 1a

4.3.a Procedure

For the development of TxEQ a **second** sample of renal transplant recipients was recruited from another transplant centre. Following ethics committee approval all (*n* = 333) renal transplant patients registered at Royal Free Hospital (RFH) were sent a covering-invitation letter and a questionnaire pack consisting of the 51-item TxEQ, and questions about their medical history, and demographic details. To ensure and encourage frank responses the questionnaire had a code number but not the participants' name. Four weeks were allowed to return the questionnaire. After that time a reminder letter and another copy of the questionnaire were sent to non responders and another 2 weeks were allowed for completion after which time data collection was terminated.

4.3.b Participants – TX Sample 2: (RFH-TX)

For the postal survey all adult transplant recipients (n = 333) registered at the Royal Free Hospital, London UK (RFH-TX), Transplant outpatient clinic were invited to participate. No exclusion criteria other than age below 18 years of age were applied. Out of the 333 patients contacted, two hundred and thirty one (n = 231) patients completed and returned the questionnaire giving a response rate of 69.4%. This is higher than the anticipated response rate for this type of study (Grady & Wallston, 1988).

Participants were almost equally divided between male and female, had a mean age of 45 years and had been living on a renal transplant for a mean of 9.93 (SD = 6.76) years (see Table 5.3)

Table 5.3: Sociodemographic and clinical characteristics of the RFH-TX sample

	RHF TX	
	M (SD)	*% (N)*
Age	45.15 (14.51)	
Gender (% female)		48.9 (113)
Source of TX (% LRD)		22.1 (51)
Time since TX (in years)	9.93 (6.76)	
No of comorbidities	.67 (1.11)	
Diabetes (%)		9.1 (21)
Hypertension (%)		59.5 (138)
Heart conditions (%)		6.9 (16)
Number of previous transplants	1.19 (.45)	
On Dialysis prior Transplant (%)		91.7 (210)
Time on dialysis (months)	34.52 (42.47)	
Education (age years left school)	18.07 (4.47)	
Relationship status (% in a relationship)		57.6 (133)
Work status (% employed f/t, p/t, student)		136 (58.6)
Able to work (f/t, p/t)		68.8 (154)
Annual family income		
0 - £10,000		18.2 (40)
£ 10,001 - £ 20,000		18.2 (40)
£ 20,000 - £ 30,000		12.7 (28)
> £ 30,000		18.6 (41)
do not wish to answer		32.3 (71)
Own home (%)		60.5 (138)

Note: TX = transplantation; LRD = living related donor transplant; f/t = full time; p/t = part time

4.3.c Postal Survey-Measures

i. *Sociodemographic and medical assessment*

Sociodemographic questions included: age, gender, ethnic background, first language, marital status, time with current partner if any, educational qualification, years in schooling, working status pre and post transplantation and one question on perceived ability to work (Evans *et al.*, 1985).

A list of items was also compiled to obtain basic medical information on patients' dialysis and transplant history including ESRD diagnosis, previous transplant failures, time spent on dialysis, type of dialysis treatment and time elapsed since their current kidney transplant.

Patients were also asked to list any other disability, comorbidity or infirmity. Participants' medical records were subsequently reviewed to confirm and verify presence or absence of the following comorbid conditions: diabetes, hypertension, ischaemic heart disease, coronary heart disease, atrial fibrillation and previous incidence of myocardial infarction. A comorbidity total score was computed by simply adding the number of diagnosed comorbid conditions.

ii. *TxEQ*

The 51-item Transplant Effects Questionnaire was used to assess transplant specific outcomes. The instructions of the TxEQ were as follows: 'We are interested in your own personal views of how you now see your experience with your kidney transplant. These are statements other people have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box.'

Questionnaire items were positively and negatively worded. A positive and negative item wording was used to avoid acquiescence, affirmation or agreement bias. They were presented in a mixed order and rated by the participants in a five point Likert scale ranging from strongly disagree to strongly agree (scored from 1 to 5).

See Appendix C for the TxEQ questionnaire sent to RFH TX participants

4.3.d Analysis

Statistical analysis was performed using the SPSS for Windows (version 10.1). Item responses in the TxEQ from the study 1 sample were subjected to an exploratory principal components analysis (PCA) with varimax rotation (Kaiser normalisation). As a means of eliminating items to achieve a simple coherent structure extraneous items were omitted on the basis of: the Kaiser Meyer Olkin (KMO) statistic for each item, factor scree plot and final factor loading as described below (Norusis, 1992). The numbers of factors extracted was determined though observation of the altering gradient of a scree plot (a graph of Eigen values against factors) and an Eigen value of more than 1.

4.3.e Results – Internal structure of TxEQ

Initial PCA resulted in a 15-factor structure. A factor scree plot suggested a six factor solution (46.7%). Subsequent omission of 27 items with low loadings (<.45) spread across these factors and less than 30% overlapping variance replicated the six factor solution, accounting for 64.2 % of the variance in the responses to the TxEQ. The KMO statistic for the remaining 24 items ranged from 0.69 to 0.86 (mean = 0.79). All six factors identified had acceptable internal reliabilities. Cronbach alphas ranging from .72 to .86 (thus satisfying Nunnally's criterion of 0.7; Nunnally, 1978) (Table 5.4 below).

Items were found to be largely grouped in conceptually coherent factors.
Factor 1 comprised six items relating to worries regarding the transplant (22.31%; α = 0.81). Items loading on factor 2 referred to feelings of guilt towards the donor (11.94%; α = 0.76). Three items loaded respectively on the third factor tapping disclosure issues regarding the transplant (9.58%; α = 0.86) and on the fourth factor reflecting medication adherence (8.73%), whereas factor 5 contained items relating to perceived responsibility towards others (6.63%; α = 0.72). Factor 6 (5.04%), however, appeared to be thematically incoherent, with two items (C9 and D1) relating to adherence and a third (G2) to taking on qualities of the donor. However the two adherence items did load on the adherence factor (factor 4) (0.22 and 0.29, respectively) despite varimax rotation. It was therefore decided to group items C9 and D1 into factor 4 and drop item G2 from further analysis. The resulting adherence factor showed high internal consistency (α = 0.79).

In summary the exploratory factor analysis (EFA) determined 6 factors which were reduced to 5 thematically coherent factors: worry about the transplant, guilt, adherence, disclosure and responsibility.

All five sub-scales had acceptable levels of internal consistency (Cronbach α ranged from .72 to .86).

Table 5.4: PCA of theTxEQ*: factor loadings, variance explained, communalities, Cronbach alpha

	ITEMS	Loading	h^2
	Factor 1: '*worry about transplant*' Eigenvalue = 3.14; Cronbach alpha = **.81** Total R^2: **13.1%**;		
B2	I am worried about damaging my transplant	.82	*.71*
B1	With regard to my transplant I feel that I am carrying around something fragile	.76	*.64*
B5	I am hesitant to engage in certain activities because I am afraid of doing harm to my transplant	.75	*.60*
B3	I keep wondering how long my transplant will work	.71	*.59*
C1	I monitor my body more closely	.64	*.46*
D2	I worry each time my anti-rejection drug regime is altered by my doctor	.47	*.53*
	Factor 2: '*guilt regarding donor*' Eigenvalue = 2.94; Cronbach alpha = **.76**; ΔR^2: 12.2%; Cumulative R^2: **25.3%**		
E4	I feel guilty about having taken advantage of the donor	.83	*.77*
E1	Sometimes I think that I have 'robbed' the donor of a vital part	.76	*.63*
E3	The donor had to suffer to make me feel better	.73	*.58*
F2	I have the feeling that the donor/the donors' family has some control over me	.66	*.61*
E2	I do not have any feelings of guilt towards the donor	-.56	*.44*
	Factor 3: '*disclosure*' Eigenvalue = 2.47; Cronbach alpha = .86; ΔR^2: 10.4%; Cumulative R^2: 35.7%		
I2	I avoid telling other people that I have a transplant	.90	*.83*
I1	I am uncomfortable with other people knowing that I have a transplant	.86	*.75*
I4	I have difficulty in talking about my transplant	.85	*.80*
	Factor 4: '*adherence*' Eigenvalue = 2.46; Cronbach alpha = .79; ΔR^2: 10.3%; Cumulative R^2: 45.9%		
C6	Sometimes I do not take my anti-rejection medicines	.85	*.77*
C2	Sometimes I forget to take my anti-rejection medicines	.83	*.77*
C4	When I am too busy I may forget my anti-rejection medicines	.80	*.68*
C9	*Sometimes I think I do not need my anti-rejection medicines*	.22	*.76*
D1	*I find it difficult to adjust taking my anti-rejection medicines*	.29	*.62*

* the final questionnaire consists of 23 items as 1 item was dropped for conceptual reasons

	Factor 5: '*responsibility*' Eigenvalue = 2.22; Cronbach alpha = .72; ΔR^2: 9.3%; Cumulative ΔR^2: 55.1%		
F3	I think that I have a responsibility to the transplant team to do well	.77	*.60*
F6	I think that I have a responsibility to my friends and family to do well	.75	*.60*
F5	I feel that I owe the donor/the donor's family something that I will never be able to repay	.73	*.60*
F1	I feel that I have a responsibility to the donor/the donor's family to do well	.65	*.55*

Note: ΔR^2 = additional variance explained

4.4 Study1b: TxEQ reproducibility and test-retest reliability - face to face assessment

4.4.a Procedure

The TxEQ was completed by consenting transplant patients (TX-MIDDX) who took part in the full study protocol (see section 1.1). Questionnaires were completed in the presence of a researcher in order to clarify any queries. The TxEQ was administered within the first 30 minutes of the assessment. To evaluate the test-retest reliability, another copy of the TxEQ was sent to all participants four weeks later together with an explanatory cover later. Recruitment, consenting and data collection procedures are described in more detail in section 2.2.

4.4.b Participants

Table 5.2 presented earlier depicts the sociodemographic and medical characteristics of the recruited sample (MIDDX-TX). Of 115 that completed the first administration of the TxEQ, eighty-two patients returned the same questionnaire at the second administration (postal survey) giving a response rate of 71.3% (attrition rate = 29.7%).

T-tests analyses between the two transplant samples (RFH-TX and MIDDX-TX) on sociodemographic and medical history variables revealed four significant differences. RFH TX participants were significantly older ($t(251.13) = 3.25$; $p = .001$), had developed or been diagnosed with kidney disease at an older age ($t(326) = 3.51$, $p = .001$), were significantly older when received their current kidney TX ($t(259.27) = 5.62$,

p = .0001), and had been living on their current transplant for less time compared to MIDDX TX participants (t(286.30) = -5.49; p = .0001).

4.4.c Analysis

To confirm the internal structure observed in the TxEQ postal survey (RFH-TX; study 1a) TxEQ data from the MIDDX-TX sample were subjected to confirmatory factor analysis (CFA) using structural equation modelling. Statistical analysis was conducted using the windows version of AMOS 3.1.

There are a number of different fit indices that can be used in CFA, although no widespread agreement currently exists about which is the best (Maruyama, 1998). Closeness of fit based on the Root Mean Square Error of Approximation index (RMSEA) (Browne & Cudeck, 1993) was used to examine the extent of fit in the questionnaire factor structures from the two study samples.

The RMSEA is a measure of discrepancy of fit, as it illustrates how much error there is between the estimated parameters and the actual parameters taken from the data after taking into account number of degrees of freedom. The RMSEA measure was used in preference to the CFI (or any other measure of fit) because it provides a robust measure of closeness of fit for the model, which is considered by Browne and Cudeck (1993) to be "more reasonable than the requirement of exact fit". In addition, McCallum *et al.* (1996) recommend the use of RMSEA instead of point estimates of model fit in the population. Work by Rigdon (1996) has demonstrated the utility of the RMSEA as an index of the degree to which a confirmatory structure approximates the data being modelled. Hu & Bentler (1999) suggest optimal cut-off of close to 0.6 for RMSEA, with values of 0.08 being acceptable. Browne & Cudeck (1993) have suggested that values of 0.05 and below indicate a close fit of the model and the values of the RMSEA between 0.05 and 0.08 approximate a reasonable error in approximating a given structure. They also provide a test of the hypothesis that the population RMSEA for the model is no greater than 0.05. Failure to reject this hypothesis at $p < .05$ signifies that the model is a close fit to the data.

4.4.d Results

i. *Internal structure*

CFA was performed using the AMOS structural equation modelling application (Arbuckle, 1997). A measurement model was defined with 5 uncorrelated latent variables (as described in the exploratory factor analysis section above).

The resulting model was found to be a good fit for the data (RMSEA =0.08; *p*close = 0.005) as defined by Browne & Cudeck (1993). Analysis of the second (MIDDX-TX) TxEQ data set confirmed the 5 factor structure: 'worry about the transplant', 'guilt', 'disclosure', 'adherence' and 'responsibility'.

ii. *Test-retest reliability*

One-month test retest reliability of the TxEQ was found to be acceptable for all sub-scales (see Table 5.5). Test-retest correlation coefficients were r = .797 for factor 1 ('worry about the transplant'), r = .689 for factor 2 ('guilt'), r = .60 for factor 3 ('disclosure'), r = .772 for factor 4 ('adherence') and r = .703 for factor 5 ('responsibility')

4.4.e Discussion

The TxEQ was designed to allow a comprehensive, sensitive and easy to administer instrument of those aspects of transplantation that have been identified to be the most important. Although it was developed on individuals in receipt of a renal transplant it has been designed to be applicable to all forms of organ transplantation.

Principal components analysis of the TxEQ items produced a conceptually coherent factor structure, which was further confirmed on another data set using structural equation modelling. The resulting five TxEQ sub-scales were concerns and worry specific to the transplant, feelings of guilt regarding the donor, disclosure, perceived responsibility and medication adherence.

The first two sub-scales appear to tap emotional responses that are likely to be triggered by transplantation (i.e. worrying over graft function and feelings of guilt towards the donor). These two dimensions tie in with earlier research findings (Castelnuovo-Tedesco, 1981; Chambers, 1982; Chaturvedi & Pant, 1985; Franke *et al.,* 1999; Freyberger, 1983; Gubby, 1998; Kong & Molassiotis, 1999; Schlebusch, 1986; Schlebusch *et al.*, 1989; Sutton & Murphy, 1989; Viederman, 1981).

Patients concerns regarding the viability of their transplanted organ are well-rooted in reality despite the major advances made in recent years. Although the figures for different transplanted organs do vary (Gruessner & Sutherland, 1989; Keck *et al.,* 1999; US Renal Data System, 1999; 2001), in the case of renal transplantation in the UK, the rejection rate of kidneys is approximately 36% over 5 years (UK Renal Association Standards Subcommittee, 1997). Patients' awareness of this possibility is likely to be further confirmed by the need to take anti-rejection medication, the experience of symptoms or possibly the occurrence of episodes of infection.

Feelings of guilt towards the donor have been reported in a range of other, mainly qualitative, studies (Basch, 1973a; 1973b; Chaturvedi & Pant, 1985; Cramond, 1971; Kemph, 1971; Mai, 1986). There is little research evidence on guilt however, in what may be considered the most pertinent area, where the organ may have been sourced from a living donor as is the case in renal transplantation, bone marrow transplantation and in some cases of lung and liver transplantation. Further research is required to establish the extent to which transplant recipients of other organs experience guilt and what underlies this dimension. The TxEQ specifically assesses guilt in relation to the donor and their family.

Whether to disclose the fact that one has a chronic illness is an option where the treatment or illness is not easily observed (Adams *et al.*, 1997; Greene, 2000; Sheon & Crosby, 2003). In the case of kidney transplantation it appears that this is an important issue for some individuals. One may speculate that some are concerned about how they will be responded to, whilst others may be relatively unconcerned with others knowing that they have had a kidney transplant. Ndlovu & Louw (1998) noted the reluctance of African transplant recipients to talk about their transplant experience. The

generalisability of this finding to transplant recipients from other ethnic groups has not been examined.

Disclosure may be perceived as a double-edged word; it may open up social support opportunities or conversely may lead to added stress due to stigmatisation, discrimination and disruption of personal relationships (Baker *et al.*, 1999). The decision to disclose may be influenced by a range of factors, including sociodemographics of the individual, significant other, group or family dynamics or cultural or normative beliefs to name a few.

The fourth factor identified was that of adherence. Treatment adherence has been widely studied in transplant populations. Although existing research has been hampered because of various assessment methods each of which with its own strengths and weaknesses (Brickman & Yount, 1996), there is evidence to suggest that some transplant patients do not follow the advice and recommendations made regarding immunosuppressive medication (Wainwright & Gould, 1997), despite the associated health risks that this behaviour might precipitate.

The last TxEQ factor refers to 'responsibility towards family, friends, or the medical team to do well', an issue which has not received attention in transplantation research. The 'responsibility' dimension of the TxEQ appears to tap issues related to outcome responsibility likely to encompass both a cognitive (i.e. perceptions of responsibility) as well as an affective component (i.e. feelings of responsibility). Responsibility as measured by the TxEQ may hence be seen as qualitatively distinct from concepts such as locus of control or responsibility for graft survival studied in previous research (Bremer, 1995; Bremer *et al.*, 1995; Frazier *et al.*, 1994; Kiley *et al.*, 1993; Kugler *et al.*, 1994). Responsibility towards others may well be dependent on a range of other factors such as perceived social support and/or patients' satisfaction with interpersonal relationships or with health care received. Further research is warranted to examine its relationship to these and other variables.

4.5 Study 1b: TxEQ Validation analysis

To demonstrate the convergent and discriminant validity of TxEQ sub-scales, their associations with conceptually similar measures were examined. These psychometric properties were assessed using the MIDDX-TX transplant data set (see section 1.1).

The TxEQ guilt sub-scale is thought to measure the same basic affect as the corresponding 'guilt' sub-scale from the PANAS-X (Watson & Clark, 1994).
Likewise, similarities were hypothesised between TxEQ worry and PANAS general negative affect, PANAS-X fear, PANAS-X sadness and the SF-36 mental health and mental composite score (Ware & Sherbourne, 1992), and between the TxEQ adherence and the 'reported adherence to medication scale' (RAM; Horne *et al.*, 1999).
This latter measure was also used to investigate validity of the responsibility TxEQ sub-scale, as it was hypothesised that TX patients with a strong sense of responsibility to do well will also demonstrate high treatment adherence rates.
Somewhat more tentative was the link assumed between PANAS-X shyness sub-scale and TxEQ disclosure but in the absence of other disclosure related measures in our assessments, this was explored.

Intercorrelations among these conceptually overlapping or linked scales are presented in Table 5.5.
Moderate-sized correlations were found between TxEQ adherence and BMQ adherence. TxEQ adherence scores were also found to be negatively associated with 'concerns regarding medication' and positively associated with 'medication-necessity' beliefs. Perceived responsibility was also associated with BMQ adherence scores, with stronger sense or feelings of responsibility to do well-being correlated with better, (i.e. more faithful) treatment adherence.
Correlations between mainly TxEQ worry, and other measures (PANAS sadness and fear sub-scales) although small in magnitude were in the predicted direction and statistically significant.
As anticipated TxEQ disclosure was not associated with PANAS shyness sub-scale suggesting that tendency to disclosure TX related information has little to do with being timid, shy or bashful and is more likely to reflect other factors.

Table 5.5: Correlations between TxEQ sub-scales and other scales

	TxEQ worry	TxEQ Guilt	TxEQ disclosure†	TxEQ adherence†	TxEQ responsib†
PNS NA	.143				
PNS Fear†	.206*				
PNS Sadness†	.206*				
SF 36-MH	-.404****				
SF 36-MCS	-.314***				
CDI†	.199*	.006			
PNS Guilt†		-.075			
PNS Shyness†			-.043		
BMQ-c				-.343****	
BMQ-n†				.529****	
RAM adh†				.629***	.208*

Note: PNS = positive and negative affect scale; PNS NA: negative affect from PANAS; MH = mental health; MCS = mental component score; CDI = cognitive depression index; BMQ = Beliefs about your Medicines Questionnaire; BMQ-c = concerns about medication from the BMQ; BMQ-n = necessity sub-scale from BMQ; RAM adh = adherence from the Reported Adherence to Medication

* $p < .05$. ** $p < .01$. *** $p < .001$. **** $p < .0001$

On the other hand disappointing and unexpected was the lack of significant associations between TxEQ guilt and PANAS guilt and cognitive depression, which is likely to reflect the difference between generalised feelings of guilt to feelings of guilt in relation to the act of donation. Guilt towards the donor might be confined to this experience and not manifest itself in more generic affective states. The implication of this interpretation is that the two measures truly reflect different aspects of the concept of guilt.

The evaluation of TxEQ validity is limited by the fact that due to the lack of availability of validated measures for some of the sub-scales (TxEQ disclosure; TxEQ responsibility), their criterion validity could not be established at this stage. Despite these limitations, the data described above provide preliminary evidence for the criterion-related validity, discriminant validity and the reliability for the TxEQ sub-scales and support its use in this study.

4.6 Comparisons between CAD and LRD TX recipients

A secondary analysis of the aggregated TxEQ dataset, i.e. including both RFH and MIDDX TX recipients (study 1a and 1b) was then performed to examine the TxEQ sub-scales in relation to transplant source, namely cadaver and living related transplantation. These were conducted to assess differences between cadaver and living related donor TX recipients in TxEQ sub-scales. Such comparisons were also considered essential in elaborative validity phase (Foster & Cone, 1995), in which the meaning and utility of sub-scale scores are examined. There were no apriori hypotheses as to if or how transplant type might affect emotional and behavioural post-transplantation responses but such comparisons are valid ones to make in the context of validating a new instrument.

4.6.a Methods

Out of 453 patients contacted for study 1a and 1b, 347 patients consented to the protocols (response rate = 76.6 %).

The overall recruited transplant sample consisted of 54.4% males with a mean age of 46.8 years (SD = 13.95) and a mean of 8.6 (SD = 6.55) years since their transplant. Approximately 25% (n = 75) had received their transplant from a living related donor.

Sociodemographic and medical characteristics of the CAD and LRD transplant patients are shown in Table 5.7 below.

Age, annual income and time spent on dialysis differed significantly between the two groups. LRD transplant recipients were younger ($F(1, 340) = 21.37$, $p = .0001$), reported higher annual income ($\chi^2(334) = 11.04$, $p = .014$) and had spent significantly less time on dialysis prior to their transplant than CAD transplant patients ($F(1, 296) = 16.04$, $p = .0001$). The difference in time on dialysis was anticipated given the elective nature of LRD transplantation that allows shorter delay between dialysis and transplantation. In subsequent comparisons between the two groups these differences were controlled for statistically.

Table 5.7: Sociodemographic and clinical characteristics of the combined MIDDX and RFH TX sample

	LRD TX (n = 75)	**CAD TX** (n = 271)		
	M (SD) / % (N)	*M (SD) / % (N)*	*t*-value/ χ^2	*p value*
Age	40.37 (11.93)	48.59 (14.03)	5.06	.001
Gender (% female)	40.8% (31)	47.3% (129)	1.00	.317
Time since TX (yrs)	9.28 (6.20)	8.37 (6.65)	-1.10	.261
No of comorbidities	1.54 (1.54)	1.95 (1.75)	1.96	.064
Diabetes (%)	6.6% (5)	8.8% (24)	.381	.537
Hypertension (%)	56.6% (43)	72.5% (198)	7.076	.008
Heart conditions (%)	6.6% (5)	15% (41)	3.70	.054
No of previous transplants	1.11 (.31)	1.14 (.35)	-.90	.368
Dialysis prior TX (%)	81.1% (60)	96.3% (260)	20.71	.001
Time on dialysis (months)	17.07 (24.94)	37.88 (40.78)	5.19	.001
Education (age yrs left school)	18.38 (3.46)	17.67 (4.68)	-1.16	.273
Relationship status (% in a relationship)	65.3% (49)	60.1% (163)	.66	.414
Work status (% employed))	75.3% (55)	50.5% (138)	13.07	.001
Able to work (f/t, p/t)	82.2% (60)	66% (175)	7.049	.008
Annual family income			10.59	.014
0 - £10,000	15.8% (9)	29.5% (56)		
£ 10,001 - £ 20,000	19.3% (11)	27.4% (52)		
£ 20,000 - £ 30,000	21.1% (12)	19.5% (37)		
> £ 30,000	43.9 % (25)	23.7% (45)		
Own home (%)	60.5% (46)	63.8% (171)	1.54	.792

Note: LRD TX = living related donor transplant recipients; CAD TX = cadaver transplant recipients; TX = transplantation; No = number; yrs = years; f/t = full time; p/t = part time

4.6.b Results

i. *The effects of transplant type*

Analyses of covariance (covarying for age, income and dialysis duration) revealed a significant transplant type effect only on TxEQ guilt (see Table 5.8).

LRD transplant patients expressed significantly stronger feelings of guilt towards the donor (*mean* = 2.70, *SD* = .80) relative to CAD transplant recipients (*mean* = 2.05, *SD.* = .63; $F(3, 200) = 26.27$, $p < .000$). There was a tendency for LRD patients to be more reluctant to disclose or talk about their transplant experience (*mean* = 4.03, *SD.* = .85)

relative to CAD transplant counterparts (*mean* = 3.68, *SD.* =1.10; $F(4, 207) = 3.58$, p = .06). There was no significant difference in reported levels of worry with regard to transplant, with both groups being equally concerned with the viability and functioning of their graft.

Table 5.8: TxEQ scores of CAD and LRD patients

	LRD TX	CAD TX		
TxEQ Sub-scales	*M (SD)*	*M (SD)*	*F*	*p value*
Worry about transplant	3.29 (.80)	3.02 (.85)	.384	.536
Guilt	2.70 (.80)	2.05 (.63)	26.269	.0001
Disclosure	3.68 (1.10)	4.03 (.85)	3.585	.06
Adherence	4.26 (.81)	4.34 (.68)	.008	.930
Responsibility	3.76 (.81)	3.76 (.78)	.829	.364

Note: LRD TX = living related donor transplant recipients; CAD TX = cadaver transplant recipients

ii. *Associations between variables*

Correlational analysis between sociodemographic, medical variables and TxEQ sub-scales showed that increasing age was associated with less worry regarding the transplant ($r = -.25$, $p = .0001$), less guilt ($r_s = -.14$, $p = .012$), more disclosure ($r_s = .24$, $p = .0001$), higher adherence to immunosuppressive medication ($r_s = .12$, $p = .029$) and more perceived responsibility to do well ($r_s = .28$, $p = .0001$).

In addition the number of comorbid conditions was positively correlated with more disclosure ($r_s = .17$, $p = .005$).

Significant, albeit weak associations were also found between the five TxEQ sub-scales suggesting links between emotional and behavioural aspects of post-transplantation adjustment.

Stronger feelings of guilt were significantly correlated with more worry about the transplant ($r_s = .25$, $p = .0001$), higher perceived responsibility ($r_s = .19$, $p = .001$), lower disclosure ($r_s = -.24$, $p = .0001$), and poorer medication adherence ($r_s = -.20$, $p = .0001$). Worry about the transplant also correlated with feelings of greater responsibility to do well ($r_s = .21$, $p = .0001$) and less disclosure about the transplant ($r_s = -.14$, $p = .013$).

4.6.c Discussion

This subsidiary analysis indicated that different forms of transplantation (LRD vs. CAD) may lead to different emotional responses albeit with no apparent QoL differences.

In particular feelings of guilt appear to be prominent in living related transplantation. The significantly higher levels of guilt reported by LRD recipients are understandable given the different relationship between the transplant recipients and donor and their family (Aikawa, 1989) and the recognition of the sacrifice made by the donor. Most living related transplant recipients continue to have a relationship with the donor and in this study all donors were relatives of the recipients. The sacrifice made by the donor, the physical cost of donation and the perceived ongoing risk of having only one kidney may understandably lead to feelings of guilt (Pillay *et al.*, 1992). Although their incidence rates are very low, both early post-operative as well as later risks are attached to living donor transplantation (Johnson *et al.*, 1997a; 1997b; Najarian *et al.*, 1992). It is likely that transplant recipients will be very well aware of these risks (Jones *et al.*, 1993). Recipients of cadaver transplantation do not have any pre-existing relationship with the donor or his/her family and the prospect for future personal contact was limited, given the current practice in UK of discouraging or prohibiting direct contact between cadaver transplant recipients and donor families. Even in cases where some contact, typically in the form of correspondence, is established between cadaver recipients and donor families, this form of interaction tends to be more impersonal and exclusively regulated via the transplant co-ordinating centres. Although the recipient of a LRD kidney may well have increased levels of guilt and there have been some reports of depression and disrupted family relationships after donation to a family member (Russell & Jacob, 1993), most published reports have indicated an improved sense of well-being, quality of life and a boost in self-esteem for living kidney donors (Johnson *et al.*, 1999; Peters *et al.*, 2000; Switzer *et al.*, 2000).

These observed associations provide indirect support for the validity of the new instrument. The preliminary data reported here indicate that the psychometric properties of TxEQ are acceptable and support its use as a transplant specific research tool. TxEQ is self explanatory, simple to use and time cost-effective, features that make it an ideal instrument for use in a clinical environment. The TxEQ has potential to monitor on a

regular basis the responses, psychological adjustment and treatment adherence in transplant recipients alongside the routine post-transplant medical assessments. From a research perspective, TxEQ may be used separately or in conjunction with more generic HQoL measures.

CHAPTER 6: RESULTS NEUROPSYCHOLOGY

This chapter describes the results[1] on the NP outcomes of ESRD patients. It is organised into three major sections: dialysis, TX and summary of results

Section 1: Dialysis Sample

1.1 Data analysis

All statistical analysis described in this thesis was performed using SPSS version 11 for Windows (Norusis, 1993).

First, the distributions of the NP tests and related psychological measures were examined by means of the Kolmorogov-Smirnov goodness-of-fit test. Depression scores (BDI; CDI), negative affect, TMT-A, TMT-B, BVRT-C, BVRT-E, GP-DOM, GP-NDOM and RAVLT-D were found to be non-normally distributed. Logarithmic and square root transformations rendered most of these variables (BDI, CDI, TMT-A, TMT-B, GP-NDOM) to a normal distribution. It was not possible to render the BVRT scores (number correct and number of errors), RAVLT-D and GP-DOM, and negative affect scores to a normal distribution. These were nevertheless analysed as described below (using parametric tests when dialysis groups were compared across time) as the large study sample (> 20 df) provided some tolerance to violation of normality (Tabachnic & Fidell, 1989) but caution must be used in interpreting the findings in relation to these tests, because of the non-normal nature of the distribution.

To assess the need to incorporate control variables into the comparisons between dialysis groups several preliminary analyses were conducted. Independent *t* tests, analyses of variance (ANOVAs) and Chi square test or Fisher's exact as appropriate (for categorical data) were performed to compare the dialysis groups on sociodemographic and clinical characteristics. Univariate statistics (Pearson's or Spearman's correlation coefficients as appropriate) were then used to examine

[1] Exact p values are reported. If p was less than .000 then this was reported as = .0001

relationships between casemix differences and other background variables and NP scores at Time 1 (T1: pre-dialysis) and Time 2 (T2: 24-hours post-dialysis) as well as changes in the dependent variables (NP scores) over time. If any of these background variables differed significantly among dialysis groups (at $p < .05$) and were significantly associated with the outcome in question, they were statistically controlled in subsequent comparative analyses.

The study had a prospective 2 (treatment as the between-subjects factor; HD vs. PD) by 2 (time as the within subjects factor; T1 and T2 assessment) design. A series of 2 x 2 repeated measures analyses of (co)variance (ANCOVAs) were performed to examine acute neuropsychological, biochemical and mood changes in HD and PD patients over 24 hours. Covariates used included anxiety and fatigue (for NP analyses only) and other variables were included according to the criteria described above. Significant main and treatment-by-time interaction effects were followed up with within-group repeated measures ANCOVAs run separately for the HD and PD group and between-groups ANCOVAs at T1 and T2 assessments.

In the 2 x 2 repeated measures ANCOVAs to compare the two dialysis groups over time, p values, uncorrected for multiple comparisons, were considered significant if $p < .05$. It is recognised that this would result in an increase in the Type I error rate. However, controlling for the Type I error rate by applying the Bonferroni adjustment would have resulted in a higher Type II error rate. This might have yielded an acceptable power for the main effects, but not for the interaction effect, which was of specific interest in this study. Subsequent post-hoc tests were controlled for overall Type I error by virtue of being conditional on the significance of the omnibus ANCOVA test, and therefore were not further controlled for multiple comparisons.

1.1.a Absolute NP scores

The independent contributions of mood, biochemical, clinical, and sociodemographic measures to cognitive function were assessed using a series of hierarchical multiple linear regressions. This was preferred over simple correlations to reduce the number of analyses conducted and in order to demonstrate that any contributions of mood and

biochemical factors were independent of the effects of age and education on neuropsychological performance.

Predictors were entered in four blocks as follows: sociodemographic (age, education) and clinical (ESRD-SI, diabetic status, Kt/V), mood variables (CDI, STAI, PANAS) and biochemical measures. To determine entry into the models the stepwise method was used within blocks to avoid the problem of multicollinearity among variables (Tabachnick and Fidell, 1989). Only the variables bearing significant associations with the specific NP outcome at a criterion of $p < .05$ were included in the regressions. In addition to providing R^2, adjusted R^2, and standardised beta coefficients for significant associations, a variance-based measure of effect size was calculated as follows $f^2 = \Delta R^2 / (1- R^2_{Total})$. Thus f^2 is defined as the ratio of additional variance explained by a predictor (or a regression model step) to the amount of variance that remains unexplained in the dependent variable (Cohen & Cohen, 1983). Small, medium and large effects correspond to f^2 values of 0.06, 0.56 and 1.56 respectively.

Two competing hypotheses, i.e. whether mood or biochemistry are driving NP performance were examined by altering the order of entry for the last two blocks in the regression analyses. Specifically, to test the biochemistry hypothesis, biochemical variables were entered last in the regression equations after demographic, clinical and mood variables so as to examine the degree of improvement in prediction when biochemistry is added. The same approach was taken to assess the impact of mood variables after controlling for biochemistry. To test the mood hypothesis, mood variables were entered last preceded by biochemistry. In these last regressions to minimise the cases to number of variables ratio only the biochemical indices identified as significant predictors in the earlier set of regressions were included

1.1.b Change NP scores

Finally the relationship between changes in biochemistry, mood and NP performance was explored in HD and PD patients controlling for baseline levels. There are several methods to calculate change scores: simple delta-change scores (subtracting T1 from T2) and residualised change scores. In this study we opted for residualised change

scores for all neuropsychological (NP), biochemical, and mood measures in order to control more strictly for baseline covariation.

Residualised change scores were computed as follows: first, T2 scores were regressed onto corresponding baseline (T1) scores to derive covariance (i.e. baseline) adjusted scores. Residualised change scores were then obtained by adding the individual unstandardised regression coefficients to respective T2 group means. This method is preferable to the use of simple change (delta) scores (Llabre *et al.*, 1991).

Hierarchical multiple regressions, as described above, were then conducted in which mood and biochemistry change scores were regressed on NP change scores controlling for sociodemographic and clinical variables. As above, two sets of linear regressions were performed in which mood or biochemistry preceded each other in the last two steps of the analyses so as to evaluate their relative importance. This analysis was possible only for a subset of HD (n = 54) and PD patients (n = 54) for whom two suitable blood samples were obtained at the time of the assessments.

1.2 Sample characteristics

As there were no significant differences in any of the NP scores between the two forms of HD (hospital and home), nor between the two forms of PD (CAPD and APD) the sample was collapsed to form a single HD group (n = 75) and a single PD group (n = 68) (see Appendix F).

Baseline characteristics of the resulting two groups including sociodemographic factors and clinical presentation of the patients are shown in Table 6.1.

The only sociodemographic factor differentiating between the two groups was gender with significantly more female participants on HD than PD ($\chi^2(145) = 4.25$, $p = .05$). There were also significant group differences in four medical variables. Significantly more PD patients had diabetes relative to HD patients ($\chi^2(145) = 10.27$, $p = .001$).

Table 6.1: HD and PD participants' sociodemographic and clinical characteristics

	HD (n = 77)			PD (n = 68)				
	M	**SD**	%	**M**	**SD**	%	*T*	χ^2
Age (years)	48.22	14.92		52.26	13.26		-1.7	
Gender (% female)			42.9			26.5		4.25*
Ethnicity (% white)			68.8			58.8		3.29
% Married			57.1			70.1		2.81
% Employed			36.4			35.13		0.17
Income								.002
£0-£10,000			58.4			58.8		
£10,001-20,000			27.3			22.1		
£20,001-30,001			7.8			11.8		
£30,001- above			6.5			7.4		
Education (years)	12.26	5.69		12.49	5.11		-.26	
Time DL (months)	52.41	55.03		20.75	22.37		4.63****	
Time RRT (months)	96.35	83.18		30.26	40.82		6.18****	
ESRD severity	10.57	9.13		11.81	9.87		-.79	
Kt/V[a]	1.69	.24		1.94	.42		.03	
URR	.65	.07		-	-			
% previous TX			94.1			50.6		33.1**
% on TX list			89.6			89.7		.00
% Diabetes			7.8			27.9		10.2**
% Hypertension			94.8			88.2		2.05
% Heart Disease			39			41.2		.073
Primary cause ESRD								
% GN			23.4			2.9		****[b]
% APKD			13			14.7		.09
% Reflux			9.1			10.3		.06
% Diabetes			6.5			16.2		3.44
% hypertension			5.2			16.2		3.58

* p <.05. ** p <.01. *** p <.001. **** p <.0001

Note. HD = haemodialysis; PD = peritoneal dialysis; DL = dialysis; RRT = renal replacement therapy; Kt/V = K is defined as the total urea clearance rate, t represents the number of minutes of dialysis and V is the urea distribution within the patient; URR = urea reduction ratio; GN = Glumeronephritis; APKD = Adult Polycystic Kidney Disease; ESRD = End Stage Renal Disease; URR = urea reduction ratio; TX = transplant

[a] = absolute values not directly comparable between HD and PD patients. [b] = Fisher exact test

PD patients were found to have been on current dialysis treatment ($t(140) = 4.50$, $p = .0001$) and on renal replacement therapy in general (RRT) ($t(143) = 6.08$, $p = .0001$) for less time compared to HD patients. HD patients were more likely to have glumeronephritis as their primary cause of ESRD relative to PD participants (Fisher's exact Test $p = .0001$). Some of these differences were anticipated as PD is often

regarded as the preferred initial modality for diabetic ESRD patients (Blake, 2001; Pasadakis & Oreopoulos, 2001).

Mean Kt/V levels indicated adequate dialysis levels for both dialysis groups and inspection of individual levels showed that the vast majority of the patients (86%, n = 128) had Kt/V values equal or greater than the recommended standards. Seventeen patients (11.2%) did not have Kt/V measurements within the 6-month period (n = 7 HD and n = 10 PD patients). However an alternative measure for the HD patients (urea reduction ratio) indicated adequate dialysis and the Kt/V measure for the PD patients outside of the 6 months period also indicated adequate dialysis. The percentage of PD and HD patients for whom treatment was designated adequate was not associated with dialysis treatment ($\chi^2(135) = .338$, $p = .56$) although the numbers of non-adequately dialysed patients were extremely low.

Likewise, there were no significant differences in Kt/V levels achieved in the two groups (analysis performed on standardised z-scores), suggesting that HD and PD patients had comparably efficient dialysis delivery. Standardised z-scores were used as the absolute Kt/V scores in HD and PD are not directly comparable, because of the differences between continuous and intermittent removal in terms of the prevailing extracellular concentration of uraemic solutes (Mallick *et al.*, 1998).

1.3 Absolute NP performance

The absolute NP scores of the HD and the PD patients in the two assessments are reported in Table 6.2.

A total NP score at T1 and T2 assessment (NP-TO) was computed by adding the standard z-scores on the 10 NP indices. Scores in TMT-A, TMT-B, GP-DOM, GP-NDOM, BVRT-C and BVRT-E were reversed so higher scores in those individual tests and hence the derived summary index (NP-TO) signify better or more efficient cognitive functioning.

Table 6.2: NP scores at T1 and T2 in HD and PD

		HD		PD	
		Time 1	**Time 2**	**Time 1**	**Time 2**
TMT-A[a]	*M*	53.73	45.13	50.49	46.60
	SD	37.32	32.34	25.98	26.35
TMT-B[a]	*M*	97.92	90.02	99.32	99.96
	SD	51.72	51.72	44.74	46.74
SDMT-W[b]	*M*	40.92	47.10	41.31	44.73
	SD	12.96	15.20	12.66	14.56
SDMT-O[b]	*M*	45.82	52.10	44.91	48.61
	SD	14.22	16.58	13.24	15.87
RAVLT-T[b] **(1-5)**	*M*	39.36	43.53	38.65	39.16
	SD	11.94	11.78	9.20	8.77
RAVLT-1 trial	*M*	5.14	5.79	4.85	5.11
	SD	1.73	1.95	1.37	1.43
RAVLT-2 trial	*M*	7.13	7.92	6.99	7.08
	SD	2.39	2.45	1.86	1.78
RAVLT-3 trial	*M*	8.14	8.99	8.07	8.34
	SD	2.72	2.80	2.25	1.93
RAVLT-4 trial	*M*	9.19	10.13	9.09	8.89
	SD	3.11	2.84	2.55	2.37
RAVLT-5 trial	*M*	9.75	10.70	9.65	9.73
	SD	3.22	3.06	2.57	2.50
RAVLT-D (7-5)	*M*	2.35	2.64	2.75	3.03
	SD	1.70	2.09	2.20	1.61
BVRT-C[b]	*M*	5.08	5.97	4.75	4.97
	SD	2.30	2.31	1.98	1.74
BVRT-E[c]	*M*	8.64	6.61	8.47	7.82
	SD	5.46	5.30	4.51	3.85
GP-DOM[a]	*M*	88.66	85.12	93.65	91.95
	SD	29.78	28.81	34.28	32.16
GP-NDOM[a]	*M*	100.19	95.40	104.61	103.25
	SD	34.59	34.31	43.64	39.71
NP-TO[d]	*M*	.291	1.09	-.333	-1.28
	SD	7.94	7.89	6.58	6.31

Note. T1 = time 1 assessment; T2 = time 2 assessment; HD = haemodialysis; PD = peritoneal dialysis; TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; BVRT-C = Benton Visual Retention Test number of correct reproductions; BVRT-E = Benton Visual Retention Test number of reproduction errors; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; NP-TO = total NP performance score

[a] = Time to completion in seconds. [b] = number correct. [c] = number of errors. [d] = total of the 10 NP indices (z-scores)

1.4 NP performance of dialysis patients relative to normative data

To examine whether the NP performance of HD and PD groups was different to healthy controls, patients' performance was compared to available age-related normative data and test norms (Lezak, 1995; Mitrushina *et al.*, 1999).

1.4.a Definition of NP impairment

Available norms that most closely matched the characteristics of the study sample as well as administration and scoring procedures were identified (Mitrushina *et al.*, 1999).

The relative performance of dialysis participants compared to the normative group was evaluated. NP impairments were defined as follows (for detailed description see Appendix G). It should be stressed these criteria do not correspond to those set for clinical neuropsychological diagnoses/assessments and for the detection of clinically significant NP deficits.

- Cut-off score of one or more Standard Deviations (*SD*) below the respective age norm (SDMT-W; SDMT-O; GP-DOM; GP-NDOM). In percentile ranking terms this would correspond to scores lower than the 16^{th} percentile (low average performance). In normal distribution one would expect 15.86% scores being 1 *SD* or more below norms. The purpose of this criterion classification was to determine if the observed frequency of NP scores falling more than 1 *SD* below norms in dialysis patients exceeds 15.86%, i.e. that expected in normal distribution.
- Score below the 25^{th} percentile (TMT-A; TMT-B) indicative of borderline to low average performance.
- Score, which is 3 points below the expected score in BVRT-C (suggestive of deficit) or in a more conservative fashion an obtained BVRT-C score 4 points lower than expected (strong indication of impairment).
- In BVRT-E a score 4 points above the expected was considered as suggestive of impairment and in a similar fashion, more conservative classification was also made, with a BVRT-E score 5 points above expected considered a strong indication of impairment.
- Total cognitive dysfunction was defined as the number of NP test scores (TMT-A; TMT-B; SDMT-W; SDMT-O; RAVLT-T; BVRT-C; BVRT-E; GP-DOM; GP-

NDOM) in the impaired range of standard norms. This could range from 0 to 9, with higher scores signifying NP impairments in more areas of cognition.

1.4.b Prevalence of NP impairments

Having agreed on what constitutes impaired NP performance for each NP test used, normative comparisons were undertaken using two methods, i.e. group level/performance and individual level/performance:

i. *Group based comparisons*

These were performed by comparing patient group mean scores to test norms to determine whether dialysis patients as a group performed within or below normal population (see Appendix G). Consistent with previous research dialysis groups' mean age was used to select the appropriate age brackets for these normative comparisons. These group comparisons showed that the mean scores of both dialysis groups at T1 and T2 were within normal range on the following NP tests (TMT-B, SDMT-W, SDMT-O, BVRT-C) whereas mean group scores in the remaining tests (TMT-A; GP-DOM; GP-NDOM; BVRT-E) across the two assessments indicated mild to moderately impaired NP performance.

Classification analysis of the type of errors in the visual memory task (BVRT) revealed that distortion errors were by far the commonest in both NP assessments (see Table 6.3).

Table 6.3: BVRT errors at T1 and T2 assessment in dialysis patients

	Time 1			Time 2		
BVRT – errors	*%*	*Mean (Sd)*	*Range*	*%*	*Mean (Sd)*	*Range*
Distortion	93.8	3.91 (2.92)	0-15	86.6	3.87 (2.83)	0-13
Rotation	81.9	1.52 (1.18)	0-5	76.2	1.09 (1.1)	0-5
Misplacement	64.1	1.10 (1.08)	0-5	61.4	.85 (1.05)	0-4
Omission/addition	55.5	1.11 (1.69)	0-7	33.8	.63 (1.11)	0-5
Preservation	36.6	.48 (.72)	0-3	38.7	.47 (.69)	0-4
Size	24.8	.39 (.93)	0-8	17.6	.28 (.76)	0-5

Note: BVRT = Benton Visual Retention Test

Normative comparisons with respect to RAVLT were complicated by the limitations of appropriate normative databases. On one hand, large normative databases (e.g. Query & Megran, 1983) were inappropriate for comparisons to our study sample, as there were based on mainly older male subjects. The most suitable normative data were stratified by gender and had relatively small sizes in resulting age/gender cells (Gefen *et al.*, 1990). For study purposes this smaller size normative database was preferred as the sociodemographic characteristics of the normative sample resembled more closely those of the study sample and because the same scoring method was applied.

Comparisons to these norms indicated that dialysis patients' mean total verbal recall scores were borderlining those of normal population.

Table 6.4: Frequencies of dialysis patients below NP tests norms

	Time 1			Time 2		
	All DL	**HD**	**PD**	**All DL**	**HD**	**PD**
	% (n)	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
TMT-A	39.3% (57)	39% (30)	39.7% (27)	30.5% (43)	29.9% (23)	31.3% (20)
TMT-B	16.6% (24)	14.3% (11)	19.1% (13)	19.1% (27)	18.2% (14)	20.3% (13)
SDMT-W	42.1% (61)	42.9% (33)	41.2% (28)	29.8% (42)	22.1% (17)	39.1% (25)
SDMT-O	46.2% (67)	41.6% (32)	51.5% (35)	34% (48)	27.3% (21)	42.2% (27)
RAVLT-T	53.8% (78)	49.4% (38)	58.8% (40)	44.8% (65)	37.7% (29)	52.9% (36)
BVRT-C	80% (116)	75.3% (58)	85.3% (10)	64.8% (92)	51.9% (40)	80% (52)
BVRT-E	80.7% (117)	79.2% (61)	82.4% (56)	67.6% (96)	55.8% (44)	81.5% (56)
GP-DOM	43.1% (62)	42.1% (32)	44.1% (30)	39.6% (55)	30.3% (23)	50.8% (32)
GP-NDOM	50% (72)	52.6% (40)	47.1% (32)	44.6% (62)	39.5% (30)	50.8% (32)

Note. DL = dialysis; HD = haemodialysis; PD = peritoneal dialysis; TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; BVRT-C = Benton Visual Retention Test number of correct reproductions; BVRT-E = Benton Visual Retention Test number of reproduction errors; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand

There was a great variability in individual performance irrespective of dialysis mode. The observed *SD*s in all NP scores are large, clearly indicating large individual differences in NP performance between patients on the same dialysis treatment. The heterogeneity of the dialysis sample (for example, they range in age from 20-81 years) may have contributed to the variability in the NP scores (see Table 6.2) and the 'inflated' NP impairment rates (see Table 6.4).

Group-based comparisons overlook individual differences, thereby producing less sensitive and accurate normative comparisons. For instance, given the wide age range in the dialysis sample (20-81), group based comparisons might have created unfavourable comparisons for the more elderly participants. In the light of these shortcomings, evaluation of individual rather than group NP scores was deemed more appropriate.

ii. *Individual based comparisons*

This strategy involved evaluating individual rather than group performance against his or her respective age and gender (when available) norms to determine presence or not of impairment and then comparing the prevalence of NP impairments between groups and across the two assessments. This method enabled individuals performing at a level below norms, to be identified. The same criteria (described in section 1.4.a) to define NP impairments were used (see Appendix G).

Inspection of the individual scores relative to reference age norms showed that some patients had scores signifying pronounced NP impairments despite groups' mean scores being within normal range (see Table 6.5).

In the combined dialysis sample, more than one third of patients (32.4% - 49.3%) performed at least 1 *SD* lower than norms described above at T1 assessment (SDMT-W; SDMT-O; TMT-A; GP-DOM; GP-NDOM; RAVLT-T). Individual T1 BVRT-C and BVRT-E scores for 21.4% and 37.9% of dialysis patients respectively 'strongly' indicated an impairment of visual memory. A lower but still considerable percentage (13.5% - 41%) of dialysis patients remained in the impaired NP score range at T2 assessment (see Table 6.5).

Table 6.5: Individual classification: Prevalence of NP impairments (% of patients performing below their respective norms)

	ALL Dialysis % Impairments (*N*)		HD % Impairments (*N*)		PD % Impairments (*N*)	
TMT-A						
Time 1	35.9% (52)		39% (30)		32.4% (22)	
Time 2	23.4% (43)		23.4% (18)		23.4% (15)	
TMT-B						
Time 1	15.2% (22)		16.9% (13)		13.2% (9)	
Time 2	13.5% (19)		13% (10)		13.2% (9)	
SDMT-W						
Time 1	32.4% (47)		32.5% (25)		32.4% (22)	
Time 2	28.4% (40)		24.7% (19)		32.8% (21)	
SDMT-O						
Time 1	41.4% (60)		37.7% (29)		45.6% (31)	
Time 2	30.5% (43)		26% (20)		35.9% (23)	
RAVLT-T						
Time 1	47.6% (69)		50.6% (39)		35.1% (27)	
Time 2	34.8% (49)		44.1% (30)		34.4% (22)	
BVRT-C						
Time 1	36.6% (53)[a]/21.4%(31)[b]		31.2% (24)[a]/18.2%(14)[b]		42.6% (29)[a]/25% (17)[b]	
Time 2	27.5% (39)[a]/13.8% (20)[b]		28.6% (22)[c]/22.1% (17)[d]		33.8% (22)[a]/15.4% (10)[b]	
BVRT-E						
Time 1	47.6% (69)[c]/37.9% (55)[d]		46.8% (36)[c] / 39% (30)[d]		48.5% (33)[c]/36.8% (25)[d]	
Time 2	32.4% (46)[c]/24.6% (35)[d]		28.6% (22)[c]/22.1% (17)[d]		36.9% (24)[c]/27.7% (18)[d]	
GP-DOM						
Time 1	41.7% (60)		40.8% (31)		42.6% (29)	
Time 2	37.4% (52)		32.9% (25)		42.9% (27)	
GP-NDOM						
Time 1	49.3% (71)		51.3% (39)		47.1% (32)	
Time 2	41% (57)		35.5% (27)		47.6% (30)	
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
Count of NP Impairments						
Time 1	3.22	2.68	3.25	2.83	3.19	2.52
Time 2	2.40	2.53	2.25	2.65	2.57	2.03

[a] = 3 or more below expected score for number correct. [b] = 4 or more lower than expected scores for number correct. [c] = 4 or more errors than expected norms. [d] = 5 or more errors than expected norms

Whereas the percentages of NP impairment in the region of 15% to 20% (e.g. TMT-B) do not raise concern as a similar percentage of general population would be expected to perform similarly (based on a normal distribution), this clearly does not apply to some NP tests, i.e. GP-DOM, GP-NDOM, SDMT-O and RAVLT-T. The prevalence of NP

impairments in these tests at T1 and T2 far exceeded those expected in a normal population.

Mc Nemar change tests (using the combined dialysis sample) showed significant changes in the presence of NP impairments from T1 to T2 in all NP tests except for TMT-B, SDMT-W, and GP DOM. Overall results indicated the observed frequency of NP impairments was significantly lower at T2 compared to T1: RAVLT-T ($\chi^2(143) = 11.115$, $p = .001$); GP-NDOM (bionomial distribution used exact $p = .008$); SDMT-O (bionomial distribution used exact p = 000); TMT-A (bionomial distribution used, exact p = .000); BVRT-E ($\chi^2(143) = 8.028$, $p = .005$); and BVRT-C (bionomial distribution used exact $p = .035$).

iii. *Dialysis treatment (HD vs. PD) and prevalence of NP impairments*

Chi-square analysis indicated little association between the prevalence of NP impairments and dialysis modality. The percentage of patients falling into the impaired range of NP tests was roughly equivalent in the PD and HD groups at both assessments. Similar results were found with regard to number of NP impairments across NP tests. There were no significant group differences in the count of NP impairments at T1 (U = 2573, $p = .859$) nor T2 (U = 2322, $p = .231$) between HD and PD patients.

Repeated measures ANCOVAs (controlling for ESRD severity, diabetes, and dialysis duration) to examine changes in the count of NP impairments between HD and PD patients showed only a significant time effect ($F(4, 141) = 48.831$, $p = .0001$). This indicated that the count of NP impairments decreased significantly for T1 to T2 in the combined dialysis sample. The group effect was not significant hence suggesting that the count of NP impairments when averaged across time was equivalent in the two dialysis groups. The time by treatment interaction effect approached but did not reach significance ($F(4, 141) = 3.250$, $p = .074$).

Mc Nemar tests were performed to examine changes in the prevalence of NP impairments across the two assessments separately in the two groups. These analyses indicated marked changes in the HD but not the PD group.

In HD patients, the observed frequency of NP impairments changed significantly across the two assessments (i.e. for immediately pre- to 24 hours post-dialysis): TMT-A (p = .0001); SDMT-O (p = .004); RAVLT-T (p = .002); BVRT-E (p = .002); and GP-NDOM (p = .0001). Changes in GP-DOM approached but did not reach significance (p = .070). In contrast, the frequency of NP deficits in the PD groups remained unchanged from T1 to T2 with only SDMT-O being significant (p = .021).

1.5 Sociodemographic, medical variables and NP performance

1.5.a Absolute NP scores

The associations between sociodemographic, medical and absolute NP scores were examined with correlations, ANOVAs or their non-parametric equivalents as appropriate. These were performed on the combined dialysis sample, collapsing across PD and HD groups. This analysis was also used to identify which of the casemix differences might require statistical control in subsequent comparative analyses.

First the associations between casemix differences (diabetes, time on dialysis, gender) and NP scores were examined. Diabetes was strongly associated with all NP scores. ANOVA comparisons indicated that diabetic patients performed significantly worse than non-diabetic patients in all NP tests across the two assessments except for BVRT. These differences in all NP tests (except for RAVLT) remained significant even after the effects of age and education were partialled out using ANCOVAs (see Appendix H).

Gender, time spent on dialysis (either on current dialysis treatment or RRT in general) and primary kidney disease diagnosis had no significant relationship with any of the NP scores (data not shown).

The associations of various medical (Kt/V; ESRD severity) and demographic variables (e.g. age, employment status) with NP outcomes were also examined. Several significant correlations emerged (see Table 6.6).

Table 6.6: Correlations between sociodemographic, medical variables and absolute NP scores in the combined dialysis sample

		Age	Education†	Kt/V	ESRD SI†
TMT-A	T1	.426****	-.276***	-.31****	.411****
	T2	.524****	-.309****	-.279**	.461****
TMT-B	T1	.450****	-.230**	-.267**	.332****
	T2	.513****	-.275***	-.295***	.389****
SDMT-W	T1	-.499****	.328****	-.499****	-.411****
	T2	-.494****	.345****	-.494****	-.377****
SDMT-O	T1	-.525****	.345****	-.525****	-.458****
	T2	-.512****	.329****	-.512****	-.406****
RAVLT-T	T1	-.448****	.325****	.195*	-.341****
	T2	-.407****	.350****	.148 ns	-.308****
RAVLT-D	T1	.129 ns	-.100 ns	-.005 ns	.046 ns
	T2	.104 ns	-.053 ns	.112 ns	.067 ns
GP-DOM†	T1	.589****	-.223**	-.271**	.453****
	T2	.562****	-.211*	-.34****	.403****
GP-NDOM	T1	.522****	-.285**	-.224*	.485****
	T2	.542****	.318****	-.296***	.452****
BVRT-C†	T1	-.367****	.323****	.228**	-.332****
	T2	-.449****	.335****	.214**	-.283***
BVRT-E†	T1	.377****	-.392****	-.261**	.332****
	T2	.473****	-.379****	-.245**	.355****

† Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

Increasing age and ESRD severity were associated with more compromised cognitive functioning in all NP scores across the two assessments. The observed correlation coefficients ranged from r = .367 to r = .589 for age and from r = .224 to r = .499 for ESRD severity indicating moderate-sized correlations. Analysis of the associations between dialysis adequacy (z-scores) and NP performance at T1 showed that higher Kt/V and values were associated with better NP performance (see Table 6.6).

ANCOVA comparisons between employed vs. non employed dialysis patients (covariates used: age, ESRD SI, and education) revealed that patients in employment performed significantly better in all NP tests (except RAVLT-T and RAVLT-D) than non-employed patients even after partialling out the effects of age, education and ESRD severity. Because the variables found to be significant correlates (age, education, ESRD-SI, dialysis duration, employment status, Kt/V) were not confounded with treatment status, these additional variables were not controlled for in subsequent comparative analyses.

1.5.b Residualised change NP scores

In contrast to the observed associations with absolute NP scores, only a handful of the demographic and clinical variables were significantly correlated with acute change in NP scores.

Age and ESRD severity were inversely related to NP improvements whereas education was positively correlated with NP improvements. Age correlated with residualised change scores in TMT-A ($r = .281, p = .001$); TMT-B ($r = .254, p = .002$); BVRT-E ($r = .286, p = .001$) and BVRT-C ($r = -.305, p = .0001$). Education on the other hand correlated with RAVLT-T ($r_s = .178, p = .035$) and TMT-A ($r_s = -.246, p = .003$). Finally significant associations were found between ESRD severity and TMT-A ($r_s = .323, p = .0001$); TMT-B ($r_s = .306, p = .0001$) and BVRT-E ($r_s = .173, p = .039$).

1.6 Mood differences and relation to NP performance in Dialysis

Table 6.7 shows the correlations among the mood measures used in this study.

Table 6.7: Correlations between mood measures

	BDI	CDI	STAI 1	NA 1†	PA 1	STAI 2†	NA 2†
BDI							
CDI	.93***						
STAI 1	.53***	.51***					
NA 1†	.55***	.53***	.64***				
PA 1	-.51***	-.53***	-.48***	-.48***			
STAI 2 †	.53***	.53***	.65***	.51***	-.42***		
NA 2 †	.42***	.39***	.48***	.66***	-.27***	.52***	
PA 2	-.47***	-.46***	-.38***	-.27***	.64***	-.44***	-.33***

† = Spearman's correlations

Note. BDI = beck depression inventory total score; CDI = cognitive depression index; STAI 1= Spielberger state anxiety at time 1; NA 1 = negative affect at time 1; PA 2 = positive affect at time1; STAI 2 = Spielberger State anxiety at Time 2; NA 2 = negative affect at time 2; PA 2 = positive affect at time 2.

*** p <.000

Results indicated that all negative mood measures were significantly interrelated. Depression indices (BDI and CDI) were highly intercorrelated (r = .93, p = .0001) and correlated significantly with all mood measures at both time points. All other correlations between mood measures (at each time point separately) were below .55 indicating less than 30% shared variance and some degree of independence between the scores. Significant correlations were also noted between T1 and T2 levels, with anxiety at T1 for instance being correlated with T2 anxiety or positive affect at T1 being correlated with T2 positive affect (see Table 6.7).

1.6.a State anxiety

i. *Group differences*

Table 6.8: State anxiety at T1 and T2 in HD, PD and the combined dialysis

	Time 1			Time 2		
	Mean	***SD***	***Range***	***Mean***	***SD***	***Range***
HD	10.61	3.92	6 – 24	8.90	2.35	6 – 15
PD	11.46	4.06	6 – 24	10.76	3.45	6 – 21
All dialysis	11.01	3.99	6 – 24	9.76	3.04	6 – 21

Repeated measures ANCOVA on state anxiety (covarying for gender, time on dialysis and diabetic status) revealed a significant main effect for treatment (F(4, 138) = 4.71, p = .032), with HD patients reporting less anxiety than PD patients when averaged, and a significant main effect of time (F(4, 138) = 22.69, p = .0001). Anxiety reports were reduced in both HD and PD patients from T1 to T2.

ii. *Relationship to NP functioning*

State anxiety correlated with all the NP measures at T1 (see Table 6.9). The correlation coefficients for the combined sample ranged from .22 to .27. Similar significant correlations were noted between T2 anxiety and T2 NP scores although the strength of correlations was somewhat lower than those of T1 and no correlations were found for either RAVLT scores (see Table 6.9).

Table 6.9: Correlations between state anxiety and NP scores at T1 and T2 in the combined dialysis sample

TIME 1		*TIME 2*	
NP tests	***STAI 1***	***NP tests***	***STAI 2†***
TMT-A1	.230**	TMT-A2	.267***
TMT-B1	.215**	TMT-B2	.167*
SDMT-W1	-.260**	SDMT-W2	-.182*
SDMT-O1	-.286****	SDMT-O2	-.226**
RAVLT-T1	-.259*	RAVLT-T2	-.114
RAVLT-D1†	.122	RAVLT-D2†	-.008
GP-DOM1†	.268***	GP-DOM2†	.232**
GP-NDOM1	.243**	GP-NDOM2	.211*
BVRT-C1†	-.223**	BVRT-C2†	.273***
BVRT-E1†	.219**	BVRT-E2†	-.340****
NP–TOTAL1	-.287****	NP–TOTAL2	-.264**

† Spearman's correlation coefficient

* p <.05. ** p < 01. *** p <.001. **** p <.0001.

1.6.a Positive Affect (PNS-PA)

i. *Group differences*

Table 6.10: Positive affect at T1 and T2 assessment in HD, PD, and combined dialysis

	Time 1			**Time 2**		
	Mean	***SD***	***Range***	***mean***	***SD***	***Range***
HD	24.48	8.13	10 – 41	29.17	7.-2	11 – 42
PD	22.97	6.44	11 – 37	23.41	7.18	11 – 40
All dialysis	23.77	7.40	10 – 41	26.54	7.63	11 – 42

Repeated measures ANCOVA (covarying for gender, time on dialysis, and diabetic status) was performed to examine changes in positive affect between HD and PD patients. This yielded a significant main effect for treatment group ($F(4, 137) = 6.224$, $p = .014$), time ($F(4, 137) = 29.978$, $p = .001$) and a significant treatment-by-time interaction effect ($F(4, 137) = 9.329$, $p = .003$). Post-hoc tests (ANCOVAs) showed that positive affect levels increased significantly from pre- to 24-hours post-dialysis ($F(3, 73) = 43.8$, $p = .0001$) in HD patients. In contrast, positive affect reports remained unchanged in the PD group across the two assessments ($F(3, 61) = .529$, $p = .47$).

Between groups post-hoc comparisons indicated that HD patients reported significantly higher positive affect at T2 than PD patients ($F(4, 137) = 13.28$, $p = .001$). No significant group differences were evident at T1 positive affect reports ($F(4, 140) = .927$, $p = .337$).

ii. *Relationship to NP functioning*

Higher levels of positive affect correlated with more efficient cognitive functioning at T1 in all NP tests (r_s =.25 to r =.32) except for TMT-B and RAVLT-D. Moderate-sized correlations, in the predicted direction were also observed for T2 NP scores with coefficients ranging from r = .27 to r = .35 (see Table 6.11).

Table 6.11: Correlations between positive affect and NP scores at T1 and T2 in the combined dialysis sample

TIME 1		***TIME 2***	
NP tests	***PNS-PA 1***	***NP tests***	***PNS-PA 2***
TMT-A1	-.307****	TMT-A2	-.316****
TMT-B1	-.145	TMT-B2	-.273***
SDMT-W1	.306****	SDMT-W2	.354****
SDMT-O1	.325****	SDMT-O2	.310****
RAVLT-T1	.279***	RAVLT-T2	.350****
RAVLT-D1†	-.125	RAVLT-D2†	-.045
GP-DOM1†	-.267***	GP-DOM2†	-.282***
GP-NDOM1	-.230**	GP-NDOM2	-.274***
BVRT-C1†	.255**	BVRT-C2†	.273***
BVRT-E1†	-.276***	BVRT-E2†	-.340****
NP–TOTAL1	.315****	NP–TOTAL2	.353****

Note: PNS-PA = PANAS positive affect

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

1.6.c Negative Affect (PNS-NA)

i. *Group differences*

Negative affect reports for the dialysis groups are presented in Table 6.12 below.

Table 6.12: Negative Affect at T1 and T2 in HD, PD and combined dialysis

	T1			T2		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
HD	14.61	5.24	10 – 39	12.45	2.83	10 – 23
PD	15.01	5.07	10 – 37	14.08	4.55	10 – 38
All dialysis	14.80	5.15	10 - 39	13.20	3.79	10 – 38

Repeated measures ANCOVA on negative affect (covarying for gender, time spent on dialysis and diabetic status) indicated only a significant effect for time ($F(3, 137) = 30.572$, $p = .001$) with dialysis participants reporting significantly lower negative affect at T2 relative to T1 levels. The treatment effect was not significant suggesting that both PD and HD groups had equivalent levels of negative affect when averaged across the two assessments. No significant treatment-by-time interaction effect was found.

ii. *Relationship to NP Performance*

A similar but reversed pattern of correlations was found between PNS-NA and NP performance as found for PNS-PA (see Table 6.13). Correlations coefficients at T1 indicated weak to moderate-sized correlations, ranging from $r_s = .21$ to $r_s = .39$ ($ps < .01$). Similar order correlations were also observed at T2 with coefficients in the range of $r_s = .19$ to $r_s = .34$ ($ps < .01$).

Table 6.13: Correlations between negative affect and NP scores at T1 and T2 in the combined dialysis sample

TIME 1		*TIME 2*	
NP tests	***PNS-NA 1†***	***NP tests***	***PNS-NA 2†***
TMT-A1	.330****	TMT-A2	.259**
TMT-B1	.326****	TMT-B2	.286***
SDMT-W1	-.359****	SDMT-W2	-.286***
SDMT-O1	-.384****	SDMT-O2	-.341****
RAVLT-T1	-.215**	RAVLT-T2	-.195*
RAVLT-D1†	.119	RAVLT-D2†	.024
GP-DOM1†	.290****	GP-DOM2†	.208*
GP-NDOM1	.236**	GP-NDOM2	.248**
BVRT-C1†	-.272***	BVRT-C2†	-.246**
BVRT-E1†	.339****	BVRT-E2†	.254**
NP –TOTAL1	-.398****	NP –TOTAL2	-.330****

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

1.6.c Depression (BDI; CDI)

i. *Group differences*

None of the depression scores (BDI nor CDI) were significantly different between HD (*mean* BDI = 10.96, *SD* = 7.46; *mean* CDI = 6.66, *SD* = 5.38) and PD patients (*mean* BDI = 13.24, *SD* = 9.09; *mean* CDI = 8, *SD* = 6.19).

The percentage of HD and PD patients scoring below or above the clinical cut-off for depression (i.e. a score of 15 on the BDI; Craven *et al.*, 1988) was also examined. Results showed that n = 24 (31.2%) of the HD patients and n = 28 (41.2%) of PD patients had BDI scores higher than 15 (*total* n = 52; 35.9% for combined dialysis sample). Chi square analysis showed that there were no significant differences between the two dialysis treatments in the prevalence of clinical depression ($\chi^2(145) = 1.572$, p = .21).

In the absence of CDI specific cut-off scores, CDI scores were multiplied by 21/15 and a score of 15 was used as the benchmark score to define clinical depression. Chi-square analysis indicated no significant group differences/no association between dialysis treatment and clinical depression (CDI), with twenty-two (n = 22, 32.4%) of the PD patients and sixteen of the HD patients (n = 16, 20.8%) were defined as cases ($\chi^2(145) = 2.501$, p = .114). It is of note however that compared to BDI scores, the CDI clinical cut-off evaluation resulted in a lower number of patients defined as cases (*total* n = 38; 26.3%).

ii. *Relationship to NP performance*

(a) Linear relationships between BDI, CDI, and NP scores

The associations between depression scores and NP scores were in the predicted direction with higher levels of depressive symptoms being associated with poorer cognitive functioning at both assessments (see Table 6.14). Correlation coefficients varied from .19 to .29 at T1 and from .19 to .34 at T2 for the BDI scores.

Table 6.14: Correlations between depression scores and NP scores at T1 and T2 in the combined dialysis sample

	TIME 1			*TIME 2*	
	BDI	***CDI***		***BDI***	***CDI***
TMT A1	.272***	.208*	TMT A2	.300****	. 214*
TMT B1	.187*	.112	TMT B2	.207*	.131
SDMT W1	-.249**	-.213**	SDMT W2	-.255**	-.240**
SDMT O1	-.276***	-.235**	SDMT O2	-.260**	-.242 **
RAVLT-T1	-.138	-.102	RAVLT-T2	-.186*	-.121
RAVLT-D1†	.014	-.058	RAVLT-D2†	.049	.010
GP-DOM1†	.274***	.235**	GP-DOM2†	.273***	.257**
GP-NDOM1	.320****	.259**	GP-NDOM2	.343****	.283***
BVRT-C1†	-.270***	-.233**	BVRT-C2†	-.226**	-.223**
BVRT-E1†	.293****	.263***	BVRT-E2†	.275***	.269***
NP TOTAL1	-.279****	-.218**	NP TOTAL2	-.309****	-.253**

† Spearman's correlation coefficient

* p < 05. ** p <.01. *** p <.001. **** p <.0001

Correlation coefficients for CDI were slightly lower than those observed for the total depression scores (BDI), ranging from .20 to 26 at T1 and from .21 to .28 at T2. Partial correlations controlling for ESRD severity showed no significant associations between either measure of depression and NP scores (data not shown).

(b) Clinical levels of depression (total BDI and CDI score) and NP performance

To determine if patients with higher levels of depression (BDI) demonstrated greater NP impairments across the two assessments, the combined dialysis sample was split into two groups, below and above a cut-off score of 15. This benchmark score of 15 has been proposed as the optimal cut-off point for a diagnosis of depression in dialysis patients (Craven *et al.*, 1988).

The non-depression group comprised 94 dialysis patients and had a mean total BDI of 6.78 (*SD* = 3.34, range = 0 – 14). The depression group (n = 51) had a mean total BDI of 21.40 (*SD* = 5.95, range = 14 – 38). The clinical depression group had higher ESRD severity scores (*mean* = 15.08, *SD* = 10.44) than the non-depressed group (*mean* = 8.97, *SD* = 8.15; t(83.151) = -3.748, p = .0001). The prevalence of diabetic patients was also higher in the clinical depression group ($\chi^2(145) = 14.277$, p = .0001).

Table 6.15: NP scores at T1 and T2 between depressed vs. non depressed patients (BDI clinical cut-off = 15) in the combined dialysis sample

	High BDI		Low BDI	
	Time 1	**Time 2**	**Time 1**	**Time 2**
	Mean (Sd)	*Mean (Sd)*	*Mean (Sd)*	*Mean (Sd)*
TMT A	61.46 (33.58)	56.55 (33.47)	47.03 (25.85)	40.07 (25.85)
TMT B	109.32 (52.22)	106.17 (53.93)	92.56 (49.95)	88.33 (46.25)
SDMT-W	37.65 (11.13)	41.88 (13.99)	43.03 (12.17)	48.24 (14.98
SDMT-O	41.02 (13.28)	45.78 (15.82)	47.84 (13.43)	53.04 (16.06)
RAVLT-T	37.07 (11.13)	38.75 (10.63)	40.12 (10.37)	43.03 (10.50)
RAVLT-D	2.77 (1.59)	2.80 (1.57)	2.41 (2.13)	2.83 (2.05)
BVRT-C	4.56 (2.07)	5.12 (1.94)	5.13 (2.19)	5.73 (2.19)
BVRT-E	9.38 (4.69)	8.08 (4.70)	8.10 (5.16)	6.66 (4.67)
GP-DOM	103.29 (39.93)	100.26 (37.76)	84.08 (24.03)	81.86 (23.64)
GP-NDOM	118.30 (49.72)	114.91 (46.68)	93.22 (27.94)	90.54 (27.31)
NP TOTAL	-2.60 (7.73)	-2.52 (7.68)	1.39 (6.71)	1.41 (6.71)

Before partialling out the effect of these two casemix differences ANOVA comparisons showed that the patients in the clinical depression group performed significantly worse than non depressed patients in TMT-A, TMT-B, SDMT-W, SDMT-O, GP-DOM and GP-NDOM at both assessments. Adjustments for casemix differences however removed these group differences. ANCOVA comparisons (controlling for ESRD-SI and diabetes) indicated no significant group differences in any of the T1 or T2 NP scores.

1.7 Physical Symptoms, Fatigue and NP performance

As physical symptoms and fatigue either as a result of illness, treatment or both are likely to affect NP performance, their temporal course over the 24-hours dialysis cycle and their association with concomitant NP changes were also examined.

1.7.a Fatigue

i. *Group differences*

Descriptive statistics indicated that both HD and PD patients on average, reported mild to moderate levels of fatigue immediately prior to each of their NP assessments (see Table 6.16).

Table 6.16: Fatigue levels at T1 and T2 in HD, PD, and the combined dialysis sample

	Time 1			Time 2		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
HD	62.27	21.21	0 – 100	63.44	20.82	10 – 100
PD	59.19	22.60	25 – 100	56.85	21.53	7 – 100
All dialysis	60.83	21.85	0 – 100	60.40	21.05	7 –100

Note: Higher scores in fatigue rating scale signify lower fatigue

There were no differences in self-reported fatigue levels between the two dialysis groups or across the two assessments. Repeated measures ANCOVA controlling only for diabetic status (as gender and time spent on dialysis were not significantly associated with fatigue) showed no significant main (i.e. time/treatment) or interaction effects.

ii. *Relationship to NP performance*

Spearman's correlation analysis showed weak to moderate associations between concurrently measured levels of fatigue and cognitive functioning on some tests.

Table 6.17: Correlations between fatigue and NP scores at T1 and T2 in the combined dialysis sample

TIME 1		*TIME 2*	
NP tests	***Fatigue 1†***	***NP tests***	***Fatigue 2†***
TMT-A1	-.236**	TMT-A2	-.295****
TMT-B1	-.144	TMT-B2	-.225**
SDMT-W1	.143	SDMT-W2	.183*
SDMT-O1	.196*	SDMT-O2	.170*
RAVLT-T1	.145	RAVLT-T2	.207*
RAVLT-D1	-.167*	RAVLT-D2†	.043
GP-DOM1	-.287****	GP-DOM2†	-.262**
GP-NDOM1	-.325****	GP-NDOM2	-.313**
BVRT-C1	.185*	BVRT-C2†	-.287***
BVRT-E1	-.212	BVRT-E2†	-.262**
NP –TOTAL1	.277***	NP –TOTAL2	.292****

Note: Higher scores in fatigue rating scale signify lower fatigue

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

† Spearman's correlation coefficient

Increased levels of fatigue (i.e. lower scores) correlated with more compromised cognitive functioning as indexed by longer time latencies in the time dependent tests (GP, TMT), and less number correct or more errors in other NP tests. The strongest correlations were noted between fatigue and NP scores in motor performance tasks such as GP.

1.7.b Concurrent symptoms

The effect of concurrent symptomatology on NP performance across the two assessments was investigated in two ways:

- in terms of symptoms occurrence, i.e. the number of symptoms patients reported immediately before each of the NP testing sessions.
- in a two-group analysis comparing NP scores in dialysis patients who report no symptoms/are completely asymptomatic vs. those who report one or more symptoms.

i. *Group differences*

Table 6.18: Concurrent symptoms at T1 and T2 in HD, PD, and the combined dialysis sample

	Time 1			Time 2		
	Mean	***SD***	***Range***	***Mean***	***SD***	***Range***
HD	2.65	2.62	0 – 11	2.25	2.83	0 – 17
PD	2.66	2.58	0 – 12	3.00	2.66	0 – 12
All dialysis	2.66	2.59	0 – 12	2.59	2.77	0 – 17

Dialysis patients reported on average less than 3 symptoms at the time of each of the two assessments (see Table 6.18). There was however wide inter-individual variation in number of symptoms reported in both dialysis groups. The range of reported symptoms was large, 0 to 12 for the PD group at both assessments and 0 to 11 and 0 to 17 in the HD group at T1 and T2 respectively.

Repeated measures ANCOVA (covarying only for diabetes as neither gender, nor dialysis duration were significantly associated with symptoms) were performed to compare symptom reporting between PD and HD patients across the two assessments.

This showed a significant treatment by time interaction effect suggesting that the course of symptom reporting differed between the two dialysis groups over the two assessments ($F(2, 142) = 5.497, p = .02$).

None of the post-hoc tests however yielded significant results after controlling for diabetic status. PD and HD reported an equal number of symptoms at the time of the two assessments. Symptom reporting also remained unchanged across the two assessments in both dialysis groups. Inspection of group means showed symptoms reporting across the two assessments followed a different course in PD and HD patients, that is likely to account for the significant interaction effect.

In HD patients, symptom occurrence was reduced from 2.65 (*SD* = 2.62) immediately before dialysis to 2.23 (*SD* = 2.85) at 24-hour post-dialysis although this was not significant. In PD patients, however the opposite trend was observed, with PD patients on average reporting more symptoms at T2 (*mean* = 3, *SD* = 2.67) than at T1 assessment (*mean* = 2.66, *SD* = 2.57) although this also failed to reach significance.

Inspection of the types of symptoms most frequently endorsed did not demonstrate a differential symptom profile between the two dialysis groups. Both HD and PD patients reported the same type of symptoms. The most frequently reported symptoms were fatigue, pain, loss of strength, lack of sex drive and stiff joints (see Table 6.19).

Several of the dialysis patients reported no symptoms at all at T1 (26.5% of PD and 23.4% of HD) and T2 assessments (21.2% of PD and 32.5% of HD). There were no significant differences in the number of asymptomatic patients between the two dialysis groups.

Even though treatment modality was unrelated, other clinical factors were associated with symptoms. Between groups comparisons revealed that patients who reported no symptoms at T1 had significantly lower ESRD severity scores (*mean* = 4.88, *SD* = 5.97) than patients experiencing some symptoms at T1 (*mean* = 13.23, *SD* = 9.51) (t (96.38) = - 6.17, $p = .0001$). Similar findings occurred at T2 with higher ESRD severity scores for patients with symptoms (*mean* = 12.47, *SD* = 9.57) at T2 compared to the ones with no symptoms (*M* = 7.58, *SD* = 8.29), t(143) = -2.81, $p = .005$). No other sociodemographic or medical variables were associated with symptom reports.

Table 6.19: Symptom reporting at T1 and T2 by HD and PD patients

	TIME 1		TIME 2	
	HD	PD	HD	PD[a]
Symptoms	*% (N)*	*% (N)*	*% (N)*	*% (N)*
Fatigue	39% (30)	41.2% (28)	26% (20)	40% (26)
Stiff joints	29.9% (23)	14.7% (10)	29.9% (23)	24.6% (16)
Loss of strength	28.6% (22)	32.4% (22)	18.2% (14)	26.2% (17)
Pain	23.4% (18)	27.9% (19)	15.6% (12)	27.7 (18)
Lack of sex drive	23.4% (18)	27.9% (19)	11.7% (9)	21.5% (14)
Breathlessness	15.6% (12)	19.1% (13)	7.8% (6)	24.6% (16)
Itching	15.6% (12)	19.1% (13)	11.7% (9)	30.8% (20)
Sleep difficulties	3.9% (3)	8.8% (6)	10.4% (8)	18.5% (12)
Dizziness	2.6% (2)	1.5% (1)	3.9% (3)	3.1% (2)
Headaches	11.7% (9)	5.9% (4)	11.7% (9)	9.2% (6)
Hair loss	9.1% (7)	2.9% (2)	6.5% (5)	
Loss of appetite	9.1% (7)	11.8% (8)	11.7% (9)	12.3% (8)
Restless legs	6.5% (5)	13.2% (9)	9.1% (7)	7.7% (5)
Weight loss	5.2% (4)	4.4% (3)	3.9% (3)	3.1% (2)
Sore eyes	5.2% (4)	7.4% (5)	9.1% (7)	9.2% (6)
Upset stomach	5.2% (4)	2.9% (2)	9.1% (7)	9.2% (6)
Sleep difficulties	3.9% (3)	8.8% (6)	10.4% (8)	18.5% (12)
Dizziness	2.6% (2)	1.5% (1)	3.9% (3)	3.1% (2)
Nausea	2.6% (2)	2.9% (2)	6 (7.8)	6.2% (4)
Asymptomatic pts[b]	**23.4% (18)**	**26.5% (18)**	**32.5% (25)**	**21.2% (14)**

Note: HD = haemodialysis; PD = peritoneal dialysis; pts = patients

[a] = 65 PD patients completed T2 assessment, valid percentages are reported

[b] = number of patients reporting no symptoms associated with their condition

ii. *Relationship to NP performance*

Spearman's correlational analysis revealed different patterns of correlations at T1 and T2 assessments between NP functioning and number of symptoms.

At T1 assessment the more symptoms dialysis patients reported the less efficient their cognitive performance in all NP tests except for RAVLT-D (Table 6.20). In contrast, symptom reporting appeared to be largely uncorrelated with cognitive functioning at T2. Only two significant albeit weak correlations were found between GP scores (T2) and concurrent symptoms.

Table 6.20: Correlations between concurrent symptoms and NP scores at T1 and T2 in the combined dialysis group

TIME 1		TIME 2	
NP tests	***Symptoms 1†***	***NP tests***	***Symptoms 2†***
TMT-A1	.331 ****	TMT-A2	.097
TMT-B1	.227**	TMT-B2	.012
SDMT-W1	-.272***	SDMT-W2	.071
SDMT-O1	-.315****	SDMT-O2	.012
RAVLT-T1	-.230**	RAVLT-T2	-.058
RAVLT-D1	.117	RAVLT-D2†	-.031
GP-DOM1	.360****	GP-DOM2†	.174*
GP-NDOM1	.362****	GP-NDOM2	.177*
BVRT-C1	-.258**	BVRT-C2†	-.077
BVRT-E1	.231**	BVRT-E2†	.106
NP–TOTAL1	-.346****	NP–TOTAL2	-.094

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

NP comparisons between asymptomatic dialysis patients and those experiencing or reporting symptoms at the time of the assessments were performed using ANCOVAs (controlling for ESRD severity). These analyses showed no significant main or interaction effects in cognitive functioning over T1 and T2 assessments, indicating that symptoms were unrelated to changes in NP functioning (data not shown).

1.8 NP acute changes in dialysis patients

To examine whether the HD group showed improvements over 24 hours in contrast to the PD group, a series of repeated measures ANCOVAs (covariates: fatigue, anxiety, dialysis duration, and diabetic status) comparing the NP performance of the HD and PD groups over time were performed. This revealed a consistent pattern of results across all NP tests.

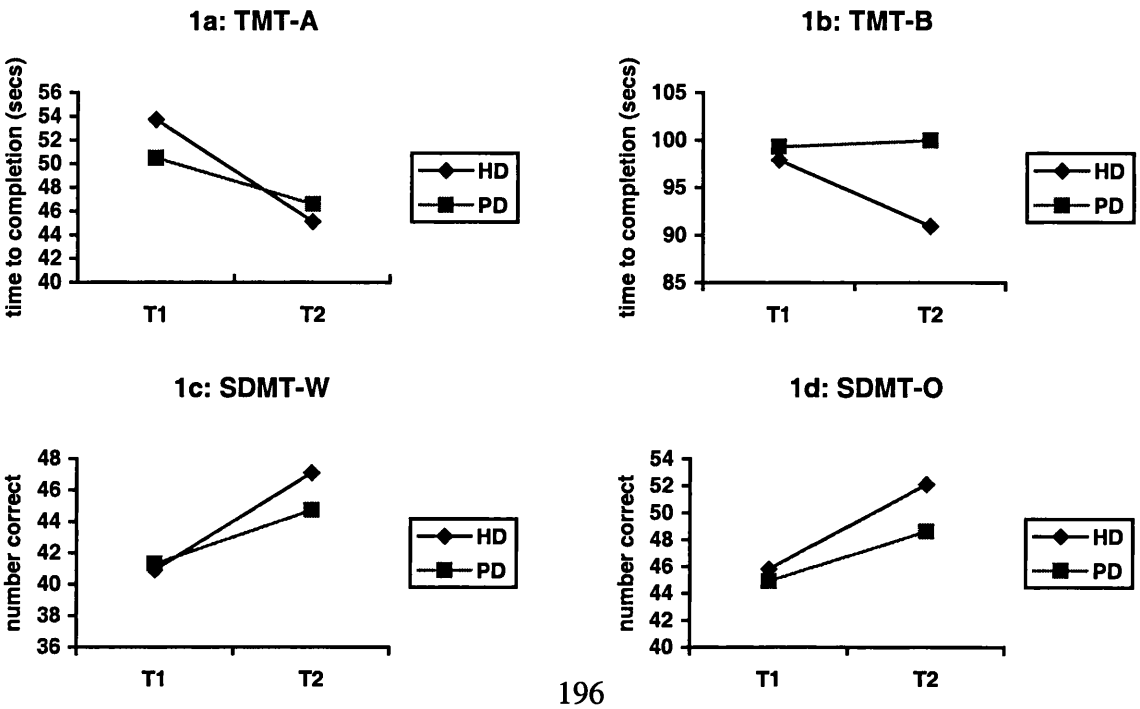
In none of the ANCOVAs was the main effect of dialysis treatment significant suggesting that both treatments result in equivalent cognitive functioning when T1 and T2 assessments are averaged. The main effects of time was significant for all NP scores (p*s* <.002) except for RAVLT-D: TMT-A ($F(6, 133) = 67.708$, $p = .0001$), TMT-B ($F(6, 133) = 11.693$, $p = .001$), RAVLT-T ($F(6, 133) = 36.104$, $p = .0001$), BVRT-C ($F(6,$

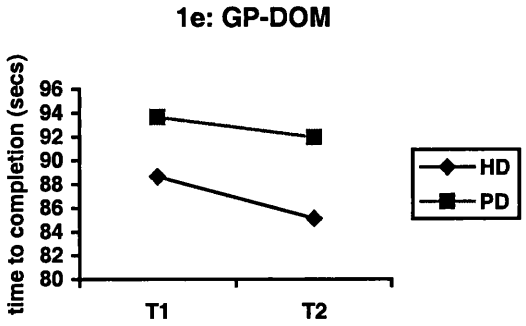
134) = 23.676, p = .0001), BVRT-E (F(6, 134) = 28.023, p = .0001), SDMT-O (F(6, 133) = 114.204, p = .0001), SDMT-W (F(6, 133) = 121.492, p = .0001), GP-DOM (F(6, 131) = 16.123, p = .0001) and GP-NDOM (F(6, 131) = 11.724, p = .002). These effects indicated improved NP performance at T2, anticipated through learning over such as a short interval (the relevant means are shown in Table 6.2 uncorrected for covariates)

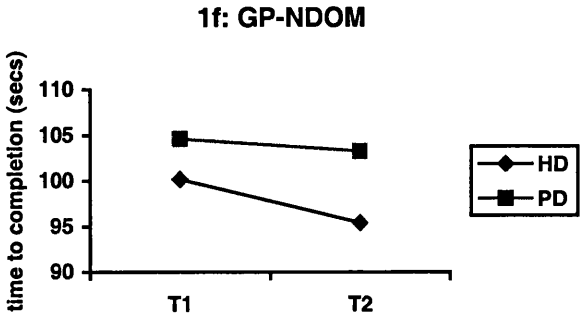
The group by time interaction effect was significant for 9 of the 10 NP scores: TMT-A (F(6, 133) = 4.929, p = .028); TMT-B (F(6, 133) = 7.822, p = .006); SDMT-W (F(6, 133) = 5.244, p = .024); SDMT-O (F(6, 133) = 4.701, p = .032); RAVLT-T (F(6, 133) = 14.292, p = .0001); BVRT-C (F(6, 133) = 4.168, p = .043); BVRT-E (F(6, 134) = 7.38, p = .007); GP-NDOM (F(6, 131) = 10.183, p = .002); and GP-DOM (F(6, 131) = 6.686, p = .0001). Follow-up simple effect tests (ANCOVAs) showed significant improvements in NP performance mainly for the HD group. HD patients' performance in all NP measures improved significantly 24-hours post their dialysis relative to pre-dialysis even after anxiety, fatigue, diabetes, and dialysis duration were controlled for (ps <.001). In contrast, PD patients' performance remained largely unchanged across T1 and T2 assessments with only TMT-A (F(6, 57) = 21.31, p = .0001), SDMT-W (F(6, 57) = 39.20, p = .0001), SDMT-O scores (F(6, 57) = 31.05, p = .0001) showing improvements. It is of note that these three NP tasks have no alternate forms, consequently greater learning was anticipated.

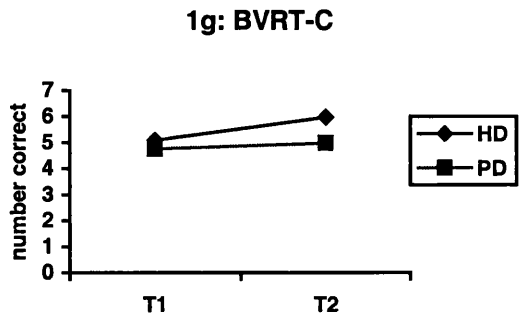
These data are depicted graphically in Figure 6.1.

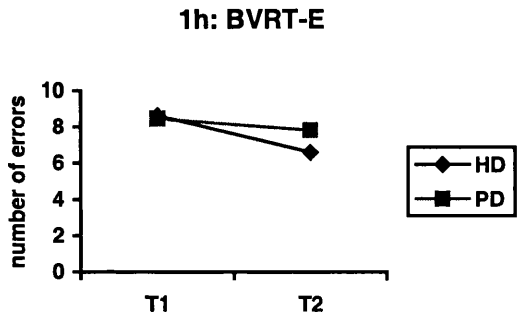
Figure 6.1 a-i: Acute NP changes in HD and PD

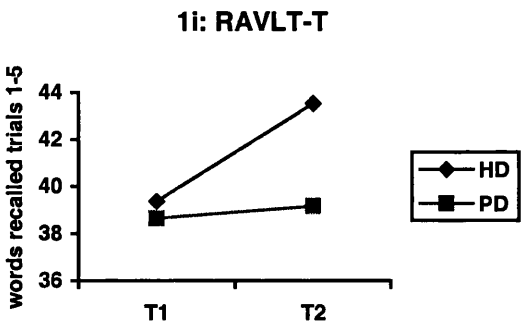












Post-hoc comparisons between the HD and PD groups on the T1 and T2 NP scores showed no significant group differences. A trend was noted in T2 RAVLT-T ($F(5, 139) = 3.352$, $p = .062$), with HD patients recalling more words than PD patients at the T2 but this did not reach significance.

1.9 Blood biochemistry over time

It was hypothesised that improved biochemical status at 24-hours post-dialysis should underline any observed NP improvement in HD patients. Biochemical data were analysed to determine the temporal course of biochemistry profiles in the two dialysis groups and their associations with absolute NP performance and NP improvements.

1.9.a Group differences

A series of 2 x 2 repeated measures ANCOVAs (covarying for gender, diabetes, and dialysis duration) showed that biochemistry levels across the two assessments differed between the two treatment groups (Table 6.21).

Table 6.21: Biochemistry and T1 and T2 in HD and PD

		HD		PD		
		T1	T2	T1	T2	*F*
Urea (mmol/l)	*M*	22.66	13.24	21.57	21.18	116.87
	SD	4.82	4.12	6.12	6.25	****
Creatinine (mmol/l)	*M*	798.5	534.1	808.60	806.00	87.13****
	SD	183.9	192.5	231.30	226.3	
Sodium (mmol/l)	*M*	139.1	136.74	136.70	136.55	.044
	SD	2.72	3.04	3.07	2.86	
Albumin (g/dl)	*M*	39.82	41.78	35.60	35.80	7.96**
	SD	3.45	4.22	4.09	4.29	
Calcium (mmol/l)	*M*	2.46	2.60	2.35	2.33	4.44*
	SD	.22	.62	.21	.19	
Haemoglobin (g/dl)	*M*	10.86	10.58	11.23	11.08	.36
	SD	1.52	1.48	1.37	1.37	
Potassium (mmol/l)	*M*	5.08	5.97	4.75	4.97	28.28**
	SD	2.30	2.31	1.98	1.74	
Phosphate (mmol/l)	*M*	8.64	6.61	8.47	7.82	18.14****
	SD	5.46	5.30	4.51	3.85	
Alk-P-Tase (U/L)	*M*	88.66	85.12	93.65	91.95	1.84
	SD	29.78	28.81	34.28	32.16	

Note. The *F test* denotes the group by time interaction effect for the 2 x 2 analysis of covariance. T1 = time 1 assessment; T2 = time 2 assessment; HD = haemodialysis; PD = peritoneal dialysis; Alk-P-tase = Alkaline Phosphatase

[a] Normal serum albumin concentrations vary by laboratory methodology

* p <.05. ** p <.01. *** p <.001. **** p <.0001

Time-by-treatment interaction effects were significant for BUN ($F(3, 103) = 116.88$, $p = .0001$), Cr ($F(3, 103) = 87.13$, $p = .0001$), K^+ ($F(3, 103) = 28.28$, $p = .0001$), PO_4 ($F(3, 97) = 18.14$, $p = .0001$), Ca^{2+} ($F(3, 98) = 4.44$, $p = .038$), and Alb ($F(3, 92) = 7.59$, $p = .006$). As anticipated, no significant differences were found in any of the biochemical assays for the PD group from T1 to T2 while in the HD group biochemistry levels changed significantly for pre- to 24-hours post-dialysis with significant decreases in BUN ($F(3, 50) = 212.06$, $p = .0001$), Cr ($F(3, 50) = 130.05$, $p < .0001$), PO_4 ($F(3, 44) =$

19.78, p = .0001), K^+ (F(3, 50) = 61.84, p = .0001) and increases in Alb (F(3, 42) = 17.49, p = .0001), and Ca^{2+} levels (F(3, 45) = 4.57, p = .038).

PD and HD patients differed in their biochemistry across the two assessments. At T1 HD patients had significantly higher Ca^{2+} (F(4, 144) = 8.942, p = .003), Alb (F(4, 139) = 44.979, p = .0001), PO_4 (F(4, 140) = 8.449, p = .004), K^+ (F(4, 140) = 37.905, p = .0001) and Sodium (F(4, 140) = 18.029, p = .0001) compared to PD. Urea levels did not differ between groups at T1 (F(4, 140) = 3.109, p = .08).

Consistent with the HD biochemistry profile, 24 hours post-dialysis Cr (F (4, 103) = 37.048, p = .0001) and BUN (F(4, 103) = 40.167, p = .0001) were lower in HD whereas Ca^{2+} (F(4, 98) = 9.014, p = .003), Sodium (F(4, 102) = 7.462, p = .007) and Alb (F(4, 93) = 44.032, p = .0001) on the other hand remained significantly higher in HD patients relative to PD.

1.9.b Relationship to NP performance: T1 absolute NP scores

To evaluate the relationship between biochemical measures and cognitive functioning, a series of hierarchical multiple regressions were performed on the combined sample (PD and HD) controlling for the effect of sociodemographic, medical, and mood variables (see Tables 6.22 - 6.27). Employment status was not included despite significant univariate associations as it was regarded an outcome/consequence of cognitive functioning rather than a predictor.

In the first instance, the biochemistry hypothesis was tested (i.e. entering biochemical values in the last step of the regression). From the mood indicators, only state anxiety and cognitive depression scores were included in these regression equations to reduce number of IVs in the models. They were selected over the remaining mood measures because they are the variables traditionally controlled for in NP evaluations (Lezak, 1995) and because both (STAI and CDI) were strongly correlated with the other mood indicators, i.e. total BDI scores and positive and negative affect (see Table 6.7) with correlations ranging from r = .46 to r =.93.

Multiple regression analysis was not performed for RAVLT-D as none of the sociodemographic, medical, or mood measures was significantly associated with that NP score (in univariate analyses).

Table 6.22: Multiple regressions to predict TMT-A, TMT-B and SDMT-W in dialysis: standardised regression coefficient and cumulative variance explained

	TMT-A			TMT-B			SDMT-W		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	.304 ***	.21 f^2=.336	.204 f^2=315	.336 ***	.208 f^2=.318	.201 f^2=.295	-.326 ***	.230 f^2=.362	.224 f^2=.363
Educ									
Block 2									
ESRD SI	.223 *	.291 f^2=.336	.279 f^2=.336	.149 ns	.247 f^2=..06	.235 f^2=.05	-.158 ns	.284 f^2=.083	.272 f^2=.073
Kt/V	-.191*	.329 f^2=.129	.312 f^2=.051	-.151*	.273 f^2=.04	.255 f^2=.029	.168*	.314 f^2=.047	.297 f^2=.038
Diabetes									
Block 3									
STAI	.224 **	.374 f^2=.06	.353 f^2=.063	.220 **	.311 f^2=.058	.288 f^2=.048	-.237 **	.365 f^2=.08	.344 f^2=.072
CDI									
Block 4									
BUN				-.189 *	.346 f^2=.054	.318 f^2=.046			
CA									
PO_4									
K									
Cr									
Hb									
Sod									
Alb									
AlkPho									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; STAI = state anxiety; CDI = cognitive depression index; NA = negative affect; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; K = potassium; Cr = creatinine; Hb = haemoglobin; Sod = sodium; Alb =albumin; AlkPho =alkaline phosphatase

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

Table 6.23: Multiple regressions to predict SDMT-O, RAVLT-T and BVRT-C in dialysis: standardised regression coefficient and cumulative variance explained

	SDMT-O			RAVLT-T			BVRT-C		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	-.370 ***	.257 f^2=.44	.251 f^2=.42	-.392 ***	.212 f^2=.322	.205 f^2=.304	-.131 ns	.102 f^2=.144	.095 f^2=.128
Educ							.145 ns	.135 f^2=.045	.121 f^2=.035
Block 2									
ESRD SI	.145 *	.332 f^2=.128	.321 f^2=.126	.149 ns	.273 f^2=.094	.262 f^2=.085	-.214*	.172 f^2=.052	.151 f^2=.04
Kt/V	.205*	.355 f^2=.039	.340 f^2=.03						
Diabetes									
Block 3									
STAI	-.254 **	.414 f^2=.099	.395 f^2=.091	-.263 ***	.342 f^2=.105	.326 f^2=.095	-.120 ns	.203 f^2=.045	.177 f^2=.035
CDI									
NA									
Block 4									
BUN									
CA							.232 **	.265 f^2=.088	.234 f^2=.077
PO_4							.172*	.293 f^2=.040	.258 f^2=.032
K									
Cr									
Hb									
Sod									
Alb									
AlkPho									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; STAI = state anxiety; CDI = cognitive depression index; NA = negative affect; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; K = potassium; Cr = creatinine; Hb = haemoglobin; Sod = sodium; Alb =albumin; AlkPho =alkaline phosphatase

* p <.05. ** p < .01. *** p <.001. **** p <.0001. ns = non significant

Table 6.24: Multiple regressions to predict BVRT-E, GP-DOM and GP-NDOM in dialysis: standardised regression coefficient and cumulative variance explained

	BVRT-E			GP-DOM			GP-NDOM		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Educ	-.219	.105	.098						
	**	f^2=.139	f^2=.125						
Age	.122	.157	.143	.291	.167	.160	.394	.266	.26
	ns	f^2=.069	f^2=.057	**	f^2=.238	f^2=.22	***	f^2=.444	f^2=.429
Block 2									
ESRD SI	.227*	.186	.166	.125	.23	.217	.127	.230	.217
		f^2=.038	f^2=.029	ns	f^2=.088	f^2=.079	ns	f^2=.088	f^2=.079
Kt/V									
Diabetes				.148	.257	.239	.162*	.362	.347
				ns	f^2=.038	f^2=.030		f^2=.044	f^2=.051
Block 3									
STAI									
CDI				.255	.298	.274	.223	.402	3827
				**	f^2=.058	f^2=.05	**	f^2=.057	f^2=.064
NA									
Block 4									
BUN									
CA	-.239	.242	.217						
	**	f^2=.075	f^2=.067						
PO_4									
K									
Cr									
Hb									
Sod									
Alb									
AlkPho									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; STAI = state anxiety; CDI = cognitive depression index; NA = negative affect; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; K = potassium; Cr = creatinine; Hb = haemoglobin; Sod = sodium; Alb =albumin; AlkPho =alkaline phosphatase

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

The resulting regression models were moderately successful in predicting absolute NP scores in dialysis. Total adjusted R^2 explained was 21.7% in BVRT-E, 27.6% in BVRT-C, 32.6% in RAVLT-T, 27.5% in GP-DOM, 38.2% in GP-NDOM, 35.3% in TMT-A, 31.9% in TMT-B, 34.4% in SDMT-W and 39.5% in SDMT-O (see tables 6.22 - 6.24 above).

Age significantly predicted all NP test scores. As indexed by beta weights (standardised regression coefficients), increasing age was associated with poorer performance in NP tasks. Greater ESRD severity and lower dialysis adequacy were also associated with more compromised cognitive functioning. Dialysis adequacy accounted for only a small, albeit significant percentage of the variance in TMT-A (ΔAdj.R^2 = 3.3%, f^2 = ***.0608***), TMT-B (ΔAdj.R^2 = 2.1%, f^2 = ***.0402***), SDMT-O (ΔAdj.R^2 = 1.8%, f^2 = ***.0397***), and SDMT-W (ΔAdj.R^2 = 2.5%, f^2 = ***.0478***).

State anxiety was consistently associated with verbal memory and all four attention NP scores explaining 4.1% (f^2 = ***.0719863***), 3.3% (f^2 = ***.058041***), 4.7% (f^2 = ***.0798***), 5.5% (f^2 = ***.0998***), 6.5% (f^2 = ***.1023***) (Δadj.R^2) of the variance in TMT-A, TMT-B, SDMT-W, SDMT-O and RAVLT-T respectively. Cognitive depression alone predicted psychomotor performance accounting for 3.6% (ΔAdj.R^2) in both GP-DOM (f^2 = ***.0561***) and GP-NDOM (f^2 = ***.0642***) scores.

Among the biochemical measures, urea accounted for an additional ΔAdj.R^2 = 3.1% (f^2 = ***.0536***) of the explained variance in TMT-B but was not a significant predictor of any of the other NP tests. Interestingly regression coefficients (β = -.189, p =.012) indicated counterintuitive relationships in that lower urea levels were associated with longer time latencies in TMT-B task. Calcium contributed a small percentage in the explained variance in BVRT-E (ΔAdj.R^2 = 5.1%, f^2 = *.0746*) and BVRT C (ΔAdj.R^2 = 5.1%, f^2 = ***.0873***) scores. Phosphate was similarly associated with BVRT-C (ΔAdj.R^2 = 2.3%, f^2 = ***.0397***). None of the biochemical indices were significant predictors in the regression models for TMT-A, SDMT-W, SDMT-O, RAVLT-T, GP-DOM, GP-NDOM.

To further evaluate the role of biochemistry and mood another set of regressions were performed. NP scores at T1 were regressed to mood indicators (STAI, positive affect negative affect, CDI) controlling for demographic (age and education), clinical (ESRD

severity, diabetes, Kt/V) and biochemical measures (urea, calcium and phosphate). Only these three biochemical values were included, as in previous regressions (see Tables 6.22 - 6.24) showed that they were the only ones significantly associated with cognitive functioning. The exclusion of the other biochemical values was also deemed necessary so as to have a more favourable subjects-to-predictors ratio.

Those analyses yielded a similar pattern of results as the ones reported earlier when mood and biochemistry entered the regression in reverse order (see Tables 6.25 - 6.27).

Table 6.25: Multiple regressions to predict TMT-A, TMT-B and SDMT-W in dialysis with mood at the last step: standardised regression coefficient, cumulative variance

	TMT-A			**TMT-B**			**SDMT-W**		
	β	**Cum R^2**	**Cum Adj R^2**	β	**Cum R^2**	**Cum Adj R^2**	β	**Cum R^2**	**Cum Adj R^2**
Block 1									
Age	.284	.199	.204	.314	.198	.191	-.369	.236	.23
	***	f^2=.31	f^2=315	***	f^2=.295	f^2=.274	***	f^2=.39	f^2=.366
Educ									
Block 2									
ESRD SI	.24	.284	.272	.143	.235	.223	-.146	.289	.278
	***	f^2=.128	f^2=.113	ns	f^2=.056	f^2=.042	ns	f^2=.088	f^2=.076
Kt/V	-.191*	.323	.306	-.155*	.262	.244	.168*	.319	.303
		f^2=.063	f^2=.053		f^2=.04	f^2=.029		f^2=.05	f^2=.04
Diabetes									
Block 3									
BUN									
CA	-.199	.346	.324				.130	.341	.320
	ns	f^2=.037	f^2=.028				ns	f^2=.036	f^2=.027
PO_4				-.170*	.299	.276			
					f^2=.056	f^2=.046			
Block 4									
STAI	.205	.382	.357	.184*	.329	.302			
	**	f^2=.06	f^2=.051		f^2=.045	f^2=.038			
CDI									
PNS-NA							-.273	.395	.37
							***	f^2=.09	f^2=.08
PNS-PA									

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1 - R^2_{Total})$.

Table 6.26: Multiple regressions to predict SDMT-O, RAVLT-T and BVRT-C in dialysis with mood at the last step: standardised regression coefficient, cumulative variance explained

	SDMT-O			RAVLT-T			BVRT-C		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	-.374	.26	.254	.-354	.22	.214	-.107	.104	.097
	***	f^2=.468	f^2=.44	***	f^2=.342	f^2=.322	ns	f^2=.145	f^2=.129
Educ				.226	.285	.273			
				***	f^2=.099	f^2=.089			
Block 2									
ESRD SI	-.188*	.334	.323	-.093	.307	.29	-.260	.172	.152
		f^2=.133	f^2=.12	ns	f^2=.034	f^2=.026	**	f^2=.051	f^2=.04
Kt/V	.157*	.357	.342						
		f^2=.041	f^2=.033						
Diabetes									
Block 3									
BUN									
CA	.136*	.381	.361				.251	.248	.224
		f^2=.043	f^2=.042				**	f^2=.106	f^2=.096
PO_4							.187*	.282	.252
								f^2=.046	f^2=.037
Block 4									
STAI				-.236	.357	.336			
				**	f^2=.078	f^2=.07			
CDI									
PNS-NA	-.273	.445	.422						
	***	f^2=.113	f^2=.106						
PNS-PA									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; STAI = state anxiety; NA = negative affect; BUN = blood urea nitrogen; PA = positive affect; CA = calcium; PO_4 = phosphate

* p <.05. ** p < 01. *** p <.001. **** p <.0001. ns = non significant

Table 6.27: Multiple regressions to predict BVRT-E, GP-DOM and GP-NDOM in dialysis with mood at the last step: standardised regression coefficient, cumulative variance explained

	BVRT-E			GP-DOM			GP-NDOM		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Educ	-.221	.109	.103						
	**	f^2=.146	f^2=.131						
Age	.123	.163	.149	.296	.170	.164	-.396	.266	.26
	ns	f^2=.07	f^2=059	***	f^2=.243	f^2=.227	***	f^2=.469	f^2=.421
Block 2									
ESRD SI	.227*	.191	.171	.128	.223	.221	.126	.330	.320
		f^2=.037	f^2=.028	ns	f^2=.09	f^2=.078	ns	f^2=.109	f^2=.097
Kt/V									
Diabetes				.149	.261	.243	.162	.362	.346
				ns	f^2=.029	f^2=.03		f^2=.053	f^2=.042
Block 3									
BUN									
CA	-.238	.247	.223						
	**	f^2=.074	f^2=.067						
PO_4									
Block 4									
STAI									
CDI				.223	.301	.278	.225	.403	.383
				**	f^2=.057	f^2=.048	**	f^2=.069	f^2=.06
PNS-NA									
PNS-PA									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate STAI = state anxiety; PNS-NA = PANAS negative affect; PNS-PA = PANAS positive affect;

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

The resulting regression models explained 22.2% to 42.2% (Adj.R^2) of the variance in T1 absolute NP scores in the total dialysis sample: 22.2% in BVRT-ER; 25.2% in

BVRT-C; 33.6% in RAVLT-T; 35.7% in TMT A; 30.2% in TMT B; 37% in SDMT-W; 42.2% in SDMT-O, 27.8% in GP-DOM; and 38.3% in GP-NDOM (see Tables 6.25 - 6.27).

The same demographic, clinical and biochemical measures emerged as significant predictors. The observed multivariate associations indicated that increasing age, higher ESRD severity, lower dialysis adequacy, lower calcium and higher phosphate were associated with more compromised cognitive functioning.

Entering the biochemical measures before mood increased their predictive power as expected. For instance, results showed that calcium emerged as a significant predictor in SDMT-O, SDMT-W and TMT-A models explaining in order 1.9%, 1.7% and 1.8% (ΔAdj.R^2) of the total variance. These associations however had failed to reach significance in the previous regressions in when biochemical measures were entered in the last step after mood (see Tables 6.22 - 6.24).

The addition of mood in the last step further improved the models. Mood measures predicted all NP scores with the exception of visual/non verbal memory (BVRT scores). They contributed an additional (ΔAdj.R^2) 3.2% (f^2 = *.0592*), 2.5% (f^2 = *.0448*), 6.1% (f^2 = *.1138*), 5% (f^2 = *.0886*), 4.6% (f^2 = *.0759*), 3.5% (f^2 = *.0570*), 3.7% (f^2 = *.0681*) in the total variance of TMT A, TMT B, SDMT-O, SDMT-W, RAVLT-T, GP-DOM, and GP-NDOM respectively.
Specific mood predictors varied across NP scores. State anxiety was associated with RAVLT-T, TMT-A, TMT-B. Negative affect was associated with SDMT-O and SDMT-W whereas cognitive depression predicted psychomotor performance, namely GP-DOM and GP-NDOM scores.

1.9.c Relationship to NP performance: Residualised change NP scores

To examine whether the observed NP improvements at T2 were associated with biochemical changes, the multivariate associations among biochemical and NP residualised change scores were analysed with similar hierarchical multiple linear regressions. In the first set of regressions, biochemical variables were entered at the last step after sociodemographic (age, education), clinical (ESRD-SI, diabetes, Kt/V) and

mood variables (CDI, STAI). The models had limited success in predicting NP change scores. Resultant models comprised single variables, i.e. either age or a biochemical /clinical parameter with little consistency across NP scores. Significant predictors varied depending on the NP outcome and the total percentage of variance explained was small, ranging from Adj.R^2 = 5.3% to Adj.R^2 = 15.2% (see Tables 6.29 – 6.30).

Significant predictors were calcium (SDMT-W: Adj.R^2 = 10%, β = .335, p = .004, f^2 =.*1267*; SDMT-O: Adj.R^2 = 9.3%, β = .326, p = .005, f^2 =.*1186*), phosphate (GP-NDOM: Adj.R^2 = 7.6%, β = .299, p =.011, f^2 =.*0985*), and urea (RAVLT-T: adj.R^2 = 7.9%, β = -.304, p = .005, f^2 =.*1094*). The observed associations signify small effect sizes and indicated that improvements in NP performance were associated with concomitant increase in calcium and decrease in inorganic phosphate and in urea levels Age was the only variable to be significantly associated with acute changes in BVRT-C; BVRT-E; TMT-A and TMT- scores (see Tables 6.29 - 6.30) .

Table 6.28: Multiple regressions to predict acute changes in SDMT-W; SDMT-O; RAVLT- T: standardised regression coefficient, cumulative variance explained

	SDMT-W			SDMT-O			RAVLT-T		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age									
Education									
Block 2									
ESRD SI									
Kt/V									
Diabetes									
Block 3									
State anxiety									
Cognitive depression									
Block 4									
Urea							-.304 **	.092 f^2=.101	.080 f^2=..87
Calcium	.335 **	.112 f^2=.126	.100 f^2=.111	.326 **	.106 f^2=.119	.093 f^2=.103			
Phosphate									
Potassium									
Creatinine									
Haemoglobin									
Sodium									
Albumin									
AlkPho									

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Table 6.29: Multiple regressions to predict acute changes in GP-DOM; GP-NDOM; BVRT-E: standardised regression coefficient, cumulative variance explained

	GP-DOM			GP-NDOM			BVRT-E		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age							.281 **	.079 f^2=.086	.066 f^2=.071
Education									
Block 2									
ESRD SI									
Kt/V	.260 *	.73 f^2=.079	.06 f^2=.064						
Diabetes									
Block 3									
State anxiety									
Cognitive depression									
Block 4									
Urea									
Calcium									
Phosphate				.257 *	.090 f^2=.099	.076 f^2=.082			
Potassium									
Creatinine									
Haemoglobin									
Sodium									
Albumin									
Alkaline Phosphatase									

Table 6.30: Multiple regressions to predict acute changes in TMT-A; TMT-B: BVRT-C: standardised regression coefficient, cumulative variance explained

	TMT-A			TMT-B			BVRT-C		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	.269 *	.073 f^2=.079	.06 f^2=.064	.257 *	.066 f^2=.071	.053 f^2=.059	-.405 ***	.164 f^2=.196	.152 f^2=.179
Education									
Block 2									
ESRD SI									
Kt/V									
Diabetes									
Block 3									
State anxiety									
Cognitive depression									
Block 4									
Biochemistry[a]									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy;
[a] = biochemistry change scores entered: urea; creatinine; potassium, phosphate, sodium; albumin haemoglobin; albumin; alkaline phosphatase
* p <.05. ** p <.01. *** p <.001. **** p <.0001.

In the second set of multiple regressions performed, the order of entry of biochemical and mood variables was reversed. Predictors entered the regression equations in the following order: sociodemographics, clinical variables, biochemistry (only urea, calcium, phosphate) and mood variables (CDI, STAI, positive affect and negative affect) (see Tables 6.31 - 6.33).

Three points in relation to the results need mentioning:

Firstly, the inclusion of more mood measures at the last step improved the overall predictability of the constructed models. The total amount of variance explained in the various NP outcomes increased somewhat albeit would still considered rather small (Adj.R^2 ranging from 4.1% to 16.6%). Constructed models accounted for a small amount of variance in NP change scores. Total Adj.R^2 are as follows: 12.56% in TMT B; 4.1% in TMT A; 12.24% in SDMT-W; 9.1% in SDMT-O; 14.4% in RALVT-T; 12.8% in GP-NDOM; 11.7% in GP-DOM; 16.5% in BVRT-C; and 16.7% in BVRT-E residualised change scores.

Secondly, stronger associations were observed between changes in biochemistry and changes in cognitive functioning. It is of note that the effect of urea became significant on more NP outcomes when biochemistry was entered before mood. This was in the expected direction with decreases in urea being associated with improved functioning mainly in memory tasks, namely RAVLT-T (Adj.R^2 = 10.3%; f^2 = *.12*), BVRT-E (ΔAdj.R^2 = 4.3%; f^2 = *.052*), BVRT-CO (ΔAdj.R^2 = 4.5%; f^2 = *.054*) and also in GP-DOM (Adj.R^2 = 4.9%; f^2 = *.055*) change scores.

Thirdly, changes in positive and negative affect were similarly associated with changes in NP performance. Increased positive affect predicted improvement in NP performance on SDMT-W (ΔAdj.R^2 = 3.5%; f^2 = *.042*), RAVLT-T (ΔAdj.R^2 = 4.1%; f^2 = *.048*) and BVRT-E (ΔAdj.R^2 = 5.6%; f^2 = *.067*). On the other hand decreases in reported levels of negative affect was associated with better performance in TMT-B (ΔAdj.R^2 = 5.4%; f^2 = *.062*), GP-DOM (ΔAdj.R^2 = 6.8%; f^2 = *.77*) and GP-NDOM (ΔAdj.R^2 = 4.3%; f^2 = *.049*). Interestingly, depression or changes in levels of anxiety failed to emerge as significant predictors when entered together with positive and negative affect, despite being associated with absolute levels of NP performance at T1.

Table 6.31: Multiple regressions to predict acute changes in TMT-A; TMT-B: SDMT-W in dialysis (mood at the last step): standardised regression coefficient, cumulative variance explained

	TMT-A			TMT-B			SDMT-W		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	.232	.054	.042	.293	.084	.072			
	*	f^2=.057	f^2=.044	**	f^2=.098	f^2=.075			
Education									
Block 2									
ESRD SI									
Kt/V									
Diabetes									
Block 3									
BUN									
CA							.288	.096	.085
							**	f^2=.056	f^2=.042
PO_4									
Block 4									
STAI									
CDI									
PNS-NA				.252	.147	.126			
				*	f^2=.75	f^2=.062			
PNS-PA							.220	.144	.122
							*	f^2=.056	f^2=.042

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; STAI = state anxiety; CDI = cognitive depression index; PNS-NA = PANAS negative affect; PNS-PA = PANAS positive affect

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Table 6.32: Multiple regressions to predict acute changes in SDMT-O; RAVLT-T; BVRT-C in dialysis (mood at the last step): standardised regression coefficient, cumulative variance explained

	SDMT-O			RAVLT-T			BVRT-C		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age							-.333	.131	.120
							**	f^2=.161	f^2=.144
Educ									
Block 2									
ESRD SI									
Kt/V									
Diabetes									
Block 3									
BUN				-.286	.114	.103	-.234	.185	.165
				**	f^2=.136	f^2=.120	*	f^2=.066	f^2=.054
CA	.320	.102	.091						
	**	f^2=.114	f^2=.100						
PO_4									
Block 4									
STAI									
CDI									
PNS-NA	-.273	.445	.422						
	***	f^2=.113	f^2=.106						
PNS-PA				.232	.165	.144			
				*	f^2=.061	f^2=.048			

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; STAI = state anxiety; CDI = cognitive depression index; PNS-NA = PANAS negative affect; PNS-PA = PANAS positive affect

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Table 6.33: Multiple regressions to predict acute changes in BVRT-E; GP-DOM; GP-NDOM in dialysis (mood at the last step): standardised regression coefficient, cumulative variance explained

	BVRT-E			GP-DOM			GP-NDOM		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Educ									
Age	.239	.079	.068						
	*	f^2=.098	f^2=.082						
Block 2									
ESRD SI									
Kt/V									
Diabetes									
Block 3									
BUN	.176	.133	.111	.186	.061	.049			
	ns	f^2=.067	f^2=.052	ns	f^2=.071	f^2=.055			
CA									
PO_4							.263	.096	.085
							*	f^2=.113	f^2=.097
Block 4									
STAI									
CDI									
PNS-NA				.285	.139	.117	.236	.150	.128
				*	f^2=.090	f^2=.077	*	f^2=.064	f^2=.049
PNS-PA									

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; Cum = cumulative; Educ = education; ESRD SI = end-stage renal disease severity index; Kt/V = dialysis adequacy; BUN = blood urea nitrogen; CA = calcium; PO_4 = phosphate; STAI = state anxiety; CDI = cognitive depression index; PNS-NA = PANAS negative affect; PNS-PA = PANAS positive affect

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

1.10 Subjective Cognition Scale (SCS)

1.10.a Acute changes in subjective cognition

Dialysis patients' responses to the nine-item questionnaire on perceived cognitive changes between T1 and T2 are shown in Table 6.34.

Whereas almost all PD patients reported no changes in their cognitive abilities over the two assessments, a considerable percentage of HD patients perceived positive cognitive changes from pre- to 24-hours post-dialysis. Although the percentages of HD patients reporting cognitive change varied depending on the specific cognitive domain, 31 HD patients (40.6%) in total reported more efficient cognitive abilities in one or more area of cognition. The most frequently self-reported areas of improvement post-dialysis with HD patients were concentration, followed by clarity of thinking and attention.

Table 6.34: Subjective cognition scale: acute changes at T1- T2

	HD			PD			
Cognitive domain	+ve	=	-ve	+ve	=	-ve	χ^2
1. memory$_1$	6.5% (5)	87% (67)	6.5% (5)		96.9% (62)	3.1% (2)	4.309 ns$_2$
2. problem solving$_1$	14.3% (11)	83.1% (64)	2.6% (2)	1.6% (1)	93.8% (60)	4.7% (3)	5.724*
3. clarity of thinking$_1$	33.8% (26)	63.6% (49)	2.6% (2)	4.7% (3)	87.5% (56)	7.8% (5)	16.353****
4. concentration$_1$	35.1% (27)	59.7% (46)	5.2% (4)		87.5% (56)	12.5% (8)	25.538****
5. making mistakes$_1$	2.6% (2)	94.8% (73)	2.6 (2)		100% (64)		ns = .501
6. attention$_1$	24.7% (19)	74% (57)	1.3% (1)		98.4% (63)	1.6% (1)	16.197****
7. clumsiness$_1$	2.6% (2)	94.8% (73)	2.6% (2)	1.6% (1)	98.4% (63)		.180 ns$_2$
8. decision making$_1$	2.6% (2)	96.1% (73)	1.3% (1)		100% (64)		1.868 ns$_2$
9. speed of response$_1$	20.8% (16)	76.6% (59)	2.6% (2)		98.4% (63)	1.6% (1)	13.006****

*p <.05. **** p <.0001. ns = non significant

Note: +ve = positive change/improvement, = no change, -ve = negative change/deterioration

$_1$ = Negative change and no change were combined as cells in negative change category had an expected frequency of less than 5 and values reported are Pearsons's Chi-square with Yate's correction

$_2$ = Fisher exact test

Chi-square analysis indicated that significantly more HD patients reported improvements in clarity of thinking, concentration, attention, and response speed 24-hours post-dialysis compared to PD (see Table 6.34 above).

1.10.b Acute subjective cognition and acute NP change

The following analyses were restricted to the HD group as the PD group reported little change in their cognition.

In order to examine the relationship between subjective reports of cognitive change and changes in objectively assessed NP performance, HD patients were grouped into those reporting 'improvement' and those reporting either 'no change' or 'deterioration' post-dialysis on the individual SCS items (clarity of thought, attention, concentration, speed of response). This two-group categorisation was necessary, as the small number of patients and their response distribution did not allow for a three-group analysis. Repeated measures ANOVAs were then performed to compare objective NP performance over time between those HD patients reporting 'improvement' and those reporting either 'no change' or 'deterioration' post dialysis on four SCS items.

In this analysis only the objective NP scores considered to reflect the particular cognitive dimension assessed by the grouping SCS items were used (see Table 6.35 - 6.36).

Table 6.35: Absolute NP scores (*Means and SDs)* in acute cognitive improvement vs. no change or decline dialysis sub-groups: attention concentration

		Attention		**Concentration**	
		+ve	**-ve/=**	**+ve**	**-ve/=**
		Mean (SD)	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***
TMT-A	T1	60.93 (45.91)	51.36 (34.17)	55.90 (28.33)	44.05 (35.29)
	T2	53.12 (43.35)	42.52 (27.97)	47.13 (26.51)	94.95 (59.00)
TMT-B	T1	112.09(71.01)	93.27 (46.12)	103.42(41.74)	94.94 (58.99)
	T2	104.07(67.63)	85.41 (45.10)	95.09 (41.09)	87.27 (56.83)
SDMT-W	T1	39.42 (13.18)	41.41 (12.48)	37.41 (11.75)	42.82 (12.74)
	T2	47.58 (16.47)	46.95 (14.91)	45.05 (13.86)	48.22 (15.89)
SDMT-O	T1	44.58 (15.41)	46.22 (13.92)	42.19 (11.98)	47.78 (15.04)
	T2	52.32 (18.40)	52.03 (16.11)	49.85 (14.39)	53.32 (17.67)

Note: +ve = positive change/improvement post dialysis; =/-ve = negative change/deterioration or no chnage post dialysis; TMT-A = trailmaking test part A; TMT-B = trailmaking test part B; SDMT-W = symbol digit modality test written; SDMT-O = symbol digit modality test oral

Table 6.36: Absolute NP scores (*Means and SDs)* in acute cognitive improvement vs. no change or decline dialysis sub-groups: clarity of thinking; response speed

		Clarity of thinking		**Speed of response**	
		+ve	**-ve/=**	**+ve**	**-ve/=**
		Mean (SD)	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***
TMT-A	T1	51.05 (29.72)	55.09 (40.86)	46.38 (21.43)	55.65 (40.38)
	T2	44.85 (27.38)	45.28 (34.85)	40.55 (22.10)	46.32 (34.57)
TMT-B	T1	96.83 (44.82)	98.47 (57.76)	88.31 (27.67)	100.44(58.27)
	T2	88.49 (44.32)	90.79 (55.51)	85.46 (38.30)	91.21 (54.90)
SDMT-W	T1	39.73 (13.29)	41.53 (12.32)	42.06 (12.41)	40.62 (12.73)
	T2	46.23 (15.21)	47.55 (15.32)	50.13 (15.29)	46.31 (15.20)
SDMT-O	T1	44.69 (13.38)	46.39 (14.72)	47.63 (12.58)	45.34 (14.76)
	T2	51.92 (16.12)	52.20 (16.97)	56.50 (16.38)	50.95 (16.57)
RAVLT-T	T1	40.50 (11.28)	38.78 (12.33)		
	T2	43.69 (11.09)	43.45 (12.22)		
RAVLT-D	T1	2.50 (1.70)	2.27 (1.72)		
	T2	3.00 (2.28)	2.45 (1.98)		
BVRT-C	T1	4.96 (2.34)	5.13 (2.31)		
	T2	5.54 (2.39)	6.20 (2.25)		
BVRT-E	T1	9.42 (6.03)	8.23 (5.16)		
	T2	7.11 (5.11)	6.35 (5.42)		
GP-DOM	T1	93.69 (26.17)	86.04 (31.42)	90.63 (24.97)	88.13 (31.10)
	T2	89.46 (27.29)	82.86 (29.58)	86.06 (25.82)	84.86 (29.75)
GP-NDOM	T1	101.62 (29.3)	99.45 (37.29)	103.37(31.03)	99.35 (35.67)
	T2	97.08 (30.19)	94.52 (36.53)	94.31 (28.61)	95.68 (35.89)

Note: +ve = positive change/improvement post dialysis; =/-ve = negative change/deterioration or no change post dialysis; TMT-A = trailmaking test part A; TMT-B = trailmaking test part B; SDMT-W = symbol digit modality test written; SDMT-O = symbol digit modality test oral; RAVLT-T = Rey auditory verbal learning test total recall (1-5) score; RAVLT-D = Rey auditory verbal learning test-drop in retention score; BVRT-C = Benton visual retention test-number correct; BVRT-E = Benton visual retention test-number of errors; GP-DOM = grooved pegboard dominant hand; GP-NDOM = grooved pegboard non dominant hand

The 26 (33.8%) patients reporting improved clarity of thinking were compared to the 51 (66.2%) patients reporting either no change or deterioration on all NP scores (as clarity of thought was considered pertinent to all of them).

Nineteen HD patients reported attention improvement post dialysis. Their performance was compared to that of the remaining 58 patients on the tests considered to reflect attention (TMT-A; TMT-B; SDMT-W; SDMT-O).

The 27 (35.1%) patients reporting improved concentration abilities were likewise compared to the 50 (64.9%) patients endorsing either no change or deterioration in concentration on the same tests as above (TMT-A; TMT-B; SDMT-W; SDMT-O).
Finally NP scores in time-dependent tests (TMT-A; TMT-B; GP-DOM; GP-NDOM; SDMT-W; SDMT-O) were compared between patients reporting improved or not response speed post dialysis.

There were no significant group effects or group by time interaction effects in any of the comparisons performed (*p*s < 1), suggesting that perceived cognitive perceptions are unrelated to the objective indices of NP performance.

1.10.c Acute Subjective cognition and mood

The associations between concurrent measures of mood (anxiety, positive affect, negative affect and depression) and subjective cognition ratings were examined by oneway ANOVAs using the T2 mood absolute scores. This analysis was performed only on HD patients, as the PD group perceived little to no variation in the subjective reports of cognition from T1 to T2.

As before, HD patients were grouped into those reporting cognitive improvement versus those reporting no change or deterioration in the cognitive domains. Results indicated little association between mood and perceptions of acute cognitive improvements.

There were no significant differences in BDI nor CDI scores between the resulting HD subgroups. HD patients who perceived enhanced clarity of thinking post dialysis tended to have higher total BDI scores (*mean* = 12.81, *SD* = 6.87) than patients reporting no change or deterioration (*mean* = 10.02, *SD* = 7.64) but this trend did not reach significance level ($p = .06$). State anxiety and negative mood were also unrelated to all but one of the SCS items, concentration albeit in a counterintuitive manner. Comparative analysis showed that HD patients reporting improvements in their ability to concentrate had significantly higher state anxiety at T2 (*mean* = 9.67, *SD* = 2.50) than those endorsing no change or deterioration (*mean* = 8.5, *SD* = 2.19; $F(1, 75) = 4.514$, $p = .037$).

Negative affect also differed between these two subgroups with patients in the improved concentration group reporting higher levels of negative affect at T2 (*mean* = 13.37, *SD* = 3.59) relative to the other group (*mean* = 11.96, *SD* = 2.20; $F(1, 75) = 4.571$, $p = .036$). The opposite pattern was evident with respect to positive affect. Patients in the cognitive improvement group had higher level of positive affect (*mean* = 31.26, *SD* = 5.07) than the no change or deterioration group (*mean* = 28.04, *SD* = 7.69) although this trend approached but did not reach significance ($F(1, 74) = 3.82$, $p = .054$).

In addition to comparing T2 absolute mood scores, a similar analysis was performed on residualised change mood scores to determine whether reports of cognitive improvements were associated with concomitant mood changes rather than current mood.

There was only one significant finding. HD patients reporting improvement in their concentration abilities had significantly greater increase in their positive mood reports from pre- to 24-hours post-dialysis relative to those reporting no changes or deterioration ($F(1,75) = 21.333$, $p = .0001$). Changes in negative mood measures (anxiety and negative affect) were unrelated to subjective reports of cognitive improvement.

1.10.d Long term changes and subjective cognition

Patients' reports of changes in their cognitive abilities experienced since the onset of dialysis treatment were also examined.

A substantial number of dialysis patients (66.2%, $n = 96$) reported deterioration in one or more aspects of cognition compared to their cognitive abilities/NP performance before dialysis onset. In contrast only 18.2 % ($n = 25$) of the dialysis respondents perceived improvement in their cognitive functioning since dialysis initiation.

The most frequently reported area of deterioration in the combined HD and PD sample was memory with 54.5% reporting that their memory abilities have deteriorated since dialysis initiation. Lack of concentration was the next most common cognitive complaint (44.8%) followed by clarity of thinking (29%), and problem solving (24.1%) (see Table 6.37).

Table 6.37: Subjective Cognition: Long term changes in Dialysis

	HD			PD			
Cognitive domain	+ve	=	-ve	+ve	=	-ve	χ^2
1. memory$_1$	1.3% (1)	44.2% (34)	54.5% (42)	4.4% (3)	41.2% (28)	54.4% (37)	.000 ns
2. problem solving$_1$	2.6% (2)	72.7% (56)	24.7% (19)	1.6% (1)	93.8% (60)	4.7% (3)	.000 ns
3. clarity of thinking	10.4% (8)	59.7% (46)	29.9% (23)	2.9% (2)	73.5% (50)	23.5% (16)	2.10 ns
4. concentration$_1$	1.3% (1)	45.5% (35)	53.2% (41)	11.8% (8)	52.9% (36)	35.3% (24)	4.008*
5. making mistakes$_1$		88.3% (68)	11.7% (9)	1.5% (1)	94.1% (64)	4.4% (3)	1.651 ns
6. attention$_1$	2.6% (2)	77.9% (60)	19.5% (15)	7.4% (5)	77.9% (53)	14.7% (10)	.291 ns
7. clumsiness$_1$		87% (67)	13% (10)		85.3% (58)	14.7% (10)	.003 ns
8. decision making$_1$		87% (67)	13% (10)	2.9% (2)	80.9% (55)	16.2% (11)	.095 ns
9. speed of response$_1$	2.6% (2)	81.8% (63)	15.6% (12)		88.2% (60)	11.8% (8)	.180 ns

Note: +ve = positive change/improvement, = no change, -ve = negative change/deterioration

$_1$ = Positive change and no change were combined as cells in positive change category had an expected frequency of less than 5 and values reported are chi-square with Yate's correction

* p <.05. *** p <.001. ns = non significant

Significantly more HD patients felt that their concentration deteriorated since starting on dialysis compared to PD patients ($\chi^2(145) = 4.008$, $p = .045$). As however the two dialysis groups differed significantly in age at dialysis onset, time on RRT, time on current dialysis modality, and gender distribution the observed associations might reflect these differences rather than being solely due to dialysis modality effects.

In addition to examining the distribution of responses, three summary SCS scores were computed:

- number of positive cognitive changes since dialysis (possible range from 0 to 9) with higher scores signifying improvement in more areas of cognitions

- number/count of negative changes since dialysis (possible range from 0 to 9 with higher scores signifying deterioration in more areas of cognition)

- A summary score for subjective cognition was calculated by adding responses on all nine items. A score of 1 was given to reports of cognition improvement, a score of 2 to reports of no change and a score of 3 was assigned to reports of cognitive deterioration. Scores could thereby range from 9 to 27, with higher scores signifying cognitive deterioration.

There no significant group differences in subjective cognition summary scores (see Table 6.38).

Table 6.38: Summary subjective cognition scores in dialysis

	All DL		HD		PD	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Total cognitive decline since DL	19.90	2.50	20.14	2.47	19.63	2.53
No + ve changes since DL	.297	.746	.207	.592	.397	.883
No – ve changes since DL	2.20	2.15	2.35	2.20	2.03	2.10

Note: DL = dialysis; HD = haemodialysis; PD = peritoneal dialysis; +ve = positive; -ve negative

1.10.e Long term subjective Cognition scale and NP scores

To examine if perceived long-term cognitive deterioration is associated with actual NP performance, the data from the self-reported changes were collapsed into 'improved' and 'no change' versus 'worse'. Between groups comparisons were then performed on the objective NP test scores, considered to reflect the particular cognitive dimension assessed by the grouping subjective cognition item (see Tables 6.35 – 6.36 and section 1.10.b for NP tests related to subjective cognition items).

The reports of deterioration were as follows: Forty-two (29%) patients reported worsened clarity of thinking. Seventy-nine patients (54.5%) reported deterioration in memory. Sixty-five patients (44.8%) reported concentration decline since dialysis onset. Twenty-five (17.2%) patients reported decline in attention. Finally twenty dialysis patients reported deterioration in both response speed and motor abilities.

Results indicated some significant group differences, suggesting that perceptions of long-term changes in cognitive abilities bear some association with objective indices of NP performance but not consistently across all cognitive domains (Tables 6.39 – 6.41).

Table 6.39: NP scores in cognitive decline vs. no change or improvement dialysis sub-groups (clarity of thinking; response speed)

		Clarity of thinking		Response speed	
		-ve	+ve/=	-ve	+ve/=
		Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
TMT-A	T1	56.5 (32.3)	50.4 (32.2)	66.1 (42.6)	49.9 (30.1)
	T2	49.9 (27.7)	44.2 (30.3)	60.3 (33.9)	43.5 (42.6)
TMT-B	T1	102.6 (42.7)	96.9 (51.9)	114.9 (54.7)	95.9 (48.2)
	T2	102.1 (47.0)	91.6 (50.4)	111.9 (52.7)	91.8 (48.7)
SDMT-W	T1	38.4 (10.9)	42.2 (13.1)	34.3 (12.4)	42.2 (12.3)
	T2	42.5 (12.7)	47.3 (15.5)	38.2 (16.7)	47.2 (14.3)
SDMT-O	T1	42.7 (12.5)	46.4 (14.1)	39.1 (15)	46.4 (13.3)
	T2	46.8 (14.1)	51.9 (16.9)	43 (18.2)	51.7 (15.7)
RAVLT-T	T1	38.2 (10.1)	39.3 (11)		
	T2	40.6 (11.1)	41.9 (10.6)		
RAVLT-D	T1	2.5 (1.86)	2.55 (1.9)		
	T2	2.84 (1.88)	2.8 (1.9)		
BVRT-C	T1	4.24 (1.87)	5.2 (2.21)		
	T2	4.77 (1.85)	5.8 (4.77)		
BVRT-E	T1	9.69 (4.82)	8.09 (5.04)		
	T2	8.47 (4.12)	6.64 (4.85)		
GP-DOM	T1	96.2 (29)	88.8 (33)	104 (38.2)	88.9 (30.5)
	T2	95.2 (29.7)	85.4 (30.4)	95.1 (30.4)	87.2 (30.4)
GP	T1	104.7 (30.1)	101.2 (42.2)	119.9 (52.2)	99.42 (35.9)
NDOM	T2	102.7 (30.7)	97.4 (39.1)	111.6 (38.3)	97 (36.5)

Note: +ve = positive change/improvement or = no change, -ve = negative change/deterioration;

Perceptions of diminished clarity of thinking were associated with worse scores in BVRT-C at T1 (U = 1594, p = .012) and at T2 (U = 1471, p =.009), BVRT-E in T2 (U = 1439, p = .006) and finally longer time latencies in GP-DOM at T2 (U = 1529, p =.048). Differences in T1 GP-DOM and BVRT-E approached but did not reach significance (U = 1715.5, p = .06; U = 1722, p = .054 respectively).

Likewise, patients who perceived that their response time has deteriorated since dialysis performed significantly worse than those who reported no such effects in some time-dependent NP tasks. These effects were significant for SDMT-W at T1 (t(143) = 2.637, p = .009) and T2 (t(139) = 2.486, p = .014), SDMT–O at T1 (t(143) = 2.238, p = .027) and T2 (t(139) = 2.191, p = .03) and for TMT-A at T2 (t(139) = -2.34, p = .021).

Table 6.40: NP scores in cognitive decline vs. no change or improvement dialysis sub-groups (attention; concentration)

		Attention		Concentration	
		-ve	+ve/=	-ve	+ve/=
		Mean (SD)	*Mean (SD*	*Mean (SD*	*Mean (SD*
TMT-A	T1	58.6 (37.7)	50.8 (31.2)	54.1 (30.7)	50.6 (33.8)
	T2	50.8 (31.2)	44.7 (29.4)	47.8 (28.5)	44.2 (30.6)
TMT-B	T1	106.2 (57.5)	96.9 (47.6)	102.6 (45.3)	95.3 (52.5)
	T2	102.6 (54.3)	92.8 (48.6)	97.7 (46.5)	92.1 (51.9)
SDMT-W	T1	38.5 (12.1)	41.6 (12.6)	39.1 (11.7)	42.7 (13.1)
	T2	44.4 (15.1)	46.3 (14.9)	44.1 (14.1)	47.5 (15.4)
SDMT-O	T1	43.9 (14.4)	45.7 (13.6)	43.2 (12.9)	47.1 (14.2)
	T2	48.6 (16.9)	50.9 (16.2)	48.4 (15.1)	52.1 (17)
GP-DOM	T1				
	T2				
GP-NDOM	T1				
	T2				

Note: +ve = positive change/improvement, = no change, -ve = negative change/deterioration

Table 6.41: NP scores in cognitive decline vs. no change or improvement dialysis sub-groups (memory; motor abilities)

		Memory		Motor abilities	
		-ve	**+ve/=**	**-ve**	**+ve/=**
		Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
RAVLT-T	T1	38.8 (10.8)	39.2 (10.6)		
	T2	40.9 (11.6)	42.2 (9.57)		
RAVLT-D	T1	2.41 (1.88)	2.68 (2.04)		
	T2	2.68 (2.02)	2.97 (1.73)		
BVRT-C	T1	4.67 (2.17)	5.23 (2.12)		
	T2	5.17 (2.11)	5.91 (2.07)		
BVRT-E	T1	9.2 (5.45)	7.79 (4.36)		
	T2	7.86 (4.90)	6.35 (4.90)		
GP-DOM	T1			116.6 (49.9)	86.9 (26.1)
	T2			110.5 (45.6)	84.9 (26.2)
GP-NDOM	T1			141.2 (61.8)	95.9 (29.9)
	T2			135.8 (55.5)	93.4 (29.9)

Note: +ve = positive change/improvement, = no change, -ve = negative change/deterioration

Patients who felt that they have been having more minor accidents (e.g. dropping things) since dialysis onset took significantly longer time to complete the psychomotor task compared to patients who perceived either no change or improvement. This was

evident at both assessments for GP-DOM (U = 722, p = .003 for T1; U = 669, p = .008 for T2), and GP-NDOM (t(142) = -.3.689, p = .001 for T1; t(137) = -4.627, p= .0001 for T2).

Similar trends were also noted for memory. Patients who felt that their memory had deteriorated since dialysis tended to perform worse in the visual memory task at T2; with less number correct (U = 2074.5, p = .07) and more reproduction errors (U = 2068, p = .07).

1.10.f Factors associated with subjective cognition (long- term)

i. *Sociodemographic and medical factors and subjective cognition*

Complaints of cognitive deterioration were found to be significantly associated with clinical factors such as disease severity. Correlations using the three summary SCS scores indicated that ESRD severity was positively associated with overall perceptions of cognitive decline (r_s = .32, p = .0001), count of perceived negative changes in cognition (r_s = .30, p = .0001) and inversely associated with count of positive changes in cognition (r_s = -.20, p = .015).

Analysis of the individual SCS items showed that ESRD severity was significantly higher in the 'cognitive decline' group for clarity of thinking (U = 1514, p = .005), memory (U = 2022, p = .020), clumsiness (U = 844.5, p = .020), and concentration (U = 1945, p = .009).

Finally patients reporting deterioration in their attention had been on RRT for longer (U = 1069, p = .024) and so did patients complaining of decline in their concentration (U = 2004, p = .018).

Among sociodemographics, age, gender, and work status had significant associations with long-term SCS perceptions.

Patients reporting deterioration in motor abilities (clumsiness) since dialysis onset were significantly older (t(143) = -2.008, p = .043) and had started dialysis at an older age (t(143) = -2.553, p = .012) compared to patients reporting either no change or improvement. Perceptions of worse response speed were similarly associated with advanced age (t(143) = -1.99, p = .048).

Gender (female) was associated with perceptions/complaints of worsened attention ($\chi^2(145) = 4.696$, $p = .030$), and concentration ($\chi^2(145) = 7.134$, $p = .008$). Female dialysis patients also had higher scores in overall perceptions of cognitive decline (*mean* = 20.55 *SD* = 2.52) than males (*mean* = 19.55 *SD* = 2.44; U = 1886.5, $p = .033$) and reported more negative changes in their cognitive abilities (*mean* = 2.75 *SD* = 2.26) since the onset of dialysis compared to male patients (*mean* = 1.90 *SD* = 2.04; U = 1873.5, $p = .026$).

Employment status was significantly associated with both summary SCS scores and individual SCS items. Overall perceptions of cognitive decline (U = 1681.5, $p = .002$) and count of negative changes in cognitions (U = 1650, $p = .001$) differed between employed and non-employed patients. The latter perceived greater cognitive deterioration (*mean* = 20.34 *SD* = 2.45) and reporting more negative changes (*mean* = 2.60, *SD* = 2.11) in their cognitive abilities relative to employed patients (*mean* = 19.11 *SD* = 2.43; *mean* = 1.48 *SD* = 2.05; respectively). These group differences were no longer significant after adjustment for ESRD severity and age (*ps* <. 06).

Chi-square analysis indicated significant associations between employment status and 'specific' cognitive complaints although these may also reflect the effect of casemix differences in age and ESRD severity. Significantly more employed patients reported improvement in memory ($\chi^2(145) = 4.846$, $p = .028$); speed of response ($\chi^2(145) = 4.390$, $p = .036$); decision making ($\chi^2(145) = 4.970$, $p = .026$) and concentration ($\chi^2(145) = 10.509$, $p = .001$) since dialysis compared to non-employed patients.

ii. *Mood and subjective cognition*

A series of independent t-tests or Mann-Whitney tests were performed to investigate the association between mood measures and subjective complaints of cognitive decline since dialysis initiation. Patients in the cognitive decline groups as described above were compared to those reporting either no change or improvement on BDI, CDI, and concurrent levels of anxiety, positive and negative affect (see Table 6.42).

Table 6.42: Long term subjective cognition scale and mood at T1 in dialysis

	BDI	CDI	STAI	PNS-NA$_1$	PNS-PA
	t-value Mean/ SD	*t-value* Mean/SD	*t-value* Mean/SD	*U-value* Mean/SD	*t-value* Mean/SD
Memory	**-2.73****	**-2.75****	**-2.70****	**2070***	**ns**
- ve	13.73 (8.68)	8.37 (5.83)	11.81 (4.09)	15.68 (5.79)	22.98 (7.66)
=/+ ve	9.98 (7.4)	5.98 (5.49)	10.04 (3.66)	13.74 (4.05)	24.71 (7.01)
Pr. Solving	**-5.08*****	**-4.49*****	**-2.98****	**1315.5****	**3.31*****
- ve	17.77 (8.54)	10.77 (5.83)	12.71 (4.47)	16.54 (5.59)	20.28 (6.99)
=/+ ve	10.2 (7.38)	6.18 (5.34)	10.46 (3.68)	14.24 (4.9)	24.88 (7.2)
Thinking Cl.	**-3.08****	**-2.53***	**-2.45***	**1409.5***	**2.63****
- ve	15.26 (9.18)	9.1 (6.20)	10.29 (3.45)	16.54 (5.4)	21.28 (6.98)
=/+ ve	10.7 (7.59)	6.55 (5.47)	9.54 (2.85)	14.08 (4.89)	24.78 (7.35)
Concentration	**-3.75*****	**-3.37*****	**-2.01***	**1971.5***	**ns**
- ve	14.06 (8.56)	8.76 (5.76)	12.32 (4.16)	15.93 (5.86)	22.61 (7.42)
=/+ ve	9.93 (7.52)	6.08 (5.56)	9.93 (2.55)	13.87 (4.31)	24.71 (7.28)
Mistakes	**ns**	**-2.20***	**ns**	**ns**	**ns**
- ve	16.16 (9.25)	10.75 (6.82)	12.16 (3.27)	15.33 (4.22)	23.66 (6.38)
=/+ ve	11.65 (8.16)	6.97 (5.61)	10.9 (4.04)	14.75 (5.23)	23.78 (7.5)
Attention	**-3.06****	**3.04****	**-2.74****	**1051.5***	**2.17***
- ve	16.56 (9.35)	10.4 (6.45)	12.96 (3.94)	16.4 (4.89)	20.88 (7.6)
=/+ ve	11.08 (7.79)	6.64 (5.45)	10.6 (3.89)	14.46 (5.15)	24.37 (7.24)
Clumsiness	**-2.578***	**-2.156***	**ns**	**ns**	**ns**
- ve	16 (7.6)	9.35 (4.94)	11.6 (2.99)	14.8 (3.44)	22.8 (6.05)
=/+ ve	11.39 (8.27)	6.96 (5.86)	10.91 (4.13)	14.8 (5.38)	23.92 (7.6)
Decision Mk	**-2.173***	**ns**	**ns**	**ns**	**ns**
- ve	15.66 (10.1)	9.14 (7.22)	12.04 (4.57)	15.33 (4.95)	22 (6.87)
=/+ ve	11.41 (7.85)	6.97 (5.48)	10.83 (3.87)	14.7 (5.19)	24.07 (7.46)
Resp Speed	**ns**	**ns**	**ns**	**ns**	**-2.25***
- ve	14.95 (5.30)	9.15 (5.81)	12.85 (4.01)	15.6 (4.1)	21.95 (7.3)
=/+ ve	11.56 (8.14)	6.99 (5.75)	10.71 (3.92)	14.67 (5.3)	24.06 (7.39)

* p <.05. ** p <.01. *** p <.001. ns = non significant

Note. BDI = Beck depression inventory total score; CDI = cognitive depression index; STAI = Spielberger state anxiety; PNS-NA = PANAS negative affect; PNS-PA = PANAS positive affect; - ve = negative; =/+ ve = no change or positive; Pr. Solving = problem solving; Thinking Cl = clarity of thinking; Decision Mk = decision making

Even though observed differences varied depending on the particular aspect of cognition, a consistent pattern of results emerged. On the whole results indicated that patients who felt that their cognitive abilities have deteriorated since dialysis onset had significantly higher negative mood as indexed by higher mean group scores in BDI, CDI, STAI and PANAS-NA and reported significantly lower positive affect (see Table 6.42).

Among mood indicators, CDI depression scores consistently differentiated between the 'cognitive decline' group and those who reporting no change or improvement with respect to all cognitive aspects except for 'response speed'.

Likewise, correlational analysis showed that negative mood indicators (BDI, CDI, STAI, PANAS-NA) were positively associated with overall perceptions of cognitive decline (r_s = .40, p = .0001; r_s = .36, p = .0001; r_s = .33, p = .0001; r_s = .23, p = 006 respectively) and number of perceived negative changes in cognition (r_s = .39, p = .0001; r_s = .34, p = .0001; r_s = .32, p = .0001; r_s = .23 , p = .0001 respectively). They were also found to be negatively associated with number of perceived positive cognitive changes (r_s = -.21, p = .013; r_s = .-21, p = .011; r_s = -.17, p = .037 for BDI, CDI, and STAI respectively). In contrast, increased positive affect was significantly associated with less perceived long-term cognitive decline (r_s = -.23, p = .005).

iii. *Prediction of subjective cognitive complaints*

To evaluate the contribution of demographic, medical, neuropsychological, and affective variables upon self-reported cognitive changes, hierarchical multiple regression using the stepwise method (at $p < .05$) was performed. The stepwise method was preferred to avoid the problem of multicollinearity due to the significant intercorrelations among the predictor variables (particularly for mood indicators) (Tabachnick and Fidell, 1989).

The summary subjective cognition score was regressed to sociodemographic, medical, neuropsychological and mood variables. To produce a more favourable cases-to-variables ratio, data reduction procedures were applied. First, only the variables within each domain found to be significantly associated with the outcome were used. Second, T1 absolute NP scores were standardised and then added to produce a total NP score (NP-TO; see section 1.3). This composite score reflected overall NP functioning at T1 with higher scores signifying more efficient cognitive functioning.

This composite NP score was used in subsequent regression analyses as a varimax rotated principal component analysis on T1 NP data (factor calculated using standardised z-scores) that was performed earlier in order to identify an underlying factor structure, failed to produce a clear-cut structure. In the PCA analysis (data not

shown) two orthogonical factors were identified accounting for 77.5% of the variance. The first factor accounted for 66.94% of the variance and comprised tests measuring attention concentration and psychomotor speed TMT-A, TMT-B, SDMT-W, SDMT-O and GP-DOM, GP-NDOM. It was hence labelled 'attention/ psychomotor'. The second factor, 'memory recall' explained 11.57% of variance. It comprised RAVLT total recall, BVRT correct and BVRT error, capturing the ability to recall information from recent memory. As however some measures (TMT-A and TMT-B) had almost equal loadings on both factors (loadings on factor 1 and factor 2 were only marginally different), it was considered inappropriate to use the resulting factor scores in the regression analysis. Thereby the composite NP score has been used in preference to factor scores.

Predictors entered the regression equation as follows: To control for any influence of participants' age and educational level, these variables were entered in Block 1 and likewise dialysis modality and ESRD severity index were entered in Block 2 under forced entry criteria even though they did not correlate significantly with overall subjective cognitive decline/complaints. At step three the overall absolute NP score at T1 and number of NP impairments were entered followed by mood variables in the last step of the regression.

The final hierarchical regression model revealed that higher levels of cognitive depressive symptoms (CDI) were significantly associated with greater perceived cognitive decline since dialysis onset. The associations between ESRD severity and cognitive complaints were only significant at the first two steps, accounting for R^2 = 8.3% (Adj.R^2 = 7.7%) but ceased to be significant when CDI entered next (β = .161, p = .057). Likewise count of NP impairments explained ΔR^2 = 2.7% (β = .110, p = .188) but was not significant in the last step of regression (i.e. with CDI entry). The decrease in the standardised regression coefficients (beta weights) with CDI entry suggests that CDI symptoms may mediate the associations between disease severity and NP deficit and subjective evaluation of cognition.

CDI explained an additional 5.8% (ΔAdj.R^2 = 5.3%; β = .266, p = .002) of the cognitive complaints increasing the overall variance explained to 16.8% (ΔAdj.R^2 = 15%). Neither objective NP test performance, nor any of the clinical or demographic variables were significantly associated with long-term subjective cognitive complaints.

Section 2: Transplantation sample

2.1 Data analysis

Variables' distributions were examined by Kolmorogov-Smirnov goodness-of-fit test. With respect to NP variables, TMT-A, TMT-B, GP-DOM, GP-NDOM and RAVLT-D were found to be non-normally distributed in the transplant population. Logarithmic transformations rendered some of these tests (TMT-A, TMT-B, GP-DOM) to a normal distribution. It was not possible to render the RAVLT-D and GP-NDOM to a normal distribution. Among the mood variables measured in the transplant sample (PANAS PA, PANAS NA, BDI, CDI) only the cognitive depression index was found to be non-normally distributed. Logarithmic transformation successfully rendered CDI scores into normal distribution.

Chi-square, Pearson's correlation coefficient, one way ANOVAs or their non parametric equivalent (as appropriate) were performed to examine univariate associations between sociodemographic, clinical, and mood variables with absolute NP scores. A series of hierarchical multiple regressions were also performed to identify the combination of variables that can best explain NP performance in transplant patients.

Univariate analyses of covariance (ANCOVAs) were performed to compare NP performance between (a) living related and cadaver transplant recipients and (b) transplant and dialysis patients. Covariates for these comparisons included the variables that were significantly different between groups on the condition that they were also significantly associated with the dependent variable in question (at $p < .05$).
In comparisons involving more than two groups (as for instance in the comparisons of PD, HD and TX participants), post-hoc tests (Tukey's Honest Difference Test; HSD) were conducted to isolate significant treatment group differences.

2.2 Sample characteristics

Sociodemographic and medical characteristics of the transplant sample and the LRD and CAD transplant patients separately are shown in Table 5.1 (see Chapter 5; section 1.1).

There were several statistically significant differences between the two transplant groups with respect to medical and sociodemographic variables.
LRD patients were significantly younger ($t(114) = 3.95$, $p = .0001$) and had higher educational level ($t(107) = -2.68$, $p = .01$) than cadaver transplant recipients.
Higher employment rates were also noted for the LRD group ($\chi^2(254) = 10.344$, $p = .0001$) although this is likely to be a reflection of age, and clinical group differences and not necessarily evidence of better work rehabilitation associated with that type of transplant. Significant associations were indeed found between employment and age ($t(104.12) = -5.02$, $p = .0001$), education ($t(106) = 3.12$, $p = .002$) and renal disease severity ($t(95.12) = -3.41$, $p = .001$). LRD TX patients were also more likely to perceive themselves as able to work full or part time than CAD TX patients ($\chi^2(254) = 3.998$, $p = .045$). Annual income also differed between groups, as expected given the differences in employment status. There were significantly more CAD TX patients in the lowest income group (< £10,000) compared to LRD recipients ($\chi^2(254) = 6.054$, $p = .0138$).
Clinical characteristics also differed between groups. ESRD severity scores were lower in the LRD group ($t(102.67) = 5.38$, $p = .0001$). Living related transplant recipients had also spent significantly less time on dialysis prior to their transplant ($t(73.18) = 4.47$, $p = .0001$) and had their current functioning graft longer than cadaver transplant patients ($t(115) = -3.37$, $p = .01$). The former was anticipated given the elective nature of LRD transplantation that allows shorter delay between dialysis and transplantation. In fact, there were significant more cases of pre-emptive transplantation in LRD patients compared to CAD patients ($\chi^2(254) = 4.846$, $p = .028$).

2.3 Absolute NP performance

Mean NP scores for the total transplant group and for CAD and LRD transplant recipients separately are presented in Table 6.36. A total NP score was computed by adding the standard z-score on the 8 NP indices used in the transplant population (TMT-

A; TMT-B; SDMT-W; SDMT-O; RAVLT-T; RAVLT-D; GP-DOM; GP-NDOM). Where appropriate scores were reversed so as higher summary NP scores express more efficient cognitive functioning.

Table 6.43: Absolute NP scores (*Means; SDs*) in TX patients

	CAD TX (n = 92)		LRD TX (n = 25)		All TX (n = 117)	
	M	*SD*	*M*	*SD*	*M*	*SD*
TMT-A [a]	38.99	19.98	32.13	19.96	37.50	20.09
TMT-B [a]	92.37	61.38	70.97	34.86	87.33	56.85
SDMT-W [b]	44.62	13.64	52.54	9.52	46.37	13.22
SDMT-O [b]	50.29	15.40	58.17	13.03	52.02	15.21
RAVLT –T [b] **(1-5)**	45.65	10.12	52.83	9.68	47.20	10.41
RAVLT – trial 1	5.93	1.89	6.91	1.65	6.14	1.88
RAVLT – trial 2	8.37	2.23	10.09	2.37	8.74	2.36
RAVLT – trial 3	9.75	2.30	11.43	2.33	10.11	2.40
RAVLT – trial 4	10.46	2.63	11.91	2.54	10.78	2.66
RAVLT – trial 5	11.14	2.72	12.48	1.93	11.43	2.62
RAVLT – D (7-5)	1.90	1.80	1.52	1.47	1.82	1.74
GP – DOM [a]	78.99	26.98	68.11	19.93	76.55	25.89
GP – NDOM [a]	90.22	31.35	75.37	21.37	86.87	29.96
NP-TO [c]	.667	4.18	2.74	4.99	1.20	4.47

Note. TX = transplant; CAD = cadaver; LRD = living related donor; TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; NP-TO = total NP performance score

[a] = Time to completion in seconds. [b] = number correct. [c] = total of the 8 NP indices (z-scores)

* p <.05. ** p <.01. *** p <.001.

2.4 NP scores and transplant type

2.4.a NP impairments: normative comparisons

The NP performance of TX patients was evaluated against normative data. Both average group and individual performance comparisons as described earlier were performed. The limitations of the former with regard to case sensitivity, which were highlighted earlier, need to be borne in mind (see section 1.4.a).

i. *Group-based normative comparisons*

Transplant patients' mean age (50.2 years for combined TX sample) was used to select the appropriate age brackets for the group based normative comparisons. Inspection of observed mean scores indicated that transplant patients' NP performance did not deviate significantly from respective norms. The mean NP scores of both the combined transplant sample as well as the CAD and LRD TX groups separately, were clearly within the normal range or better (upper average range) on all NP tests (TMT A; TMT-B, SDMT-W, SDMT-O, RAVLT-T; GP-DOM, GP-NDOM).

Unlike dialysis patients, no retention or retrieval problems were evident in the transplant sample as the average number of words forgotten after interference trial (from trial 5 and 7) was 1.82. Only for a small proportion (n = 18, 16.8%) of the transplant patients did the drop-in-retention exceeded more than 3 words.
The percentages of CAD and LRD patients missing 3 or more words at the last recall trial was equally small (n = 17, 20.2%) for CAD and (n = 1, 4.3%) LRD patients ($\chi^2(116) = 2.222, p = .136$).

ii. *Individual-based comparisons*

The performance of each individual TX patient was evaluated against his or her age appropriate norms. Table 6.44 depicts the prevalence of NP impairments based on this individual based comparison, i.e. frequencies and percentages of TX patients that performed worse than their healthy counterparts.

Table 6.44: Prevalence of NP impairments in TX patients

	All TX % impairment		CAD % impairment		LRD % impairment	
TMT-A	11% (12)		11.6% (10)		8.7% (2)	
TMT-B	7.7% (9)		9% (7)		8.3% (2)	
SDMT-W	19.3% (21)		23.5% (20)		4.2% (1)	
SDMT-O	27.6% (29)		31.7% (26)		13% (3)	
RAVLT-T	21.5% (23)		25%(21)		8.7% (2)	
GP-DOM	20.6% (22)		24.1% (20)		8.3% (2)	
GP-NDOM	27.5% (28)		31.6% (25)		13% (3)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
NP impairment	1.23	1.71	1.49	1.74	.60	1.47

Individual comparison of each TX participant with his/her respective age norm revealed that the percentage of TX patients whose NP performance fell short of their respective norms was in most cases relatively low. The prevalence of NP impairments ranged from 7.7% to 27.6% of TX patients and must be considered in relation to a normal distribution.

The observed prevalence of NP impairments in TMT-A, TMT-B is relatively low (10.3% and 7.7% respectively). The finding that 27.6% of patients scored lower than 1 *SD* below their norm in SDMT-O might be considered of more significance. Similarly, GP-NDOM appears to be affected in more TX patients than would be expected in a normal population.

Between group comparisons showed no difference between the two LRD and CAD in the prevalence of NP impairments (group or individual based classification) relative to norms (*p*s <.1). The two groups differed significantly in total number of NP tests on which normative based impairments were noted, with CAD TX recipients performing below norms in more NP tests than LRD patients (U = 777.5, p = .008). However these differences disappeared when casemix differences were controlled for. ANCOVAs, controlling for ESRD-SI (there was no need to control for age and casemix differences as individual classification was based on age and education respective norms) showed no significant group differences between the two transplant groups ($F(2, 114) = 1.883$, $p = .173$).

2.4.a Absolute NP test scores

Comparisons of absolute NP scores between the two transplant groups were performed using a series of ANCOVAs controlling for the following casemix differences: age, education, and ESRD severity. There was no need to control for RRT duration, dialysis duration, and time with TX as none of these variables were significantly associated with NP scores at $p < .05$.

Results replicated those reported earlier on the prevalence of NP impairments in that there were no significant differences between LRD and CAD transplant recipients in any of the observed absolute NP scores or the summary NP score. CAD and LRD transplant recipients were hence collapsed into one group for all subsequent NP analyses.

2.5 Factors associated with NP performance in TX patients

2.5.a Sociodemographic, medical variables and NP performance

Table 6.45: Correlations between sociodemographic, medical variables and NP scores in TX patients

	Age	Education†	GFR	ESRD SI†
TMT-A	.461****	-.443****	-.169 p<.08	.380****
TMT-B	.408****	-.582****	-.009	.248*
SDMT-W	-.564****	.49****	.261**	-.434****
SDMT-O	-.507****	.464****	.225*	-.387****
RAVLT-T	-.451****	.496****	.131	-.303**
RAVLT-D†	.028	-.083	-.117	.003
GP-DOM	.391****	-.368****	-.157	.312***
GP-NDOM†	.346****	-.378****	-.281**	.327***

Note: GFR = Glomerular Filtration Rate

† Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001

Univariate analysis indicated that higher educational level and younger age were significantly associated with better neuropsychological functioning. The observed

correlation coefficients ranged from r = .36 to r = .56 for age and r = .34 to r = .58 for educational level, indicating moderate-sized correlations.

Employment status was also significantly associated with NP test performance, with employed TX patients demonstrating more efficient cognitive functioning relative to non employed TX patients (data not shown) even after the observed differences between employed vs. non employed patients in age, education and ESRD severity were taken into account. ANCOVA analyses (controlling for these casemix differences) revealed that employed patients performed better in SDMT-W ($F(3, 98) = 6.309$, $p =. 014$), SDMT-O ($F(3, 94) = 4.731$, $p = .032$), GP-DOM ($F(3, 96) = 11.426$, $p = .001$), and GP-NDOM ($F(3, 92) = 10.12$, $p = .002$). Observed group differences in the remaining tests, which were evident only in independent *t*-test or Mann-Whitney analyses, were muted when sociodemographic and clinical differences were controlled for.

Significant correlations were also noted between medical variables and cognitive functioning. Glomerular Filtration Rate (GFR), an indicator of graft function and clearance efficiency, was also found to be associated with NP performance. Higher GFR values indicating better clearance were associated with better scores in SDMT–W ($r = .26$, $p = .007$); SDMT-O ($r = .23$, $p = .022$); and GP-NDOM ($r_s = -.28$, $p = .005$). Higher ESRD severity was significantly associated with more compromised cognitive functioning in all NP tests. The observed correlation coefficients ranged from $r_s = .25$ to $r_s = -.43$. The NP performance of patients with ischaemic heart disease fell significantly short of that of patients with no heart problems in SDMT-W ($F(1, 107) = 8.633$, $p = .004$), RAVLT-T ($F(1,105) = 9.58$, $p = .003$). These differences however ceased to be significant when the age and education were controlled for in ANCOVAs ($F(3, 99) = 1.765$, $p = .187$ for SDMT-W and $F(3, 97) = 2.079$, $p = .153$ for RAVLT-T).

Neither time spent on dialysis prior to transplantation, number and duration of previous transplants (if any), time on RRT, nor time with their current transplant (duration of functioning graft) were associated with NP scores (data not show).

2.5.b Blood pressure and NP scores in TX patients

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) recordings were performed, with measurements made in both supine and sitting positions before the NP

assessment. Pulse pressure ratings (PPR) expressed as the difference between diastolic and systolic pressure (taken when standing and lying) were also computed. Their correlations with indices of NP performance were examined and indicated several significant associations (see Table 6.46)

Table 6.46: Correlations between blood pressure and NP scores in TX patients

	DBP-ly	DBP-st	SBP-ly	SBP-st	PPR-ly†	PPR-st
TMT-A	.018	-.003	.275**	.247*	.263**	.278**
TMT-B	-.042	-.021	.218*	.247*	.221*	.287**
SDMT-W	-.048	.026	-.254**	-.218*	-.273**	-.261**
SDMT-O	.024	.086	-.22*	-.188	-.303**	-.262**
RAVLT-T	.045	-.018	-.204*	-.196*	-.144	-.204*
RAVLT-D†	.089	.179	.070	.049	.024	-.068
GP-DOM	.055	-.018	.221*	.123	.240*	.20*
GP-NDOM†	.042	-.058	.226*	.198	.212*	.214*

Note. DBP-Dly = diastolic blood pressure lying; DBP-st = diastolic blood pressure standing; SBP-Sly = systolic blood pressure lying; SBP-st = systolic blood pressure standing; PPR-ly = pulse pressure rating lying; PPR-st = pulse pressure rating standing;.

[a] = Time to completion in seconds. [b] = number correct. [c] = total of the 8 NP indices (z-scores)

† Spearman's correlations

* p <.05. ** p <.01. *** p <.001.

Concurrent levels of systolic blood pressure correlated significantly with measures of psychomotor speed (i.e. GP) and attention (SDMT-W, SDMT-O, TMT-A, TMT-B) with correlation coefficients ranging from .20 to .28. The direction of observed correlations indicated that higher levels of systolic blood pressure were associated with less efficient cognitive functioning.

Pulse pressure ratings were also significantly associated with 7 of the 8 NP scores (the exception being RAVLT-D). For instance, higher standing pulse pressure ratings correlated significantly with RAVLT-T (r = -.20, p = .045), SDMT-O (r = -.26, p = .009), SDMT-W (r = -.26, p = .008), GP-D (r = .20, p = .045), GP-NDOM (r_s = .21, p = .036), TMT-A (r = .28, p =.004) and TMT-B (r = .29, p = .005). Similar sized correlations (r_s) were found between lying pulse pressure ratings and NP scores. Interestingly, neither diastolic blood pressure measurement nor the presence of hypertension were associated with cognitive functioning (i.e. ANOVA comparisons showed no significant NP differences between patients with hypertension vs. those not diagnosed with hypertension).

2.5.c Biochemistry and NP scores in TX patients

Only a few significant albeit weak correlations, in the expected direction were found between NP scores, mainly in NP tests of attention and concentration and biochemical measures. These however were not consistently replicated across all NP scores and therefore the findings should be treated with caution.

Increasing urea levels correlated with poorer performance in SDMT-W (r_s = -.211, p = .029), SDMT-O (r_s = -.19, p = .05) and TMT-A (r_s = .205, p = .033). The correlation between urea and GP-NDOM scores approached but did not reach significance (r_s = .193, p = .054). Higher albumin levels correlated with SDMT-W (r_s = .295, p = .036), SDMT-O (r_s = .21, p = .036), and TMT A (r_s = -.218, p = .024). Creatinine correlated significantly with GP-NDOM scores (r_s = .197, p = .049).
With respect to liver function, only Gamma Glutamyl Transferase was significantly associated with SDMT-W (r_s = -21, p = .035), and SDMT-O scores (r_s = -.21, p = .038). Finally, no correlation was found between haemoglobin levels and NP scores probably due to the narrow range of haemoglobin levels observed. No other biochemical values were related to NP functioning.

2.5.d Immunosuppressive medication and NP performance

The influence of an immunosuppressive regime on NP performance was examined by comparing NP performance between TX patients on cyclosporin (n = 70) and TX patients treated with tacrolimus (n = 40). Seven patients who were on prednisolone and azathioprine only were not included in these analyses.

i. *Sample characteristics*

Significant casemix differences were found between the two groups requiring statistical control in subsequent analyses (see Appendix I) These indicated that patients on tacrolimus were significantly younger (t(107) = 2.164, p = .033), and have been on RRT (U = 843, p = .001) and with their transplant (U = 206.5, p= .0001) for less time compared to patients on cyclosporin. Results also showed that significantly more diabetic patients were managed on tacrolimus (χ^2(110) = 4.094, p = .043). There were no other clinical differences between groups.

These differences appear to reflect the changes in the selection and management of TX patients or candidates. For instance, the differences in age and duration of RRT and of functioning graft (i.e. time with transplant) were anticipated, as tacrolimus only recently became available for the management of TX patients. The finding of more diabetic patients being treated with tacrolimus may also be attributed to changes that took place over time with regard to transplant selection criteria.

ii. *NP comparisons: cyclosporin vs. tacrolimus*

ANCOVAs (covarying for age and diabetes, as neither TX duration nor RRT duration were not significantly associated with any of the NP scores) were performed to compare cyclosporin-treated to tacrolimus-treated TX patients.

There were no significant differences in any of the NP scores, indicating different types of immunosuppressive medication have comparable effects on patients' NP performance (see Table 6.47).

Table 6.47: NP performance in cyclosporin and tacrolimus treated TX patients

	Cyclosporin		**Tacrolimus**			
	Mean	*SD*	*Mean*	*SD*	*F*	*p*
TMT A[a]	37.82	18.22	35.94	20.35	.373	.543
TMT B[a]	90.90	63.24	80.52	44.91	1.172	.282
SDMT-W[b]	44.59	12.44	49.59	14.04	2.456	.120
SDMT-O[b]	50.56	14.83	54.65	15.34	.782	.379
RAVLT-T[b]	45.37	10.64	50.42	9.54	2.097	.091
RAVLT-D	1.746	1.703	1.974	1.881	.879	.351
GP-DOM[a]	76.94	27.44	75.64	21.61	.043	.835
GP-NDOM[a]	85.93	30.46	89.02	28.08	.651	.422
NP-TO	1.36	3.62	1.32	4.75	1.259	.746
NP-norm	1.17	1.45	1.35	1.98	.211	.647

Note. TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; NP-TO = total NP performance score; NP-norm = count of NP impairment relative to norms

[a] = Time to completion in seconds. [b] = number correct. [c] = total of the 8 NP indices (z-scores)

Correlational analysis showed that increasing plasma/serum levels of cyclosporin correlated significantly with longer time latencies in GP-DOM (r_s = .27, p = .035), GP-NDOM (r_s = .36, p = .006), SDMT-O (r_s = -.29, p = .024), TMT-A (r_s = .47, p = .000) and TMT-B (r_s = .33, p = .011). In contrast, tacrolimus serum levels were unrelated to measures of NP functioning.

2.5.e Mood and NP performance

Correlations were used to examine the associations between NP outcomes and mood indicators in transplant patients. A non-parametric rank correlation (Spearman's) was used for GP-NDOM and RAVLT-D, as they were not normally distributed in this sample. The strongest correlations were noted for total BDI scores, indicating poorer performance in RAVLT-T (r = -.27, p = .008), SDMT-W (r = -.31, p = .002), SDMT-O (r = -.28, p = .005) and in GP-DOM (r = .21, p =.034) with higher depressive symptoms. Interestingly, no significant correlations were identified between negative affect and cognitive depression index and any of the NP scores. Positive affect was positively associated only with RAVLT-T (r = .24, p = .027).

2.5.f Multivariate predictors of NP functioning in Transplantation

A series of hierarchical multiple regressions were performed to predict NP performance from a combination of sociodemographic and clinical variables. The results of the univariate analyses described above were used to select the predictor variables. Only the variables significantly associated with the specific NP scores at p <. 05 were entered in the regressions. This was deemed necessary as the sample size (n = 117) prevented entry of all variables (especially biochemical assays).

The predictors and order of entry were: age, education (Block 1); ESRD-SI, ischaemic heart disease, GFR, pulse pressure ratings (Block 2), positive affect (Block 3), and urea, albumin, creatinine and gamma glutamyl transferase (Block 4). These variables were entered sequentially in blocks (as indicated) using the stepwise method to determine which variables within each block made the strongest contribution to the prediction of NP outcomes.

Employment status was not included as a predictor as it was seen more as an outcome of cognitive functioning rather than a predictor. Total BDI scores were also not entered as they partly reflect symptoms of renal severity (see Chapter 5; section 2.3) and cognitive depression symptoms were not significantly associated with any of the NP scores (see previous section 2.5.e).

Multiple regression analysis was not performed for RAVLT-D as none of the sociodemographic, medical, or mood measures was significantly associated with that NP score.

Table 6.48: Multiple regressions to predict SDMT-W, SDMT-O and TMT-A in TX patients: standardised regression coefficient, cumulative variance explained

	SDMT-W			**SDMT-O**			**TMT-A**		
	β	**Cum R^2**	**Cum Adj R^2**	β	**Cum R^2**	**Cum Adj R^2**	β	**Cum R^2**	**Cum Adj R^2**
Block 1									
Age	-.466	.314	.306	-.357	.241	.232	.414	.230	.222
	****	f^2=.49	f^2=.47	****	f^2=.36	f^2=.33	****	f^2=.32	f^2=.30
Educ				.203 *	.292	.275	-.221*	.276	.26
					f^2=.08	f^2=.06		f^2=.06	f^2=.05
Block 2									
ESRD SI	-.233 *	.360	.345	-.217 *	.332	.308			
		f^2=.07	f^2=.06		f^2=.06	f^2=.05			
PPR									
GFR									
Block 3									
PNS-PA									
Block 4									
Urea									
Albumin									
Ggl									

* p <.05. ** P < .01. *** p <.001. **** p < .0001.

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; ESRD = end-stare renal disease severity index; GFR = glomerular filtration rate; PPR = pulse pressure ratings; PNS-PA = PANAS positive affect; Ggl = gamma glutamyl transferase

Table 6.49: Multiple regressions to predict GP-DOM, GP-NDOM and RAVLT-T in TX patients: standardised regression coefficient, cumulative variance explained

	GP-DOM			GP-NDOM			RAVLT-T		
	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2	β	Cum R^2	Cum Adj R^2
Block 1									
Age	.263 *	.129 f^2=.23	.12 f^2=.14	.266 **	.131 f^2=.26	.121 f^2=.15	-.389 ****	.194 f^2=.27	.183 f^2=.25
Education							.241 *	.276 f^2=.12	.235 f^2=.07
Block 2									
ESRD SI	.256 *	.186 f^2=.07	.168 f^2=.06	.297 **	.21 f^2=.10	.192 f^2=.09			
PPR									
GFR									
Block 3									
PNS-PA							.204*	.296 f^2=.03	.267 f^2=.04
Block 4									
Creatinine									-
Urea									-
Albumin									-
Ggl									-

* p <.05. ** p < .01. *** p <.001. **** p <.0001.

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; ESRD = end-stare renal disease severity index; GFR = glomerular filtration rate; PPR = pulse pressure ratings; PNS-PA = PANAS positive affect; Ggl = gamma glutamyl transferase

Table 6.50: Multiple regression to predict TMT-B in TX patients: standardised regression coefficient, cumulative variance explained

	TMT-B		
	β	Cum R^2	Cum Adj R^2
Block 1			
Educarion	-.364	.189	.18
	****	f^2=.26	f^2=.24
Age	.292	.267	.25
	**	f^2=.10	f^2=.09
Block 2			
ESRD SI			
PPR			
GFR			
Block 3			
PNS-PA			
Block 4			
Urea			
Albumin			
Ggl			

* p <.05. ** p < .01. *** p <.001. **** p <.0001.

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; ESRD = end-stare renal disease severity index; GFR = glomerular filtration rate; PPR = pulse pressure ratings; PNS-PA = PANAS positive affect; Ggl = gamma glutamyl transferase

Results indicated that the total amount of variance explained ranged from 16.8% to 34.5% across the different NP scores and that among the host of variables included as predictors in these analyses, only three variables, namely age, education, and ESRD severity emerged as significant predictors of NP performance (see Tables 6.48 – 6.50). These three variables in conjunction explained 30.8% (Adj.R^2) in the variance of SDMT-O; Age and ESRD severity accounted for Adj.R^2 34.5% in SDMT-W, 16.8% in GP-NDOM and 19.2% in GP-DOM. Finally, age and educational level were significant predictors of TMT-A (Adj.R^2 = 26%) and TMT-B (Adj.R^2 = 25%) and in conjunction with positive affect explained 26.7% of the variance (Adj.R^2) in verbal recall (RAVLT-T).

2.6 NP comparisons: Dialysis vs. Transplantation

For the transplant group three sets of comparisons were performed: (1) with the combined dialysis sample in which HD and PD patients were collapsed to form one group, (2) with the PD group only, and (3) with the HD group only.

Before comparing the NP performance between dialysis and transplant patients, it was necessary to test for any significant casemix differences between the groups that would require statistical adjustments in subsequent comparative analysis.

2.6.a Combined Dialysis vs. Transplantation

i. *Sample characteristics*

To identify casemix differences to be controlled for, the sociodemographic and clinical profile of the combined dialysis sample was compared to that of transplant recipients. With respect to sociodemographics, results indicated significant differences in annual income ($\chi^2(243) = 38.602$, $p = .0001$), work status ($\chi^2(259) = 5.234$, $p = .022$), and perceived work ability ($\chi^2(259) = 19.7$, $p = .0001$) in favour of transplantation. Transplant patients had also lower ESRD severity ($F(1, 260) = 8.515$, $p = .004$), lower prevalence of diabetes ($\chi^2(262) = 9.107$, $p = .003$) and ischaemic heart disease ($\chi^2(262) = 5.265$, $p = .022$), and had been on RRT ($F(1, 259) = 23.436$, $p = .0001$) and in their respective current form of treatment for longer relative to dialysis patients ($U = 5332$, $p = .0001$) ($F(1, 260) = 24.559$, $p = .0001$).

The differences between the dialysis and transplant groups were anticipated. This was because dialysis patients with higher ESRD severity as indexed by the presence and development comorbidities or renal complications, and those of more advanced age are rarely considered as suitable transplant candidates. The worse clinical status of dialysis patients may also at least partially explain the different employment rates and the resulting annual income disparities between dialysis and transplant groups.

ii. *Absolute NP scores*

Comparisons between the dialysis and transplant samples were performed on T1 NP scores for the dialysis sample. Only the T1 NP performance of the dialysis sample was used in this analysis to avoid learning effects.

A series of ANOVAs (covarying for ESRD severity, diabetes ischaemic heart disease and time on RRT) was performed to compare absolute NP performance between transplant and dialysis patients. Time on current treatment modality was not used as a covariate as it was highly correlated with time on RRT and the latter had stronger correlations with NP scores (data not shown). Also, no adjustments were made for employment and income differences as these were regarded as consequences rather than predictors of NP functioning.

Results demonstrated that transplant patients performed significantly better in 4 NP tests: TMT-A ($F(5, 249) = 6.147$, $p = .014$); SDMT-O ($F(5, 244) = 4.385$, $p = .037$); RAVLT-T ($F(5, 246) = 21.024$, $p = .0001$); RAVLT-D ($F(5, 246) = 8.77$, $p = .003$). Trends in the same direction were also noted in SDMT-W ($F(5, 248) = 3.137$, $p = .078$); GP-DOM ($F(5, 245) = 3.548$, $p = .061$) but did not reach significance.

iii. *Prevalence of NP impairments*

Table 6.51: Prevalence of NP impairments in TX and dialysis patients

	All TX % impairment		DL (T1) % impairment		TX vs. DL χ^2
TMT-A	11% (12)		35.9%		20.391****
TMT-B	7.7% (9)		15.2%		2.199
SDMT-W	19.3% (21)		32.4%		5.487*
SDMT-O	27.6% (29)		41.4%		5.030*
RAVLT-T	21.5% (23)		47.6%		18.081****
GP-DOM	20.6% (22)		41.7%		12.432****
GP-NDOM	27.5% (28)		49.3%		11.859****
	Mean	*SD*	*Mean*	*SD*	
NP impairment	1.231	1.714	2.627	2.182	

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Chi-square analysis indicated that significantly less TX patients fell in the impaired NP range of standard norms relative to dialysis patients: GP-DOM ($\chi^2(251) = 12.432$, $p = .0001$); GP-NDOM ($\chi^2(246) = 11.859$, $p = .0001$); SDMT-W ($\chi^2(254) = 5.487$, $p =$

.019), SDMT-O ($\chi^2(250)= 5.03$, $p = .025$), and TMT-A ($\chi^2(254) = 20.39$, $p = .0001$) (see Table 6.43).

The percentage of TX patients for which a considerable drop in retention (RAVLT-D) was noted after interference was substantially lower ($n = 18$, 16.8%) than that observed in the combined dialysis sample ($n = 41$, 28%; $\chi^2(252) = 4.50$, $p = .034$).

ANCOVAs (controlling for ESRD-SI, diabetes and ischaemic heart disease) also showed that the count of NP impairments was also significantly lower in the transplant group compared to dialysis ($F(5, 256) = 16.375$, $p = .0001$).

2.6.c PD patients vs. TX patients

i. *Sample characteristics (PD; HD; TX)*

Three group comparisons (HD, PD and TX patients) indicated significant group differences in sociodemographic and medical variables: income, perceived work ability, time on current treatment, time on RRT in general, ESRD severity index and diabetic status.

Significantly more TX patients rated themselves as able to work full or part-time ($\chi^2(259) = 21.11$, $p = .0001$) and reported an annual income in the higher brackets ($\chi^2(243) = 25.88$, $p = .0001$) than HD and PD patients. They also had been on RRT ($F(2, 259) = 28.39$, $p = .0010$) for longer compared to the two dialysis groups and were less likely to have diabetes ($\chi^2(262) = 23.16$, $p = .0001$). Comorbidity and clinical severity differences as indexed by the ESRD-SI however were only evident between PD and TX patients. Post-hoc (HSD) tests also showed that PD patients had higher ESRD severity than TX patients ($F(2, 159) = 4.598$, $p = .011$)

ii. *Absolute NP scores*

Transplant patients' NP performance was compared to NP scores of PD patients (at both T1 and T2).

It was decided to include the T2 scores for the PD group in these comparisons even though 7 of 10 NP test scores did not change significantly across the two assessments and despite the fact that T2 scores in PD patients would reflect a learning effect, not anticipated in the scores of TX patients who were only tested once. The reason for this

was that such an 'unfavourable' comparison would constitute a much stronger test of the NP benefits of transplantation over and above learning effects.

Comparisons were performed using ANCOVAs including ESRD severity, diabetes, ischaemic heart disease and RRT duration as covariates. Time on current dialysis treatment was not included as it highly correlated with RRT duration and was less consistently associated with NP scores.

These analyses showed a significant group effect in two T1 NP scores: RAVLT-T ($F(5, 169) = 13.334$, $p = .0001$) and RAVLT-D ($F(5, 169) = 5.694$, $p = .018$). Relative to TX recipients, PD patients had significantly lower memory scores, both in terms of immediate recall from short-term memory (RAVLT-T) as well as in retention ability after interference (RAVLT-D). Attention, concentration and psychomotor abilities were comparable in the two groups.

The second set of comparisons using the T2 NP scores for the PD patients replicated the above findings. Transplant patients' memory scores were superior to those of PD patients even though PD patients were administered the test twice ($F(5, 165) = 11.104$, $p = .001$ for RAVLT-T and $F(5, 165) = 14.114$, $p = .000$ for RAVLT-D).

iii. *Prevalence of NP impairments*

Chi-square analysis revealed that significantly more TX patients performed comparable to their age reference norms compared to PD patients at T1: RAVLT-T ($\chi^2(175) = 10.078$, $p = .002$); RAVLT-D ($\chi^2(175) = 8.921$, $p = .003$); GP-DOM ($\chi^2(170) = 9.822$, $p = .002$); GP-NDOM ($\chi^2(170) = 9.869$, $p = .009$); SDMT-O ($\chi^2(173) = 5.883$, $p = .015$); SDMT-W ($\chi^2(177) = 3.389$, $p = .048$); and TMT-A ($\chi^2(177) = 12.292$, $p = .0001$). NP impairments in TMT-B did not differ between the two groups.

Most of these differences persisted even when T2 NP scores were used for the PD patients: RAVLT-D ($\chi^2(175) = 16.867$, $p = .0001$); GP-DOM ($\chi^2(170) = 9.609$, $p = .002$); GP-NDOM ($\chi^2(165) = 6.949$, $p = .008$); SDMT-W ($\chi^2(173) = 4.025$, $p = .045$); and TMT-A ($\chi^2(173) = 4.729$, $p = .030$). The only exceptions were RAVLT-T and SDMT-O.

ANCOVAs (controlling for ESRD SI) indicated that TX patients presented with overall less NP impairments (i.e. in less areas of cognition) (*mean* = 1.23, *SD* = 1.71) compared

to PD patients at T1 (*mean* = 2.57, *SD* = 2.03; $F(2, 182) = 15.539$, $p = .0001$) and T2 (*mean* = 2.67, *SD* = 2.32; $F(2, 182) = 13.532$, $p = .0001$).

2.6.c HD patients vs. TX patients

i. *Absolute scores*

NP scores of HD patients at both assessments were used, as significant acute NP changes were documented for pre- to 24-hours post-dialysis. It should however be recognised that comparisons using post-dialysis (T2) scores favoured the HD group as they have been earlier exposed to the NP tests whereas TX patients were only administered the tests once. This is especially the case for TMT-A, SDMT-W and SDMT-O in which practice effects were clearly demonstrated for PD patients (see section 1.8).

A series of ANCOVAs (controlling for ESRD severity and time on current treatment) was similarly performed to compare NP scores of HD and TX patients. Results indicated more compromised cognitive functioning for the HD patients when assessed immediately before their dialysis session (T1 assessment). NP scores of HD patients at T1 fell significantly short of those of TX patients in RAVLT-T ($F(3, 180) = 17.589$, $p = .0001$); TMT-A ($F(3, 183) = 10.337$, $p = .002$), SDMT-O ($F(3, 178) = 4.351$, $p = .038$), SDMT-W ($F(3, 183) = 4.781$, $p = .030$), and GP-DOM ($F(3, 179) = 4.743$, $p = .031$). The difference in RAVLT-D was nearly significant ($F(3, 180) = 3.853$), $p = .051$).

In contrast to T1 comparisons, NP performance of HD patients at 24-hours post-dialysis (T2) did not differ to that of transplant patients. Only RAVLT-D scores differed significantly between groups, with HD patients still demonstrating at 24-hours post-dialysis, less efficient retention after interference ($F(3, 180) = 6.948$, $p = .009$) compared to TX patients. In none of the other nine ANCOVA comparisons was the main effect of treatment (HD vs. TX) significant (*p*s <.1).

ii. *Prevalence of NP impairments*

Comparisons of the frequency of NP impairments between HD and TX patients yielded a similar pattern of results in that the prevalence of NP impairments at T1 was greater in

HD patients compared to those with a transplant: TMT-A ($\chi^2(186) = 20.167, p = .0001$); RAVLT-T ($\chi^2(184) = 17.035, p = .0001$); SDMT-W ($\chi^2(186) = 4.225, p = .040$); GP-DOM ($\chi^2(183) = 8.838, p = .003$); GP-NDOM ($\chi^2(178) = 10.567, p = .001$).

The observed associations between treatment and NP impairments (SDMT-W; GP-DOM; GP-NDOM) disappeared when comparing incidence of NP impairment in HD patients based on the 24-hours post-dialysis performance (T2) vs. to that of transplant recipients. The group differences however in RAVLT-T and TMT-A impairment classification favouring transplantation persisted. Chi square analysis indicated that even at the T2 '24 hours post-dialysis' assessment significantly more HD patients performed worse than age referenced norms in TMT-A ($\chi^2(186) = 5.102, p = .024$) and RAVLT-T ($\chi^2(184) = 4.166, p = .041$) compared to TX patients.

In terms of overall neurocognitive dysfunction (as indexed by number of tests in which NP impairments were noted), ANCOVAs (covarying for ESRD severity) showed that TX patients had lower count of NP impairments (T1 (*mean* = 1.23, *SD* = 1.71) compared to HD patients at T1 (*mean* = 2.67, *SD* = 1.23; $F(2, 191) = 20.951, p = .0001$) and T2 (*mean* = 1.89, *SD* = 2.19; $F(2, 191) = 20.951, p = .048$).

2.7 Subjective Cognition Scale – Transplantation

2.7.a Post Transplantation Changes in subjective cognition

The responses of transplant patients on the SCS scale measuring perceptions of change in their cognitive abilities since transplantation are shown in Table 6.52.

The distribution of responses in the nine cognitive domains assessed indicated a greater variability in TX patients' reports compared to dialysis. Although the majority of patients (45.9% – 76.1%) perceived no cognitive changes since transplantation, there was also a substantial number of patients who reported either cognitive improvement or decline from pre- to post- transplantation.

Overall, TX patients (59.8%, $n = 70$) in total, reported more efficient cognitive abilities in one or more area of cognition. The most frequently reported area of cognitive

improvement with transplant patients was clarity of thinking (36%, n = 40), followed by attention (27%, n = 30) and speed of response (24.3%, n = 27).

An equally high percentage (52.1%, n = 61) of patients however, perceived that one or more of their cognitive abilities had deteriorated since receiving their transplant. Memory was the most frequently reported area of difficulty with these patients, with 32.4% reporting that they were worse/more forgetful since transplantation. Concentration was the next most common cognitive complaint (19.8%), followed by problem solving (18.9%).

Table 6.52: Long term changes in subjective cognition in TX patients

Cognitive domain	**+ ve change**	**= no change**	**- ve change**
2. Memory	12.6% (12)	55% (61)	32.4% (36)
3. Problem solving	15.3% (17)	62.4% (73)	18.9% (21)
4. Clarity of thinking	36% (40)	45.9% (51)	18% (20)
5. Concentration	21.6% (24)	58.6% (65)	19.8% (22)
6. Making mistakes	12.6% (14)	77.5% (86)	9.9% (11)
7. Attention	27% (30)	59.5% (66)	13.5% (15)
8. Clumsiness	7.2% (8)	80.2% (89)	12.6% (14)
9. Decision making	15.3% (17)	72.1% (80)	12.6% (14)
10. Speed of response	24.3% (27)	61.3% (68)	14.4% (16)
Improvement (1 or >)[a]	59.8% (70)		
Deterioration (1 or >)[b]			51.1% (61)

[a] improvement in just one or more of the nine cognitive domains/ subjective cognition items

[b] deterioration in just one or more of the nine cognitive domains/ subjective cognition items

2.7.b Transplant type and subjective cognition

Pearson's chi square comparisons with Yate's correction showed no association between transplant type and reports of cognitive decline or improvement since transplantation in any of the domains examined (as indexed by the SCS items) (data not shown).

In addition to examining the distribution of responses in the nine SCS items, the associations of TX type to the three summary SCS scores were examined (see Table 6.53). These were calculated as described in section 1.10.e.

Table 6.53: Subjective cognition summary scores in TX patients

	All TX pts		CAD		LRD	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Total cognitive decline since TX	17.80	3.23	17.77	3.17	17.92	3.50
No + ve changes since TX	1.72	2.17	1.79	2.15	1.46	2.26
No – ve changes since TX	1.52	1.99	1.56	1.97	1.37	2.10

Note: TX pts = transplantation patients; CAD = cadaver transplant recipients; LRD = living related donor transplant recipients; TX = transplantation; +ve = positive change/improvement; -ve = negative change/deterioration

ANCOVAs (controlling for casemix differences, i.e. time with TX) showed no significant differences between LRD and CAD TX groups in any if the three summary scores (see Table 6.53 above for group means): total of cognitive decline ($F(2, 108) = .759, p = .389$); number of positive changes ($F(2, 108) = .160, p = .690$); and number of negative changes ($F(2, 108) = .912, p = .342$).

2.7.c Absolute NP scores and Subjective cognition

The associations between objective NP scores and subjective reports of cognition were investigated using a series of Mann-Whitney or Independent group t-tests (as appropriate). Comparisons between TX patients reporting improvement vs. those reporting cognitive decline since transplantation were performed on the objective NP scores, considered to reflect the particular cognitive function assessed by the grouping subjective cognition item. Patients reporting no change were excluded from this analysis.

The 20 (18%) TX patients reporting worsened clarity of thinking were compared to the 40 (36%) TX patients reporting improvement on all NP test scores. Only the findings on RAVLT-T (total recall at trials 1 to 5) reached significance with patients reporting more clarity in thinking since transplantation recalling significantly more words than the 'cognitive decline' group ($t(29.48) = 2.21, p = .035$).

There were no significant differences in RAVLT scores between patients complaining of memory difficulties (n = 36, 32.4%) and those reporting better memory abilities (12.6%, n = 14).

TX patients reporting concentration (18%, n = 22) and attention (13.5%, n = 15) decline since transplantation were compared to the 'cognitive improvement' group on the tests considered to measure attention (TMT-A; TMT-B; SDMT-W; SDMT-O). Results showed that the latter group ('attention improved') performed significantly better in the SDMT-W than those patients registering deterioration their attention abilities (t(43) = 2.09, p = .043). A similar trend/tendency was noted in the SDMT- O but did not reach significance (t(42) = 1.91, p = .06).

The subjective complaints related to response speed were compared to performance on the speed/time dependent NP tasks (TMT-A; TMT-B; SDMT-W; SDMT-O; GP-DOM; GP-NDOM). Patients reporting deterioration (14.4%, n = 16) in their response speed were not found to perform differently/worse than those (24.3%, n = 27) reporting improvement in any of the above NP tests.

On the whole these group comparisons revealed some significant differences between objective and subjective cognition but with little consistency across NP measures and across the different SCS domains.
Correlational analysis between summary subjective cognition measures and the total/summary score of objective NP scores and number of NP deficits showed no significant correlations (ps < .1) (data not shown).

2.7.d Factors associated with subjective cognition in TX

i. *Sociodemographic and medical factors*

Correlations (Spearman's r_s) and ANOVAs (or ANCOVAs as appropriate) were conducted to examine the associations between sociodemographic and medical variables and subjective cognitions (i.e. the three summary scores).

Employment status was the only sociodemographic variable significantly associated with SCS summary scores and distribution of responses in the individual SCS items. ANCOVA showed that employed TX recipients reported significantly fewer negative

changes in their cognitive abilities (*mean* = 1.15, *SD* = 1.74) than non-employed participants (*mean* = 1.98, *SD* = 2.179) ($F(2, 105) = 6.304$, $p = .014$). chi square analysis showed that a gretaer percenatge of non employed patients reported deterioration in the attention abilities compared to employed participants ($\chi^2(108) = 7.286, p = .026$).

With respect to medical variables, the only significant correlations observed were between SCS summary scores and time spent on dialysis prior to TX, time since transplantation and GFR. The longer patients had their transplant, the more cognitive decline they reported ($r_s = .26$, $p = .009$) and less positive cognitive changes they perceived ($r_s = -.259, p = .006$).

Conversely, time spent on dialysis prior to transplantation was associated with more positive evaluation of cognition. The longer time on dialysis the more positive cognitive changes TX patients reported ($r_s = .195$, $p = .045$) and the lower their overall subjective cognitive decline score ($r_s = -.211, p = .030$)

Lower GFR levels were similarly associated with overall perceived cognitive decline($r_s = -.22$, $p = .021$) and count of negative changes in cognition ($r_s = -.21$, $p = .028$), suggesting that deteriorating TX function is associated with more negative evaluations of cognition.

No other significant associations were identified between the three SCS summary scores and sociodemographic and medical variables (i.e. age, gender, ESRD severity index, comorbidity).

ii. *Immunosuppressive medication*

The association between immunosuppressive medication and reports of cognitive change since transplantation was also examined. In contrast to findings on absolute NP scores chi-square analysis showed only one significant association between type of immunosuppressive medication and cognitive complaints.

Results indicated that significantly more TX patients treated with cyclosporin reported a deterioration in their memory abilities compared to patients on tacrolimus ($\chi^2(48) = 3.862, p = .022$).

Between group comparisons on the summary subjective cognition scores (without casemix adjustments) also showed that patients on cyclosporin reported significantly fewer positive changes in their cognitive abilities (*mean* = 1.35, *SD* = 2.00) relative to patients on tacrolimus (*mean* = 2.44, *SD* = 2.44; t (108) = -2.590, p = .011).
This difference was removed when time with TX was controlled for (F(2, 102) = 1.252, p = .266). Likewise, the count of negative changes and total cognitive decline scores did not differ between groups (F(2, 102) = 1.520, p = .220 and F(2, 102) = .0001, p = .990 respectively).

iii. *Mood measures*

Independent *t*-tests were performed to investigate the association between mood measures and subjective complaints of cognitive decline in TX patients. Patients in the 'cognitive decline' groups as described above were compared to those reporting improvement on BDI, CDI, positive affect, and negative affect.

Results indicated that levels of mood differed significantly between TX patients reporting improvement vs. those reporting deterioration since their transplant.
TX patients who felt that their cognitive abilities have deteriorated since transplantation reported more depression, more negative affect and less positive affect (see Table 6.47). Likewise, Spearman's correlational analysis showed that the more cognitive decline (summary SCS score) the lower the positive affect (r_s = -.277, p = .009) and the higher the depression scores (r_s = .322, p = .001 for BDI and r_s = .26, p = .009 for CDI). The correlation coefficient for negative affect approached but did note reach significance (r_s = .199, p = .058).

The number of negative changes was also correlated with mood, i.e. lower positive affect (r_s = - .30, p = .003), more negative affect (r_s = .31, p = .001) and more depression (r_s = .41, p= .0001; r_s = .39, p = .001 for total BDI and CDI scores respectively). No significant correlations were found between any mood measure and the number of perceived positive changes in cognition.

Table 6.54: Mood and perceptions of long-term cognitive changes since TX

	BDI	CDI	PNS-NA	PNS-PA
	t-value mean/SD	t-value mean/SD	t-value mean/SD	t-value mean/SD
Memory	ns	ns	ns	ns
-ve	9.40 (6.96)	6.15 (4.87)	18.75 (5.66)	28.23 (6.97)
+ve	9.38 (8.8)	6.31 (6.01)	16.55 (4.45)	32.45 (8.49)
Pr. Solving	-2.36*	ns	-2.28*	ns
-ve	12.42 (6.85)	8.11 (4.91)	20.56 (5.95)	26.31 (7.42)
+ve	6.5 (8.02)	4.62 (5.52)	16.5 (3.2)	30.23 (5.93)
Clarity thinking	-2.26*	ns	ns	3.63***
-ve	11.47 (6.46)	6.82 (4.17)	19.86 (7.27)	23.07 (7.9)
+ve	6.91 (6.92)	4.70 (4.92)	17.26 (3.91)	31.23 (6.49)
Concentration	ns	ns	ns	ns
-ve	11.05 (7)	7.4 (4.76)	20.78 (7.48)	25.73 (7.55)
+ve	8.08 (8.13)	5.37 (5.65)	16.28 (3.27)	29.44 (7.78)
Mistakes	ns	ns	ns	ns
-ve	10.8 (5.13)	7.3 (4.59)	18.25 (5.44)	29.2 (4.63)
+ve	11.07 (8.72)	7.64 (5.91)	17.69 (2.81)	28.82 (8.94)
Attention	-3.43**	-3.43**	ns	2.20*
-ve	14.26 (7.07)	9.33 (4.88)	19.08 (5.82)	24.36 (6.15)
+ve	6.62 (6.96)	4.2 (4.6)	16.53 (3.05)	29.81 (7.13)
Clumsiness	ns	ns	ns	ns
-ve	11.42 (8.92)	7.07 (5.7)	18.38 (3.79)	26.16 (8.73)
+ve	8.25 (9.88)	5.75 (6.58)	16 (5)	38 (3.67)
Decision	ns	ns	ns	ns
making	11.75 (7.56)	8.33 (4.94)	20.09 (6.86)	28.63 (7.2)
-ve	9.23 (9.49)	6.82 (7.07)	17.06 (4.09)	29.31 (7.76)
+ve				
Response speed	ns	ns	ns	ns
-ve	12 (7.75)	8 (6.15)	17.83 (5.63)	27.36 (7.83)
+ve	9.22 (8.33)	5.96 (5.94)	17.76 (6.31)	31.13 (8.49)
Improvement[a]	ns	ns	ns	ns
No +ve	7.71 (5.46)	5.31 (5.22)	17.57 (5.08)	30.78 (7.53)
1 or < +ve	8.19 (7.35)	4.71 (4.36)	17.35 (6.97)	28.41 (6.66)
Decline[b]	-3.99***	-3.63***	-2.88**	2.41*
1 or < -ve	10.23 (7.24)	6.58 (5.36)	19.14 (6.21)	28.13 (7.13)
no –ve	5.43 (4.93)	3.35 (3.67)	15.80 (4.87)	31.71 (7.05)

Note: BDI = total Beck depression scores; CDI = cognitive depression index; PNS-NA = PANAS = PANAS negative affect; PNS-PA = PANAS positive affect; +ve = positive change/improvement; -ve =negative change/deterioration

[a] = Comparisons between patients reporting no improvement at all in any of the 9 cognitive domains since TX vs. patients reporting improvement in at least one or more areas of cognition

[b] = Comparisons between patients reporting no decline at all in any of the 9 cognitive domains since TX vs. patients reporting decline/deterioration in at least one or more areas of cognition

* p <.05. ** p <.01. *** p <.001. ns = non significant

iv. *Prediction of subjective cognitive complaints*

The independent contribution of sociodemographic, medical and psychological variables to the prediction of cognitive complaints (total SCS score) in TX patients was estimated using hierarchical multiple regression (stepwise method).

Only the variables found to be univariately associated with subjective cognition were included in this analysis, namely employment status, time on TX, and time on dialysis and mood measures. Identified predictors entered the regression equation in separate blocks: sociodemographic variables as block 1, medical and clinical variables as block 2, followed by mood indicators at the last step of the regression. To control for any influence of participants' age and educational level, these variables were entered in Block 1 and likewise ESRD severity index (ESRD-SI) was entered in Block 2 under forced entry criteria even though they did not correlate significantly with overall subjective cognitive decline.

The resultant regression model explained $R^2 = 11.2\%$ (Adj.$R^2 = 9.6\%$) of the variance in subjective cognitive decline. Significant predictors were time elapsed since TX (β = .239, p = .008) that accounted for $R^2 = 5.5\%$ (Adj.$R^2 = 4.6\%$) of the variance and positive affect (β = -.239, p = .008) that added $\Delta R^2 = 5.7\%$ (ΔAdj.$R^2 = 5\%$). Regression coefficients indicated that the longer the time elapsed since TX, and the lower the positive affect, the greater the cognitive complaints.

Section 3: Summary of Results

- A substantial number of dialysis patients performed worse than age reference norms in attention, memory and psychomotor speed tasks

- There were no significant differences in NP scores between dialysis groups

- Acute changes in NP performance were evident only for HD in contrast to PD. This parallels the changes observed in biochemistry over the period of dialysis in the HD group although the relation to any particular biochemical change was not established.

- Concomitant changes were also noted in state mood indicators but these were also not consistently associated with acute NP changes

- Dialysis patients perceived that their cognitive abilities have declined since dialysis onset, particularly memory and concentration function. Significantly more HD patients reported day to day NP improvement relative to PD.

- Objective NP scores were mainly unrelated to indices of subjective cognition. Mood on the other hand was significantly associated with complaints of cognitive deterioration since dialysis (in most areas) and reports of post dialysis concentration improvement.

- The NP performance of TX patients was within normal range and was mainly predicted by age, education and ESRD severity. TX type (CAD vs. LRD) and immunosuppression (tacrolimus vs. cyclosporin) was unrelated to cognitive functioning.

- TX patients outperformed PD on memory tasks. They also performed better than HD patients on almost all NP tests but only when compared to pre- dialysis NP scores and not when assessed at 24 hours post- dialysis.

- There was great variability/diversity in TX patients' subjective reports of their cognitive abilities since transplantation, with some patients reporting more efficient cognitive functioning and other a decline in cognitive abilities.

- Time elapsed since transplantation and positive affect predicted subjective cognition in TX recipients whereas the contribution of objective NP functioning was not significant.

CHAPTER 7:
DISCUSSION OF THE NEUROPSYCHOLOGICAL FINDINGS

One of the main focuses of this study was to evaluate NP functioning in patients with ESRD. This study revisits an area that was first addressed in the 1970's and 1980's however this earlier research was limited by methodological flaws that cast doubt on the validity and generalisability of its findings in the modern ESRD population. Many of these studies used very small samples, failed to address sociodemographic (i.e. age, education) and clinical factors (e.g. co-morbidity) and the timing of NP testing in relation to the dialysis cycle was not reported. The NP outcome of ESRD was therefore re-investigated with improved methodology to overcome previous limitations and with a wider focus to address issues not explored in the early research.
Study findings on absolute NP performance will be selectively discussed first in two sections mirroring the order that the results were presented.

Section 1: Dialysis

1.1 The prevalence of NP impairments in dialysis

To evaluate the performance of dialysis patients relative to norms, the observed prevalence of NP impairments relative to that expected in a normal distribution was calculated. For the purposes of the study NP impairments were defined as scores lower than 1 *Sd* below norms, which if expressed in 'percentile rank terms' correspond to 16th percentile and signify low average to borderline performance (Mitrushina *et al.* 1999). Such a definition of NP impairment should not be confused or be regarded as evidence of NP deficits. Caution in warranted in assigning clinical weight or significance in these findings as for example a score that occurs in less than 1% of normal sample would carry greater clinical weight than a score that occurs in 15% of normal sample.

Normative comparisons using group means indicated that dialysis patients performed comparably to their healthy counterparts in the majority of NP tests with some mild impairments mainly in motor function and selective memory functions (i.e. BVRT errors) consistent with previous studies (Churchill *et al.*, 1992).

Individual-based comparisons in which NP scores of each individual patient were evaluated against his or her respective age reference norms indicated the prevalence of NP 'impairment' might be higher than would be expected based on group comparisons. One third or more of dialysis patients performed 1 *Sd* below their respective norms, particularly in memory and motor tasks, which is double that expected in normal distribution (15.86%). Previous studies have also shown mild memory deficits in dialysis patients (Brown *et al.*, 1991; Teschan *et al.*, 1979; Wolcott *et al.*, 1988a).
Study findings suggested memory impairments were manifested in both immediate verbal recall-retrieval and in retention after interference. There was substantial reduction in the number of words recalled after interference by both dialysis groups and at both assessments. On trial VII both dialysis groups recalled an average of 2.35/2.75 (HD/PD) words less than on trials V at first assessment and 2.64/3.03 (HD/PD) less at second assessment. These findings indicate that even though the appearance of a learning curve over the previous five trials demonstrates some ability to learn, for some of the patients this gain is not maintained on the delayed recall (trial VII). It is of note that for a significant proportion of HD (20.8% at T1 and 29.9% at T2) and PD (36.8% at T1 and 44.1% at T2) patients recall dropped more than 3 words from trial V to trial VI. This is regarded an abnormal drop and probably reflects a retention or retrieval problem (Lezak, 1995). It should also be noted that this percentage increased from T1 to T2 despite the overall word retention at trials 1 to 5 increased.

Findings of impaired motor function in dialysis patients have been reported previously (Pliskin *et al.*, 1996). The observed rates of motor impairment in our sample were fairly similar for dominant and non-dominant hands. Although they reflect a central problem an alternative explanation is that they may have resulted from undiagnosed joint dysfunction, muscle weakness due to electrolyte abnormalities, subtle nutritional deficits, or de-conditioning. It is also possible that hand dysfunction due to dialysis related amyloidosis which is prevalent in HD patients (Carroll *et al.*, 1993; Limaye *et al.*, 2001) may have had complicated patients' GP performance further. The role of a fistula interfering with the psychomotor tasks was given consideration but there was no

evidence that an uncomplicated fistula interfered with motor functioning when not in use. In our sample 79.2% (n = 61) of the HD patients were dialysed using a fistula on their non-dominant hand, 11.7% (n = 9) had a fistula on their dominant hand and 9.1% (n = 8) were dialysing using a catheter line. It is important that no overall group differences were found, suggesting the presence of a fistula was not important.

Impairments in attention abilities were evident in three of the four tasks (TMT-A; SDMT-W; SDMT-O) and only in individual-based comparisons. The differential performance of patient across the TMT-A and TMT-B is noteworthy. TMT mean scores indicated that patients had more difficulty completing TMT-A than TMT-B test, a finding at odds with previous research (Bremer *et al.*, 1997). While only 15.2% (n = 22) of the dialysis patients fell below the 25th percentile for TMT-B, more than twice as many patients (n = 52, 35.9%) fell below the 25th percentile for TMT-A (individual level classification). The finding of higher incidence of impairment in TMT-A rather than TMT-B is intriguing. Previous research showed that performance of dialysis patients is more compromised in complex attention tasks (such as TMT-B) rather than more simple attention tasks (Brown *et al.*, 1991; Churchill *et al.*, 1992; Fazekas *et al.*, 1996; Rozeman *et al.*, 1992). It would also be intuitive to expect that due to its added complexity, the TMT-B is likely to pose more difficulty for patients than TMT-A.
Some authors have interpreted discrepancies in performance in the two TMT parts as an indication of a laterality of brain damage (Golden *et al.*, 1981) but this has largely been discredited in the literature (Hom & Reitan, 1990; Salthouse & Fristoe, 1996). Perhaps, a possible explanation might relate to the order of administration. TMT-A was administered first, before the TMT-B, and as such the completion of TMT-A before TMT-B might have familiarised patients to test procedures or relevant cognitive strategies and hence positively affect subsequent performance.

Although NP research involving normative comparisons is valuable, the significance of the findings is dependent on the appropriateness and quality of the normative databases against which comparisons were made and NP impairments were defined. No normative study ordinarily allows a perfect fit to the population under study and the limitations of any dataset used for inferential purposes should be borne in mind. Although existing normative databases were scrutinised to identify the one that most closely matched the characteristics of our sample, method of administration and scoring procedures, the

resulting choices on which the definition of NP deficits were based, were far from optimal. Caution is therefore warranted in interpreting and generalising these findings.

The assessment of closely matched healthy volunteers would be one advance for future investigations on the incidence or prevalence on NP impairments in ESRD. Test norms as they involve historical, non-concurrently assessed healthy controls, often in low numbers may not necessarily represent the most appropriate reference point. A study by Pliskin *et al.* (1996) clearly illustrates this point. Although there were no significant differences in NP performance between HD patients and matched healthy controls, both groups (including the healthy volunteers) demonstrated mildly impaired NP function relative to test norms.

Nevertheless it is important to emphasise that the majority of dialysis participants in this study performed within the average or low average range of the various cognitive tasks). Patients' performance in the various NP tests was also found to be comparable and in some cases superior, to that reported in previous studies of dialysis patients (Buoncristianni *et al.*, 1992; Pliskin *et al.*, 1996; Smith *et al.*, 1990; Umans *et al.*, 1998; Wolcott *et al.*, 1988a). This may reflect relative improvements in treatments or selection differences for dialysis.

1.2 Dialysis modality and NP performance

One of the key aims of this study was to compare the NP outcomes associated with different dialysis treatments. The differential biochemical profiles and patterns of renal clearance achieved by HD and PD beg the question as to how intermittent vs. continuous treatment might affect patients' cognition.

Such comparisons albeit valid, posit difficulties as they are subject to a range of potential confounding factors (Pliskin *et al.*, 2001). For instance, modality selection bias may operate. Patients' treatment mode is not purely elective. Medical and non-medical considerations (financial reimbursement, facilities, physician bias, and patients' preferences) are well recognised to impact on modality selection. (Nissenson *et al.*, 1993). Modality selection bias and case-mix differences can be thought to place bias on the results and make a true, valid treatment evaluation and between treatment comparisons difficult. In the absence of a possibility of a randomised design coupled

with the multiplicity of potential confounding factors, careful consideration was given in designing and conducting a methodological tight and adequately-powered experimental study to overcome many of the methodological shortcomings of previous research and to take into account the majority of the aforementioned considerations.

These included the relatively large sample of medically stable and adequately dialysed HD and PD patients that met stringent inclusion criteria, assessments of several cognitive abilities at two time points, careful timing of NP assessment relative to the cycle of dialysis, and inclusion of both psychosocial and biomedical variables. All confounding factors, likely to increase variability and introduce biases when comparisons were made between the two-dialysis modalities, were either eliminated by appropriate patient selection procedures or if systematically different between groups, adjusted for in all analyses. Intra-individual variability is also an issue with repeated NP assessments. Mood may influence motivation to perform the tasks, and stress, fatigue, or other physical symptoms may transiently alter performance on NP tasks across administration trials (Rasmussen *et al.*, 2001). Concurrently measured levels of mood and fatigue were hence included in the analysis even when there were no differences between groups, to ensure statistical control of such 'intra-individual' confounders. Methodological control was seen as a priority for two reasons. First, it minimises unnecessary inflation of the number and extent of differences between HD and PD participants, and hence the probability of Type 1 error. Second, it maximises the identification of differences in cognitive performance that would go undetected in a non-controlled study and may hence increase the probability of Type 2 error.

This study demonstrated that careful matching for confounding variables has a marked effect on the results obtained when comparing cognitive function in patients on different dialysis modalities.

Treatment comparisons in this study indicate that HD and PD patients present equivalent cognitive functioning. Although NP performance varied greatly between patients, there were no systematic significant differences between dialysis modalities. The prevalence of NP impairments was not different in PD and HD. These findings are similar to some studies (Rozeman *et al.*, 1992) but are at odds with some other reports of more compromised cognitive functioning in HD patients compared to PD patients (Garcia-Maldonado *et al.*, 1991; Yount *et al.*, 1998; Wolcott *et al.*, 1988a).

One potential reason for this inconsistency may relate to variations in the timing of the assessment over the dialysis cycle in many studies. In contrast, in this study NP performance was assessed at two time points, immediately before dialysis and 24 hours later. For the HD patients this is likely to reflect the worst and the best physiological state. Other differences include the size and composition of the patient groups and the heterogeneity of the population.

In addition, the inconsistency may be due to the continued improvements in the delivery and techniques of HD, such as dialysis adequacy standards and increased biocompatibility, as the bulk of conflicting studies were performed some time ago. Study findings demonstrate the importance of methodological control in studies of NP outcomes of ESRD (Pliskin *et al.*, 2001) and emphasise the need for caution in interpreting results from poorly controlled studies.

The clinical implications of these results are that adequate HD treatment leads to stable cognitive functioning and is not an inferior treatment option to PD. Other investigators have similarly failed to find significant difference in the NP performance between healthy controls and adequately dialysed HD patients (Pliskin *et al.*, 1996). Thus concerns over cognitive impairment should not enter the decision-making process when selecting renal replacement modality. However consideration regarding the see-saw effect of biochemistry and potentially of NP functioning may influence clinical judgement.

1.3 Acute neuropsychological changes

To determine whether NP performance changes over the dialysis cycle, HD patients were assessed immediately before and again 24-hours post-dialysis. These times were chosen on the grounds that HD patients' biochemical profiles would differ on these two occasions and that more normal physiology would be evident at the time post-dialysis compared to pre dialysis values (Ratner *et al.*, 1983). The main hypothesis was that normal biochemistry at 24-hours post-dialysis would produce improved NP functioning post-dialysis compared to immediately prior to dialysis. The competing hypothesis was that any discernible NP improvements in HD patients would be attributed only to learning effect.

Changes over time do suggest a greater variability in NP performance in HD during the dialysis cycle. While the PD group's NP performance showed little change over time, the HD group showed improvement in most of the tests, in line with their changing physiological state. Previous studies have demonstrated similar short-term changes but were unable to rule out learning effects (Ginn *et al.*, 1975a; Lewis *et al.*, 1980; Ratner *et al.*, 1983) as no control group was used.

The test-retest or learning effect defined as an improvement in performance after repeated presentation of a test, is a general problem for longitudinal NP studies (McCaffrey & Westervelt, 1995; Mitrushina *et al.*, 1991). Effects of implicit or explicit learning, as well as of anxiety reduction are always an issue when the same task is performed twice. To tease out the effects of biochemical changes and thus avoid such problems of interpretation of learning effects PD patients were assessed at the same time intervals. With their more stable physiological functioning it was assumed that any changes in NP functioning would be attributable to learning whereas improvements in HD patients should reflect both learning as well as improved physiological state. The assessment of a PD group enabled an assessment to be made for learning effects on the NP tests in an ESRD population (McCaffrey & Westervelt, 1995). It was hypothesised that the practice effects for HD and PD patients would be comparable and hence any additional NP improvement in HD patients 24-hours post-dialysis would be attributed to fluctuation in their physiological status.

There are other differences in the methodology of the present study, which add strength to these findings. These include a sufficiently large sample size to detect changes, and consideration and adjustment of possible confounding variables to allow for more robust analysis.

Results were in accord with our hypothesis and indicated that HD patients demonstrated significantly greater NP improvements (absolute NP scores and in the prevalence of NP impairments) in all the cognitive domains examined, across the two assessments relative to PD patients. Such improvements were evident in all NP tests employed, i.e. attention, concentration, motor abilities, and verbal learning and memory tasks after controlling for concurrently measured levels of fatigue and anxiety.

Although such improvements with repetition of NP tests over such a short time interval were anticipated, the finding of significant interaction effects signifies that the observed improvements in the NP performance of the HD group are not simply the result of a learning effect. Post-hoc analyses demonstrated significant changes (reflecting both learning coupled with actual improvements) across the two assessments for the HD group but virtually no significant changes for the PD group. The PD patients produced a relatively consistent NP performance across the two assessments except the three tests, for which no parallel administration forms were used, which showed significant improvements from T1 to T2. These improvements suggest that these tests are more susceptible to learning with repetition over a short time period.

Previous studies have reported findings in the same direction but due to small sample sizes statistical differences have not always been detected (Ratner *et al.*, 1983) or when they have, generalisation of findings was limited (Lewis *et al.*, 1980). Such uniform significant short-term changes in range of cognitive domains (attention, concentration, verbal learning and memory, and psychomotor speed) have not been reported previously in HD.

An important question attendant on the issue of dialysis modality and neuropsychological performance is the clinical significance of the acute changes exhibited by HD patients. The fact that this group's performance did show acute changes over the dialysis cycle relative to the PD group has clinical significance at least with regard to the cognitive performance reflecting the impact of the two dialysis techniques. Although the exact links to biological measures were not established in the study, it does suggest that the issue of biological fluctuations in HD is important. Perhaps the issue of whether cognitive improvements are behaviourally important becomes secondary when judging their clinical relevance as long as they are reliable markers of brain functioning and can be used to improve dialysis delivery and procedures. This fact appears to have been recognised by the shift to a more frequent (daily) HD regimen (Pierratos, 2004). It remains to be established whether the cognitive fluctuations with this regimen are reduced.

There are two further issues with regard to the importance of these acute fluctuations in cognition. One is whether these changes are evidenced in real life problems for the patients. This was not specifically addressed in the study reported only in as much as it was examined through quality of life. Further research could potentially examine patients performance in real life tasks at the two occasions studied here.

Daily performance-type measures would be essential for examining how acute/daily fluctuations in the cognitive abilities of HD patients might relate to functioning of patients on the real world. It is possible that acute NP changes might have implications on patients' everyday functioning like daily activities, work performance or social interactions but these have not been measured in this study. Compensation-coping mechanisms are also likely to operate in that patients who are aware of such daily cognitive fluctuations might strategically structure the type or the load of daily activities and routines in a different manner at dialysis and non-dialysis days or might be forced to make particular lifestyle or career choices to accommodate daily variations in cognitive functioning. The magnitude of these effects or adjustments is also likely to be highly dependent on the personal circumstances or characteristics of the person and environment. These are speculations, which need to be addressed by empirical research.
The second question revolves around the awareness of patients of these cognitive fluctuations. This was examined in the study by asking patients about changes in their cognitive performance over the 24-hour cycle. This is reported later (see Section 3: Subjective Cognition).

The aetiology of such transient effects remains elusive. The hypothesised links between biochemistry and NP performance received only limited support in this study. On one hand the observed significant changes in urea, creatinine, albumin, calcium, potassium and phosphate in the HD group were consistent with the impact of dialysis. As predicted no such changes were found in the PD group reflecting their continuous dialysis and resultant relatively stable physiological state.

The findings however failed to support a link between the accumulation of uraemic toxins and absolute cognitive performance. Biochemical measures were not reliably and consistently associated with NP performance (Ratner *et al.*, 1983).
The amount of variance explained by biochemical predictors was small and variance based measures of effect sizes indicated small effects (f^2 values ≤ 0.06). Multiple regressions indicated that levels of calcium, phosphate and urea predicted more efficient cognitive functioning in 3 out of 10 absolute NP scores (Wolcott *et al.*, 1988a). Regression coefficients however indicated counter intuitive associations in that high urea and calcium concentrations were associated with better NP absolute scores. Although associations may be considered spurious, they also prompt questions regarding the influence of urea toxicity. Other investigators have similarly concluded

that evidence on the toxicity of widely researched solutes such as urea is far from being conclusive (Dhondt *et al.*, 2001).

Changes in calcium and urea were also associated with changes in NP performance over 24 hours. It is of note that the associations between urea changes and NP improvement were in the expected direction (unlike those reported for absolute scores). A decrease in urea was associated with greater memory improvements while increases in calcium over the two assessments predicted improvement in attention (SDMT-W; SMDT-O).

In conclusion, NP improvements paralleled changes observed in biochemistry over the period of dialysis in the HD group although the relation to any particular biochemical change was not established.

Alternative physiological explanations not explored in this study are discussed overleaf.

The absence of significant associations between NP performance and other biochemical assays was to an extent expected. In untreated pre-dialysis patients, in whom biochemical levels can very over a wide range, NP impairments clearly occur in conjunction with high biochemical values reflecting the severity of the illness (Ginn, 1975a; 1975b; Hart *et al.*, 1983; Teschan *et al.*, 1974a; 1974b; Teschan, 1979). In dialysis patients, biochemical values are allowed to fluctuate only within narrow limits and in this sample, all biochemical measures were within the normal physiological range for adequately-dialysed patients. Consequently the lack of significant correlations between parameters such as haemoglobin and NP performance may reflect the lack of sufficient value range (Bergström, 1997; Vanholder *et al.*, 1994).

Significant associations may only become evident when biochemical levels fall below a certain threshold and these minimal levels were exceeded in this study. Several studies have consistently demonstrated that uncorrected anaemia is associated with cognitive deficits and that erythropoeitin treatment leads to NP improvements (Grimm *et al.*, 1990; Pickett *et al.*, 1999; Stivelmann, 2000; Temple *et al.*, 1995). Mean haemoglobin levels in the study were adequate (> 10 g/dl) and those patients who were previously anaemic were on erythropoeitin in order to obtain a haemoglobin concentration of no less than 10-11 g/dl. It is likely therefore that this explains the absence of significant associations between NP and haemoglobin.

The accumulation of different compounds, other than the group of small solutes measured in this study, namely middle or large molecules and protein-bound solutes

(Dhondt *et al.*, 2001; Vanholder *et al.*, 1995; 2001) might be responsible for changes in cognitive functioning. Their association with NP functioning has yet to be investigated.

It also remains possible that other alternative physiological pathways or molecules, not examined in this study may also account for the observed NP changes.
For example, the marked fluid shifts with their potential for inducing haemodynamic instability in haemodialysis may have NP implications for HD patients. Brain density changes have been observed across the dialysis cycle in HD with severe dehydration in the pre-dialysis phase (Detori *et al.*, 1982; La Greca *et al.*, 1980; 1982). More recent investigations using MRI have similarly noted such alterations in brain hydration during the cycle of haemodialysis although the pathological NP consequences of which remain speculative (Silver *et al.*, 1996; Walters *et al.*, 2001). Experimental research conducted in healthy volunteers has shown links between dehydration and NP performance (Cian *et al.*, 2001; Gopinathan *et al.*, 1988).

Finally, acute NP changes may also be related to other haemodynamic changes such as blood pressure or the production and release of cytokines during the cycle of haemodialysis. Studies have observed large variation in blood pressure during a HD session and the fluctuation of blood pressure levels from pre- to post-dialysis and during the interdialytic period (Elisaf *et al.*, 1996; Kooman *et al.*, 1992; Santos *et al.*, 2003). Chronic hypertension has profound effects on cognition (Elias, 1998; Swan *et al.*, 1998). However little is known about the NP implications of the observed acute blood pressure changes during the cycle of HD (Metry *et al.*, 2002).

To conclude, although study findings provided partial support for the hypothesised biochemical basis of the observed NP changes, further research pursuing this question is warranted. Taken together the overall pattern of results suggest that particular physiological changes either solely or in combination during the haemodialysis cycle should be implicated in the these transient NP effects. A simple biological explanation may not be sufficient enough to account for NP effects.

Study findings also indicated that factors other than biochemistry may be equally or perhaps more important in explaining absolute NP scores as well as changes in NP scores.

Multifactorial models for cognitive functioning including sociodemographic, medical, biochemical and mood variables were tested. Hierarchical multiple regressions assessed the contribution of mood and biochemistry over and above the effect of sociodemographic and medical variables. In these analyses the order of entry for biochemistry and mood was reversed to add to methodological rigour and not because the two were considered as strictly competing hypotheses.

Results indicated that when mood was entered after biochemistry in the equations, it contributed significantly to the prediction of both absolute NP scores and NP improvements over and above variance explained by biochemical values. There is overwhelming evidence supporting the close association between mood and cognitive functioning (Dijkstra *et al.*, 2002; Murata *et al.*, 2000; Norman *et al.*, 2002), but to our knowledge this is the first report of concomitant acute changes in mood and cognition. The observed acute changes in mood are probably the result of a combination of factors, in particular familiarisation of subjects with the testing procedures and the researcher and preference for a non dialysis day (HD) or a non PD clinic attendance day (PD).
Acute changes in NP functioning were associated with changes in positive and negative affect. Increased positive affect predicted improvement in NP performance on SDMT-W, RAVLT-T and BVRT-E. On the other hand decreases in reported levels of negative affect was associated with better scores in TMT B, GP-DOM and GP-NDOM.

Interestingly, depression traditionally associated with NP performance (Coker & Shumaker, 2003; Suhr, 2003), was unrelated to acute NP improvements. Depression and anxiety failed to emerge as significant predictors of NP change when entered together with positive and negative affect, despite being associated with absolute levels of NP performance (T1). Although the difference in timeframe of depression and PANAS measures might at least partly account for this finding, the same explanation does not apply for anxiety as this also reflected momentary affect.

The associations between positive mood and NP functioning are of note. Positive emotions have received considerably less attention, perhaps related to the prevailing view of physical and mental health as the absence of a disease and negative emotions (Ryff & Singer, 1998), as well as the fact that positive emotions are less differentiated than negative emotions (Erlsworth & Smith, 1998). Positive emotions have been associated with better health outcomes (Affleck *et al.*, 1987; Bower *et al.*, 1998;

Kiecolt-Glaser *et al.*, 2002) but their associations to NP outcomes have been overlooked. Indeed although a substantial empirical literature exists on depression and NP status (and health in general), almost none exists for 'positive affect' and cognitive functioning (La Rue *et al.* 1995). Altogether these findings point to the importance of measuring positive and not only negative affect in line with previous research on self-assessed health (Benyamini *et al.*, 2003).

Finally our results indicated that sociodemographic and clinical factors, namely age, education and ESRD severity were associated with NP functioning in both univariate and multivariate analysis. The effects of age, education, disease severity and comorbidities are well known and such associations have consistently been documented in the literature (e.g. Kutlay *et al.*, 2001; Mitrushina *et al.*, 1999).

The finding that dialysis adequacy predicted NP functioning is unique. Previous investigators have stressed the need to consider delivery of dialysis in NP investigations of dialysis patients (Pliskin *et al.*, 1996; Umans *et al.*, 1998). This study is the first report of a significant association between the two. Even though all patients met the minimum criterion for adequate dialysis, study results show that increases in urea clearance (dialysis dose) above national standards produced further improvement in NP functioning. This finding is at odds with studies investigating the association between Kt/V and survival (Held *et al.*, 1996; Owen *et al.*, 1993) in which no dose-effect relationships were found. It suggests that assessment of brain functioning and survival is different. This is perhaps not surprising given that patients do not tend to die of neurological problems.

Section 2: Transplantation

On all measures of cognitive function TX recipients fared no worse than respective age-reference populations. These formal observations accord with previous data from earlier studies (Kramer *et al.*, 1996; Teschan *et al.*, 1979). It is possible that other tests might have detected deficits not appreciated in our study, but the NP tests performed are widely used, well-standardised and covered a range of cognitive areas (Lezak, 1995). That normal or near normal NP functioning can be expected following renal transplantation will be reassuring to patients. Many are aware of the possibility of

cognitive difficulties in the wake of ESRD and some might have experienced problems while on dialysis. It also highlights the potential of renal TX to reverse some of the NP deficits associated with dialysis and to restore NP functioning back to normal or pre-morbid levels.

The hypothesis that TX patients would demonstrate more efficient cognitive functioning than dialysis patients, received modest support. TX patients outperformed dialysis patients only in certain NP tests and not across all the cognitive domains assessed. The NP advantage of TX was evident for memory function (immediate recall and retention) and for two of the four attention measures (TMT-A; SDMT-O). By contrast there were no differences on other measures of attention (TMT-B; SDMT-W) and on measures of motor abilities (GP-DOM; GP-NDOM).

Methodological factors might account for these findings. Significance levels were not adjusted for multiple comparisons, which would have negated the significance of SDMT-O and TMT-A differences (as p would have been dropped to .0071). Other investigators have similarly resorted to reporting uncorrected p values (Pliskin *et al.*, 1996) to ensure that no potential findings would be overlooked. It is important that the differences in RAVLT-T scores would still be significant even when adjusted for multiple comparisons. The effect on memory may therefore reflect true differences between dialysis and transplant patients, suggesting that this is an area of functioning particularly sensitive or vulnerable to the effects of dialysis. Alternatively it may relate to differences in the relative sensitivity of NP tests of attention and memory.

It is also possible that other aspects of the TX group's performance may have reduced the likelihood of finding NP differences in comparison to the dialysis group. Most of NP tests with the exception of non-verbal memory task are timed and involve motor activity. Slowness in execution might be related to other factors such as tremor, common in some TX patients. This is however unlikely as none of the TX recipients presented with visible evidence of tremor and no differences were found in the SDMT-O in which no manual activity is involved. In addition when comparisons (ANCOVAs not reported) were repeated controlling for concurrently reported symptoms no differences between dialysis and TX patients in other tests involving motor ability (GP-DOM; GP-NDOM; TMT-B; SDMT-W) were found.

Comparisons to TX were repeated separately for HD and PD patients. PD and TX patients performed comparably in all NP tests except for the memory tasks (RAVLT-T). More consistent differences in favour of transplantation were noted in relation to HD patients but only when compared to HD's pre-dialysis NP scores (T1), a time when NP functioning is at its worst across the dialysis cycle. This adds weight to study findings on the acute NP improvement for the HD group and highlights the importance of the timing of NP assessment when treatment comparisons are performed. Comparing HD patients on pre-dialysis NP scores would have led to a clear overestimation of the NP benefits of transplantation. A word of caution is however warranted. The HD group's second assessment (24-hours post-dialysis) would have included the effects of learning whereas the TX patients were assessed on only one occasion.

The data showed that when casemix differences are controlled for, dialysis and transplant patients have roughly equivalent cognitive functioning in tests of attention and psychomotor abilities except for memory, which contrasts with commonly held views that TX by improving the organ-system functioning and restoring kidney function should result in amelioration of NP functioning. These findings might be related to technological improvements of dialysis over recent years with resulting improved renal clearance. They may also be related to the characteristics of our dialysis sample, which consisted of clinically stable and adequately-dialysed patients. It is possible that more marked group NP differences would have emerged had study inclusion criteria been less strict. A prospective design assessing NP function before and after TX would overcome limitations related to sample selectivity and would provide a stronger test of the NP changes brought about by kidney TX.

The links between biochemical markers of renal function and NP performance in TX did not receive strong support in this dataset. Correlations, albeit in the predicted direction, were weak and inconsistent and were not replicated in the multiple regression analyses. The findings of the univariate analysis did suggest that immunosuppressive medication may adversely impact upon NP outcomes within the TX group (Tarter & Switala, 2000). Correlational analysis indicated that plasma levels of cyclosporin were inversely associated with NP scores although NP performance was equivalent between patients treated with cyclosporin and those on tacrolimus. One may speculate that the vasoconstricion properties of cyclosporin may be related to this finding but further

research is needed to examine the NP effects of these and the newer immunosuppressive agents such as sirolimus.

In addition systolic blood pressure correlated significantly with measures of psychomotor speed and attention in the univariate analysis but not in the multivariate analysis. Research on the relationship of blood pressure and cognitive functioning has not presented a clear picture with some studies finding a relationship and other not (Waldstein & Elias, 2001). The direction of the observed correlations in this study indicated that higher levels of systolic blood pressure were associated with less efficient cognitive functioning.

Regression models indicated that only age, education and ESRD severity predicted cognitive functioning post-transplantation. The first two variables have been commonly found to be associated with NP performance in non-patient samples (Lezak, 1995; Mitrushina *et al.*, 1999). Positive affect contributed significantly to the prediction of memory abilities in TX patients, which suggests that the induction and maintenance of positive mood somehow positively influences or enhances cognitive abilities and resources. The pathways through which positive emotions might impact upon NP outcomes are not known, but they are likely to occur though physiological mechanisms, as well as indirectly through motivational or psychological processes. The total variance explained was however small to moderate, suggesting that other factors other than the ones assessed in this study might have a stronger effect on NP outcomes post-transplantation and might be more important/powerful determinants of NP performance in TX patients.

The strong associations found between employment and NP performance in TX (and in dialysis) suggested that NP outcomes might impact upon other areas of functioning and wellbeing (Bremer *et al.*, 1997; Wolcott *et al.*, 1988a). Work rehabilitation is a major goal of most renal programmes and the extent to which patients return, or maintain employment while on dialysis or after a kidney transplant may be dependent on several factors: educational level, the specific work the individual engaged in prior to onset of dialysis, personality factors, public policy regarding eligibility for medical and state benefit schemes and perhaps treatment modality (Julius *et al.*, 1989a; Waiser *et al.*, 1998) The extent to which work rehabilitation or vocational function in ESRD might be

facilitated or prohibited by cognitive functioning as study findings suggest merits more investigation.

The directionality of these relationships in this study cannot be established. It is possible that employment is an outcome of efficient cognition or conversely that it acts as potent resilient factor for NP deterioration. Although there is some evidence for the adverse health implications of unemployment (Dooley *et al.*, 1996; Kasl & Jones, 2000; Ross. & Mirowsky, 1995), little is known as to whether employment opportunities and work performance are potentiated by efficient cognitive functioning or vice versa. In other words, whether cognitive abilities are preserved within the working environment as opposed to atrophying due to illness-related early and forced retirement from the working arena.

Section 3: Subjective Cognition

The study of NP outcomes in ESRD patients would not have been complete without considering patients' own appraisal of their cognitive abilities. This was termed subjective cognition.

Subjective cognition is linked to the notion of metacognition from the field of cognitive neurospychology. Metacognition refers to evaluation and control of one's cognition. It is also described as the knowledge or the cognitive processes that monitor or control cognition or the feeling/knowing states of human conscious cognition. Subjective cognition in the context of this work was broadly defined as self-reported cognitive functioning and evaluations and perceptions of cognitive abilities. It refers to 'thinking about thinking'.

Subjective cognition implies self-evaluation, self-monitoring and self-awareness and as such may also be related to other illness beliefs such as those in self-regulation theory. In that light subjective cognition may inform and complement patients' cognitive representation of their illness or treatment as it reflects beliefs about the cognitive impact of ESRD. It is also possible that subjective cognitive judgements may include 'separate' beliefs or perceptions of the nature of cognitive change: timeline (e.g. short-lived vs. long-standing), severity (e.g. perception of mild cognitive deterioration), consequences or control/cure perceptions. The measure used for the purposes of this

study did not allow us to tease out these issues and moreover used the treatment modality as a trigger point for patients to reflect upon changes.

It is not clear what people consider when judging their cognitive abilities. These evaluations might relate to the presence or absence of symptoms of cognitive performance (concrete manifestations of e.g. memory or attentional failures), their ability to do what they need to do (functioning on an intellectual level) or their general well-being and health. Contextual and situational cues as well as social prevalent schemas/norms may also exert some influence in the formation of these judgements (e.g. anticipated age-related cognitive decline; other patients with similar complaints), and in individuals' responses to them (e.g. seeking help).
Even though its relationship to psychological variables such as mood has been examined in this thesis, further work is needed to ascertain how these subjective cognitive evaluations feed into patients understanding of their condition, their subsequent coping behaviours and how they fit into and interact with patients' other self – perceptions as well as illness and treatment representations.

Another manner of examining the importance of subjective evaluation of cognitive abilities would be to examine these in relation to other generic assessments patients make of their illness and their HQoL. Subjective cognition evaluation may add to perceptions of illness burden and adversely affect outcomes such as adjustment and HQoL. Subjective cognitive functioning has also been considered as an additional dimension of QoL and relevant sub-scales are included in generic and disease-specific measures such as the SIP (Bergner *et al.*, 1981) and KDQoL (Hays *et al.*, 1994). This thesis examined the way in which these judgements related to HQoL (see Chapter 9).

For the purposes of this thesis, long-term and short-term appraisals were investigated. Patients were asked to consider how their cognitive abilities might have changed since treatment initiation (either dialysis or transplantation) and acutely from day-to-day (T1 to T2 assessment; dialysis patients only). This method on comparative judgements employed in this study is somewhat different to measures of cognitive complaints/difficulties used in other research. It was nevertheless considered more appropriate to use a comparative judgement, as the main focus of this work was acute intraindividual cognitive change.

3.1 Reports of subjective cognition in dialysis and TX

Taken together our findings indicate that patients could evaluate their cognitive abilities and had clear views on the long-term course of these abilities and their day-to-day variation.

This study indicated that compared to PD patients, who perceive little or no changes in their day-to-day cognitive functioning, a substantially larger number of HD patients report changes, namely improvement in their cognitive abilities from pre-to post-dialysis.

Long-term changes in cognitive abilities were also reported. A considerable number of dialysis patients perceived cognitive deterioration particularly with respect to memory and concentration since initiation of dialysis, in line with previous research (Brickman *et al.*, 1996). Memory complaints are common not just in the dialysis population but also in other patient groups (Klepstad *et al.*, 2002; Matotek *et al.*, 2001; Metzger & Denney, 2002; Newman *et al.*, 1989; Sullivan *et al.*, 2002) and in the general population (Comijs *et al.*, 2002) so the disease specificity of these findings is questionable. Dialysis modality was largely unrelated to reports of cognitive deterioration since treatment initiation. The only exception was concentration. A greater number of HD patients complained of deterioration in their concentration abilities compared to PD. This sole difference (significant only at $p < .05$) is more likely to be a chance finding rather than a true treatment effect.

An alternative and perhaps more plausible explanation would be that that casemix differences in time on RRT and on current dialysis modality are to account for this difference.

Firstly, the observed group difference in time on RRT, by definition implies that 'more' ageing has occurred for the HD group as more time has elapsed since treatment onset and the time of the assessment, hence more age-related cognitive decline should be anticipated for this group. This means that the reference point to base subjective cognition evaluations differs between HD and PD. This is a key issue as the subjective cognition measure used in this study in essence involved comparative judgements of cognitive abilities pre- and post- treatment onset. It stands to reason that for HD patients who have been in the RRT programme longer, their 'pre dialysis' functioning refers

back to a much younger age than that of PD patients who albeit of the same age, have been in the programme for significantly less time.
Finally, patients who have been on RRT for longer (i.e. HD group) have been exposed for longer on the non-specific accumulative adverse effects associated with chronic illness and associated treatment. These non-specific effects as well as some of the unavoidable complications of ESRD and associated treatment (such as hypertension) may only become manifest after some time, and these may in turn influence cognition and subjective reports of cognition.

There was great variability in perceptions of cognitive change (deterioration or improvement) among TX respondents. Although the majority of patients endorsed no change in their cognitive abilities since their transplant, the remainder of the sample had different views as to whether deterioration or improvement had occurred. Other than memory, which was the most frequently endorsed domain of deterioration, and clarity of thinking, which was the most frequently endorsed domain of improvement, a clear pattern of which cognitive domains were more likely to be perceived as worse or better after transplantation did not emerge.

Sociodemographic and medical factors may at least partly explain the diversity in TX patients' subjective cognitive evaluations. For instance, time since transplantation and time on dialysis prior to receiving the transplant (that varied greatly in the TX sample), were found to be associated with subjective cognition summary scores.
The associations between cognitive complaints and time elapsed since TX may be due to ageing, prolonged exposure to immunosuppressive medication with its resultant side-effects, or the response shifts in TX patients expectations with time. For instance, it may be that newly transplanted patients have different, i.e. lower expectations regarding restoration of cognitive abilities with TX. They may also be less likely or less inclined to notice/register or complain of cognitive difficulties early after a life-saving TX operation that brings about drastic improvement in their general health and physical functioning. Increased emotional well-being typically documented in recently transplanted patients might also explain these findings as mood has been shown to affect subjective cognition (Newman *et al.*, 1989).

Such psychological factors might also be driving the inverse associations between time on dialysis and reports of cognitive deterioration although mood indicators examined in

this study were not linearly associated with these two variables (time on TX and time on Dialysis). Notwithstanding, the diversity in patients' subjective reports demonstrates the extent to which post-transplantation experience (a dimension of which is subjective cognition) might differ from patient to patient and highlights the need to prospectively examine the development and course of cognitive reports post-transplantation.

3.2 NP performance and subjective cognition

It is important that there was little relation between objective NP testing and subjective cognition. Only a few significant associations were noted between absolute NP scores and complaints of long-term deterioration (most significant only at $p < .05$) but these were not consistent across cognitive domains nor in all tests of the same cognitive function and they also failed to emerge in the multiple regression analyses. Given these inconsistencies and the increased risk of type I error due to multiple testing, it is likely that the observed relationships are spurious.

Previous ESRD studies using similar self-report scales have also highlighted the lack of correspondence between self reports of cognitive functioning and objective NP scores (Brickman *et al.*, 1996). Similar findings have also been reported in different fields for other patient groups (Khatri *et al.*, 1999; Klepstad *et al.*, 2002; Kremer *et al.*, 2002; Mayou, 1986; Newman *et al.*, 1989). The lack of significant associations should not be interpreted as evident for the poor validity of patients' reports. Cognitive complaints may reflect a general state of feelings of diminished well-being and as such are critical in evaluating the impact of ESRD and treatments. They may also have implications for future cognitive functioning as one study on elderly general population has demonstrated that memory complaints predicted future memory performance (Jorm *et al.*, 2001).

It is also possible that other variables not measured in this study may mediate or moderate the relationship between objective and subjective cognition. For instance, individual exposure to cognitive demands in daily life may moderate the NP performance-complaint relationship in such a way that cognitive complaints are more likely to be reported by patients in 'high demand' than in 'low demand' situations (Gleissner *et al.*, 1998). Future studies should address this question.

3.3 Mood and subjective cognition

Our findings in conjunction with previous reports directly address the origin of reports of cognitive functioning, and suggest that they are not generally the result of brain dysfunction. The presumption of an organic aetiology is likely to lead to an inappropriate evaluation and treatment. Indeed, as measured by our extensive neuropsychological battery, objectively measured changes in cognitive functioning were not the cause of cognitive complaints in these patients. Thus the aetiology of cognitive complaints appears to be largely psychological.

Clinical experience further suggests that subjective cognitive complaint reports may have an alternative significance to that of objectively assessed cognitive functioning that warrants further investigation. For example subjective cognitive complaints are common symptoms of major depression (Diagnostic and Statistical Manual of Mental Disorders; DSM-IV 1994). Some empirical evidence exists on the relationship between perceptions of cognitive status and affect. Brickman *et al.* (1996) for instance found that affect and personality were more predictive of subjective cognitive complaints in haemodialysis patients than medical or neuropsychological factors. Similar findings have been reported in other medical populations (Comijs *et al.*, 2002; Khatri *et al.*, 1999; Moore *et al.*, 1997; Newman *et al.*, 1989; Ponds *et al.*, 2000; Tun *et al.*, 1987).

Study findings have provided equivocal support for the association between mood and subjective cognition. This hypothesis remained largely unsubstantiated in this study. Significant associations occurred with little consistency across measures (mood variables and cognitive domains as indexed by the SCS items) and across samples (dialysis and transplantation). For instance, analysis of the TX data failed to fully replicate the significant associations found in the dialysis sample between depression and reports of cognitive decline. Even within the dialysis sample mood measures were similarly unrelated to reports of acute cognitive improvement across the cycle of dialysis despite being associated with long-term subjective cognition.

Analyses indicated that affect was associated only with subjective ratings of concentration (in dialysis). Mood and anxiety however were unrelated to reports of cognitive improvement in other areas of subjective cognitions. Furthermore the observed associations appear to be at odds with previous findings. Study results indicated that perceptions of cognitive improvement in concentration abilities were

related to higher scores in both negative and positive mood indicators including anxiety, negative affect and positive affect at 24-hours post-dialysis. Higher affect whether positive or negative was associated with perceptions of improvement in concentration. The significant associations between concurrent negative mood and reports of cognitive improvements appear at first sight to be counterintuitive to study predictions and previous research findings. These warrant further discussion.

One explanation for these findings could be that patients with an anxious or negative mood might tend to focus more on monitoring, internal states and everyday functioning including cognitive abilities. They would hence, by being more introspective and more alert and vigilant to their internal state, become more likely to perceive acute changes such as improvements or less likely to dismiss a cognitive failure than others who do not have high levels of depressed and anxious mood. Numerous studies have indeed noted significant associations between affect and symptom reporting (Griffin *et al.*, 1999; Watson & Pennebaker, 1989) that provide indirect support for this explanation. An alternative explanation might be that perceptions of transient NP improvement might be causing more intense emotional responses both in terms of negative and positive affect. That is, perceiving fluctuating cognitive abilities, even in the form of day-to-day improvements might be more likely to lead to the development and maintenance of anxious and negative mood, than perceptions of stable cognitive abilities. As only a handful of HD patients ($n \leq 5$) felt a deterioration in a particular aspect of cognitive ability, group comparisons were in essence performed between patients who reported improvements and those who felt that their cognition was unaltered. Perceptions of undifferentiated or unchanged cognitive abilities across the dialysis cycle may be seen as desirable and reassuring to patients, whereas perceptions of acute improvement may provoke negative affect associated with the unreliability and inconsistency of cognitive functioning/abilities.

Methodological differences between the present and previous studies might also explain the inconsistent results. Most of these other studies have examined the objective scores of those reporting a deficit in an area of cognition. In the study of acute changes in subjective cognition, the analysis was based on a reported improvement. Subjective reports of cognitive deterioration may be more strongly associated with anxiety and depressed mood than their absence with an improvement. This may explain the lack of

significant association with the perception of cognitive performance in 8 of the 9 domains assessed.

In line with that argument, other study findings have consistently demonstrated significant associations between affect and reports of cognitive deterioration (Sawrie *et al.*, 1999). Dialysis patients who perceived that their cognitive abilities had deteriorated since dialysis onset had higher negative mood, e.g. depression and reported lower positive affect relative to patients who perceived either no change or improvement in their cognition. Regression analysis showed that depression was the only significant predictor of cognitive complaints in line with previous research (Sullivan *et al.*, 2002).

From a conceptual point of view, one could speculate that cognitive complaints and cognitive improvement may not necessarily be the opposite ends of the same dimension but rather independent aspects of subjective cognition similar to that between positive and negative affect which appear to represent distinct qualities of mood. Thus the previously reported findings of a significant association between depression and cognitive complaints or ratings of cognitive deterioration may not be generalisable to perceptions of improvements.

Section 3: Study limitations

There are a number of limitations of the present study of NP functioning and subjective cognition.

First, the dialysis sample in this study consisted of relatively healthy, clinically stable and well-dialysed patients. Consequently the results may not be generalisable to other dialysis samples. It is plausible that neuropsychological performance would be more compromised in patients whose delivered dialysis dose do not meet the minimum national standards.

A word of caution is warranted when using the term 'well or adequately dialysed' as used in this study. As is common practice we used urea kinetics to establish dialysis dose. It should be noted though that urea is only a marker solute and measures of haemodialysis adequacy such as Kt/V and URR are only surrogates for the clearance of other solutes. For example, even when appropriate minimum Kt/V or URR is routinely delivered, a patient may still be inadequately dialysed in terms of potassium removal, correction of acidosis, or failure to render the patients a sufficient protein/calorie intake to prevent malnutrition. Similarly an appropriate minimum Kt/V or URR may be routinely delivered but the duration of haemodialysis may be too short to remove an adequate volume of fluid to re-establish euvoleamia. The flux of other larger molecular solutes and membrane biocompatibility may be equally important issues but are beyond the scope of this work. The recruited dialysis patients were described as well dialysed based only on their Kt/V values.

Secondly, the study sample size limited comparative analyses to two or three way ANOVAs. Even though post-hoc power calculation indicated that the overall recruited sample size (i.e. 262) yielded a power of .88, this is qualified by the unequal sample sizes and relatively small samples for 3 subgroups: home HD; APD and LRD TX.

In the case of the last group, the particular sampling strategy employed for the recruitment of TX patients (TX patients were recruited opportunistically; i.e. based on clinic attendance during the study window) led to the over-representation of the CAD TX group as these are overrepresented in the clinic. An alternative strategy would have been to match the LRD TX patients to a comparative group of CAD patients. As the

primary hypothesis was to compare TX to the two dialysis groups it was decided to maximise the numbers in the TX group regardless of the source of their kidney.

Small sample sizes for the home HD and APD groups were unavoidable though as the overall number of patients established on these modalities in the participating units did not exceed 31. The small dialysis study sample did not allow a four group analysis to compare acute neuropsychological changes between all four dialysis modalities, namely hospital HD, home HD, CAPD and APD (post-hoc power calculation indicated that the sample of 145 patients yielded a power of .70 for medium effect size). Given that the procedures involved in these treatment are to varying degrees different, this is an issue warranting further investigation by future research. It is recommended that a sample of a minimum 180 patients (45 patients in each sub-group) would be necessary for a robust investigation of the effect of dialysis treatment on cognitive functioning (medium effect size = .25; power = .80)

Few other investigations have enlisted a larger number of dialysis and transplant patients when the focus was on NP performance. This study sample size is notably larger than most previous studies with the exception of an investigation by Yount *et al.* (1998). That study however presents methodological shortcomings (e.g. inadequate description of sample and assessment procedures, unspecified timing of the assessment, and the absence of an illness severity measure) that limit generalisability of its findings.

Finally, this study design did not allow us to determine long-term cognitive changes experienced by dialysis patients relative to controls. Although time spent on dialysis was unrelated with neuropsychological performance, it is plausible that cognitive function may deteriorate as a function of increasing time on dialysis (Baker *et al.*, 1989; Ventura *et al.*, 1990) and this may either be dependent or independent of dialysis modality. A well-designed prospective longitudinal trial of both PD and HD patients with adequate case-mix adjustment will help us to understand this complex issue better.

Given the associations of ESRD disease severity and diabetes with neuropsychological test scores in this study, it will be important to examine the effect of comorbid factors superimposed on chronic renal failure on cognitive functioning. In addition as depression is the most commonly encountered psychological problem in patients with ESRD (Finkelstein & Finkelstein, 1999; Sacks *et al.*, 1990; Wuerth *et al.*, 2001) its impact on NP outcomes deserves more attention in future research.

CHAPTER 8: PATIENTS' BELIEFS RESULTS

Section 1: Dialysis sample

1.1 Data analysis

The distribution of study variables was examined using Kolmorogov-Smirnov tests to ascertain whether the dataset was suitable for parametric analyses.

To assess the need to incorporate control variables in the comparisons between treatment groups, several preliminary analyses were conducted. Firstly, independent *t* tests, analyses of variance (for continuous data), chi square test or Fisher's exact as appropriate (for categorical data) were performed to compare the groups on sociodemographic and clinical characteristics. Secondly, univariate analysis (Pearson's correlation coefficients, ANOVAs or their non-parametric equivalents) was used to examine relationships between these variables and study outcomes (i.e. beliefs, HQoL). If any of these background variables differed significantly among dialysis groups (at $p < .05$) and were significantly associated with the outcome in question, they were statistically controlled for in subsequent comparative analyses.
Group differences in beliefs and SF-36 scores between the treatment groups were examined using ANCOVAs (covarying for casemix differences as described above), with *p* values uncorrected for multiple comparisons considered significant if $p < .05$. When appropriate Tukey's honestly significant difference (HSD) post-hoc tests were performed to explore significant effects in the omnibus ANCOVAs.

In contrast to the strong arguments stressing the importance of removing the effect of sociodemographic and other medical differences when comparing HQoL outcomes between different RRT groups, the need to control for group differences in biochemistry is questionable. The reason being that although biochemical parameters such as albumin and haemoglobin have been found to be associated with HQoL measures such as SF-36 scores (Lowrie *et al.*, 2000), their values may be directly related to aspects of the particular treatments (Xue *et al.*, 2002). Therefore, one may or may not wish to make

adjustments for them when contemplating possible HQoL differences between treatments. For the purposes of this study, the comparative analyses for HQoL data were run twice, with and without the inclusion of biochemical data.

The relationship between independent variables (sociodemographic, clinical, psychological, neuropsychological) and study outcomes (beliefs; HQoL) was explored by univariate and multivariate analysis. Univariate relationships were assessed using independent *t*-tests, ANOVAs, Pearson's correlations or where appropriate their non-parametric equivalents. Any obvious non-linear relationships were then sought by examining scatterplots of the individual dimension scores, summary scores and the independent variables. No non-linear relationships were detected so simple hierarchical multiple regression models were then constructed. All significant correlates identified from univariate analysis were included as independent variables in the regression models. These entered the regression equations in a specified order: (a) sociodemographics (b) clinical and (c) psychological variables. The 'additivity' effects were checked by evaluating the appropriate interaction terms in the last step of the regression. Missing values were replaced by means and the entry of variables into the model was determined using the 'stepwise' method with a p value for entry of .05 and for removal of 0.1. The stepwise method was preferred to avoid/address the problem of multicollinearity among variables (Tabachnick & Fidell, 1989).

To search for violations of necessary assumptions in multiple regression, normal plots of the residuals of the regression models were produced. Residuals were examined for normality and the absence of any trend in value (the prime assumption of multiple regression). In every model reported below the assumptions were met.

1.2 Sample characteristics

Sociodemographic and clinical characteristics of the four dialysis groups were described earlier (see Chapter 5; section 1.2).

Significant differences were noted between the four dialysis groups in the following variables: work status ($\chi^2(145) = 14.486, p = .002$), income ($\chi^2(145) = 13.474, p = .004$), time on RRT ($F(3, 141) = 32.809, p = .0001$), time on dialysis ($F(3, 141) = 13.099, p =$

.0001), prevalence of diabetes ($\chi^2(145) = 8.797$, $p = .003$) and albumin ($F(3, 140) = 18.455$, $p = .0001$). Subsequent Tukey's' post-hoc tests showed that home HD patients had been on RRT and on dialysis for longer than the other three groups. Albumin levels were lower in the CAPD group relative to patients on hospital HD ($p = .0001$), home HD ($p = .0001$) and APD ($p = .019$). Inspection of observed and expected frequencies indicated that there were more diabetic patients on CAPD compared to the other three treatments. A greater percentage of CAPD and hospital HD patients were not employed and in the lowest income bracket compared to APD and home HD patients.

1.3 Descriptives – beliefs in dialysis

Internal consistency, means and Standard deviations (*SD*) of the IPQ sub-scales, and the Illness and Treatment Effects Questionnaires (IEQ; TEQ) are presented in Table 8.1.

Table 8.1: Illness and Treatment Beliefs in Dialysis

			HD			PD		
		All DL	**Hospital**	**Home**	**All HD**	**CAPD**	**APD**	**All PD**
Identity	*a*	**.860**			**.861**			**.861**
	M	12.43	12.35	12.12	12.27	13.22	11.43	12.62
	SD	4.15	4.45	3.29	4.09	4.01	4.91	4.23
Timeline	*a*	**.664**			**.654**			**.670**
	M	4.344	4.34	4.54	4.40	4.21	4.42	4.28
	SD	.622	.575	.741	.636	.662	.455	.605
Control	*a*	**.651**			**.603**			**.713**
	M	3.10	3.13	3.07	3.11	2.98	3.29	3.09
	SD	.587	.537	.678	.582	.616	.510	.596
Conseq	*a*	**.708**			**.711**			**.706**
	M	3.52	3.51	3.51	3.51	3.61	3.38	3.53
	SD	.658	.642	.707	.659	.680	.609	.661
IEQ	*a*	**.887**			**.861**			**.906**
	M	74.19	73.15	70.96	72.44	82.64	63.52	76.18
	SD	27.46	26.69	25.35	26.12	28.28	26.72	28.98
TEQ	*a*	**.881**			**.848**			**.912**
	M	58.68	57.73	62.72	59.35	64.55	44.96	57.92
	SD	25.61	22.93	25.88	23.87	26.13	26.24	27.60

Note: DL = dialysis; HD = haemodialysis; PD = peritoneal dialysis; CAPD = continuous peritoneal dialysis; APD = automated peritoneal dialysis; Conseq = IPQ consequences; IEQ = illness intrusiveness; TEQ = treatment intrusiveness

Different IEQ and TEQ scores correspond to different levels of disruption/distress. Table 8.2 presents the occurrence of mild (24-55), average (56-88), moderate (89-120) or extreme (above 120) disruption across dialysis groups.

Dialysis' mean scores in the IEQ and TEQ measures signify moderate level of distress and disruption (scores 56-88) associated with illness and treatment (Greenberg & Peterson, 1997b).

APD treatment appeared to be the least intrusive or negatively perceived form of treatment. Group mean scores indicate that APD patients perceived the least disruption associated with their illness and treatment (lowest IEQ and TEQ scores) followed by hospital HD, home HD with CAPD last having the highest intrusiveness scores.

Table 8.2: Level of illness and treatment disruption in Dialysis

IEQ	***Minimal***	***Mild***	***Average***	***Moderate***	***Extreme***
	% (n)	***% (n)***	***% (n)***	***% (n)***	***% (n)***
HD	3.9% (3)	15.6% (12)	58.4% (45)	19.5% (15)	2.6% (2)
Hospital	3.8% (2)	15.4% (8)	55.8% (29)	21.2% (11)	3.8% (2)
Home	4% (1)	16% (4)	64% (16)	16% (4)	
PD	1.5% (1)	26.5% (18)	35.3% (24)	29.4% (20)	7.4% (5)
CAPD	2.2% (1)	17.8% (8)	33.3% (15)	37.8% (17)	8.9% (4)
APD		43.5% (10)	39.1% (9)	13% (3)	4.3% (1)
All DL	2.8% (4)	20.7% (30)	47.6% (69)	24.1% (35)	4.8% (7)
TEQ	***Minimal***	***Mild***	***Average***	***Moderate***	***Extreme***
	% (n)	***% (n)***	***% (n)***	***% (n)***	***% (n)***
HD	6.5% (5)	36.4% (28)	44.2% (34)	11.7% (9)	1.3% (1)
Hospital	5.8% (3)	38.5% (20)	46.2% (24)	7.7% (4)	1.9% (1)
Home	8% (2)	32% (8)	40% (10)	20% (5)	
PD	8.8% (6)	44.1% (30)	32.4% (22)	14.7% (10)	
CAPD	2.2% (1)	40% (18)	40% (18)	17.8% (8)	
APD	21.7% (5)	52.2% (12)	17.4% (4)	8.7% (2)	
All DL	7.6% (11)	40% (58)	38.6 (56)	13.1% (19)	0.7% (1)

Note: IEQ = illness intrusiveness; TEQ = treatment intrusiveness; HD = haemodialysis; PD = peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; DL = dialysis

The IPQ scores do not reflect an evaluative component to the same extent as IEQ and TEQ items and have no discriminative score range.

The percentage of patients scoring above the midpoint for the IPQ and BMQ sub-scales were hence computed (Table 8.3). This provides an indication of patients holding particularly strong beliefs about the construct being measured by each particular scale.

Table 8.3: Percentages of above midpoint IPQ scores in Dialysis

		HD			PD		
	All DL	**Hospital**	**Home**	**All HD**	**CAPD**	**APD**	**All PD**
Timeline	95.2% (138)	96.2 (50)	96% (24)	96.1% (74)	91.1% (41)	100% (23)	94.1% (62)
Control	51% (74)	48.1% (25)	44% (11)	46.8% (36)	46.7% (21)	73.9% (17)	55.9% (38)
Consequences	73.1% (106)	75% (39)	68% (17)	72.7% (56)	73.3% (12)	73.9% (17)	83.5% (50)

These figures reveal that dialysis patients view their condition as long term (chronic timeline beliefs) and as having significant consequences in their lives (n = 106, 73.1% having greater than midpoint scores).

There was a greater diversity in patients' scores in the control IPQ sub-scale, with only 51% (n = 74) of the patients scoring above midpoint (indicative of stronger beliefs that the condition is controllable).

The obtained mean IPQ scores point to the same conclusions in that timeline beliefs were stronger whereas the mean scores in the consequences and control beliefs being in the range of 3 out of 5 (i.e. uncertain), would rather reflect patients' uncertainty regarding the controllability of their condition and the extent of illness-related consequences in their life.

To evaluate symptom reports two symptom scores were obtained:

(a) the number of symptoms patients associated with their illness (consistent with previous work using the IPQ)

(b) the frequency of reports of each symptom by patients. The mean scores for each symptom and the number of patients endorsing that symptom as part of their kidney condition are shown in Table 8.4.

Table 8.4: Symptom scores in Dialysis: *Means*, *SD*s and Percentages

	All dialysis			HD			PD		
	M	*SD*	%	*M*	*SD*	%	*M*	*SD*	%
Fatigue	2.79	.914	**92.4**	2.70	.919	**92.2**	2.88	.907	**92.6**
Muscle cramps	2.38	.810	**88.9**	2.17	.719	**85.5**	2.60	.849	**92.6**
Loss of strength	2.48	1.028	**81.4**	2.42	.978	**84.4**	2.56	1.098	**77.9**
Pain	2.19	.876	**78.6**	2.08	.839	**75.3**	2.32	.905	**82.4**
Itching	2.14	.940	**72.4**	2.04	.924	**67.5**	2.25	.952	**77.9**
Lack of sex drive	2.44	1.178	**71.7**	2.35	1.189	**67.5**	2.54	1.165	**76.5**
Stiff joints	2.19	1.014	**70.3**	2.36	1.05	**76.6**	1.99	.938	**63.2**
Poor alertness and concentration	1.94	.818	**69.7**	1.92	.807	**70.1**	1.96	.836	**69.1**
Breathlessness	1.99	.837	**69.7**	1.86	.756	**64.9**	2.15	.902	**75**
Nausea	1.83	.670	**67.6**	1.79	.656	**66.2**	1.87	.689	**69.1**
Restless legs	2.05	.956	**66.7**	1.87	.885	**60.5**	2.25	.998	**73.5**
Sleep difficulties	2.11	1.028	**65.5**	1.94	1.004	**57.1**	2.31	1.026	**75**
Upset stomach	1.81	.754	**62.8**	1.78	.788	**58.4**	1.85	.718	**67.6**
Dizziness	1.69	.640	**59.3**	1.66	.620	**58.4**	1.72	.666	**60.3**
Headaches	1.73	.729	**58.6**	1.82	.773	**63.6**	1.63	.667	**52.9**
Loss of appetite	1.86	.918	**57.2**	1.68	.850	**49.5**	2.07	.951	**66.2**
Weight loss	1.57	.779	**43.4**	1.62	.779	**48.1**	1.51	.782	**38.2**
Sore eyes	1.48	.698	**37.9**	1.56	.734	**44.2**	1.40	.650	**30.9**
Hair loss	1.45	.865	**26.9**	1.49	.881	**31.2**	1.40	.849	**22.1**

The scores for the causal sub-scales were treated separately. Participants that either *'strongly agreed'* or *'agreed'* that the factor was a causal contributor to their kidney condition were placed in one group labelled 'factor was a cause' and those who either *'strongly disagreed'* or *'disagreed'* formed the second group labelled 'factor was not a cause'.

Results showed that patients endorsed few causal beliefs (*mean* = 1.68, *SD* = 1.07). External factors such as 'chance' and 'poor medical care' were the most frequently cited causes of the kidney condition, endorsed by 85.2% (n = 109) and 26.2% (n = 38) of the dialysis patients respectively. A slightly smaller percentage of patients (24.1%, n = 35) believed that their condition was hereditary.

Only a fraction of dialysis patients attributed their illness to their own behaviour (n = 15, 10.4%) or to other people (n = 16, 11.1%). There was little spread in patients' responses in the remaining six causal items. They were therefore excluded from subsequent analyses

1.4 Intercorrelations between illness and treatment beliefs

Significant moderate-to-strong sized positive correlations were found between beliefs regarding the effect of illness and treatment, namely IPQ consequences, illness intrusiveness and treatment intrusiveness. Correlation coefficients ranged from r = .52 to r = .73 (see Table 8.5). Strong control beliefs were negatively correlated with illness and treatment intrusiveness (r = -.45, p = .0001; r = -.37, p = .0001 respectively), consequences (r = -.36, p = .0001), and identity (r_s = -.29, p = .0001).
Correlations between identity and IEQ, TEQ, and other IPQ scores were in the opposite direction, with more symptoms being associated with lower control beliefs (r_s = -.29, p = .0001), more consequences (r_s = .42, p = .0001) and higher illness and treatment intrusiveness (r_s = .66, p = .0001 and r_s = .47, p = .0001 respectively).

Table 8.5: Intercorrelations between dialysis patients' beliefs

	TEQ	IEQ	Identity†	Timeline†	Control	Conseq
TEQ						
IEQ	.734****					
Identity†	.471****	.662****				
Timeline†	.031	.179*	.114			
Control	-.374****	-.455****	-.294****	-.105		
Conseq	.522****	.555****	.421*****	.115	-.364****	

Note: TEQ = treatment intrusiveness; IEQ = illness intrusiveness; Conseq = IPQ consequences
† = Spearman's correlations
* p <.05. ** p <.01. *** p <.001. **** p = .0001

Independent sample t-tests showed several significant associations between causal beliefs and other cognitions. Patients attributing their disease to poor medical care reported significantly more illness consequences (t(143) = -2.366, p = .019) and more illness related disruption (t(143) = -2.315, p =.022) than patients not endorsing such causal beliefs. Similar differences were noted between patients blaming their illness on 'their own behaviour' compared to those who did not. The 'self-blame' group had stronger identity beliefs (U = 659, p = .04), and perceived more consequences (t(143) = -2.12, p = .036) and illness intrusiveness (t(143), p = -2.382, p = .019). Finally patients regarding their illness as hereditary reported more symptoms as part of their disease (U = 1473.5, p =.036).

1.5 Group comparisons: Dialysis treatments

To examine whether illness and treatment beliefs differ between dialysis groups a series of ANCOVAs were performed comparing (a) HD to PD patients and (b) all four dialysis groups (Hospital HD, Home HD, CAPD and APD). Only the casemix differences that were significantly associated with the outcome in question were used as covariates in these analyses (see Table 8.6).

Table 8.6: The relationship of casemix differences and beliefs in dialysis

	IEQ	TEQ	IPQ Identity	IPQ Timeline	IPQ Control	IPQ Conseq	IPQ Causal
Gender	-	-	-	-	-	-	-
Work	+	+	+	+	+	+	-
Income	-	-	-	-	+	-	-
Diabetes	+	-	-	-	+	-	+
DL duration	-	-	-	-	-	-	
RRT duration	-	-	+	+	-	-	
Primary kidney disease diagnosis	-	-	-	-	-	-	+

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

1.5.a HD vs. PD

ANCOVAs HD vs. PD comparisons revealed no significant differences in patients' beliefs. Both patient groups held similar beliefs and representations regarding their illness and their treatment.

Chi-square analysis revealed that PD patients were more likely than HD patients to attribute their illness to 'poor medical care' ($\chi^2(145) = 7.381$, $p = .007$) and 'their own behaviour' ($\chi^2(145) = 4.695$, $p = .03$). These differences might reflect casemix differences in prevalence of diabetes, which could not be controlled for in Chi-square analyses. Perhaps one would expect attributions of self-blame and poor medical care in the PD group as more PD patients had diabetes and had developed ESRD as a complication of poor diabetic glucose control. Significant associations were indeed found between prevalence of diabetes (and IDDM as primary kidney disease diagnosis) and attributions of self-blame ($\chi^2(145) = 7.983$, $p = .005$) but not with 'poor medical care' causal beliefs.

1.5.b Four dialysis group comparisons

Next, differences in beliefs between all four dialysis groups (hospital HD; home HD; CAPD; APD) were examined. A series of one way ANCOVAs were performed followed by Tukey's post-hoc tests if the main treatment effect was significant.
An inherent limitation of SPSS is that it does not allow the inclusion of covariates when using the function of one-way ANOVAs with post-hoc tests. This presented a problem as some of the casemix differences were also significantly associated with some of the DVs (see Table 8.6 above), thereby indicating that their effect should be controlled for in all planned group comparisons including post-hoc tests.

To partial out the effect of these casemix differences in post-hoc comparisons, residualised scores were obtained for IEQ, TEQ, IPQ control, IPQ timeline and IPQ symptoms. These were calculated by regressing each of the beliefs to casemix differences (see Table 8.6 above). The resulting residualised scores represented the actual value of the DV minus the value predicted by the regression equation.
These reflected IEQ scores minus the effect of diabetes and work status, TEQ scores minus the effect of work, IPQ control scores minus the effect of diabetes, work and income, and finally timeline and identity scores minus the effect of RRT duration and work status. These scores were then used in the post-hoc group comparisons (if omnibus ANCOVA was significant).

Analyses showed only a significant group difference, namely on treatment intrusiveness ($F(3, 141) = 3.382, p = .020$). The group effect on IPQ identity and IEQ approached but did not reach significance ($F(4, 140) = 2.571, p = .057$ and $F(4, 140) = 2.345, p = .076$).

Post-hoc comparisons indicated significant TEQ differences only between the two PD groups, with APD patients perceiving significantly less disruption associated with their treatment (mean difference I-J/t = 19.599, $p = .014$) relative to patients on CAPD. There were no other significant differences among the four dialysis groups.

The mean difference between APD and Home HD patients' TEQ scores approached but did not reach significance (mean difference I-J/t = 17.76, $p = .071$). There was a tendency for home HD patients to perceive more treatment disruption compared to APD patients. The relatively low numbers of APD and home HD patients assessed might

have undermined the power to detect significant differences between the two home-based treatments.

Chi-square analysis showed only one significant difference in causal beliefs among the four dialysis groups. Significantly more CAPD patients believed that their illness was caused by poor medical care compared to the other three groups ($\chi^2(145) = 7.908$, $p = .048$). The extent to which this reflects casemix differences cannot be determined, as statistical adjustments are not possible in chi-square analysis.

1.6 Factors associated with beliefs in dialysis

1.6.a Sociodemographic and medical variables

Age was negatively correlated with control beliefs ($r = -.26$, $p = .002$). Education correlated with both control ($r_s = .22$, $p = .008$) and timeline beliefs ($r_s = .25$, $p = .003$), with more years of education being associated with stronger beliefs that the kidney condition is chronic, yet controllable (see Table 8.7).

ANOVAs indicated that perceptions of illness ($F(1, 143) = 5.09$, $p = .026$) and treatment disruption ($F(1, 143) = 8.94$, $p = .003$), identity ($F(1, 143) = 4.76$, $p = .031$), control ($F(1, 143) = 18.21$, $p = .0001$), and timeline beliefs ($F(1, 143) = 4.85$, $p = .029$) differed significantly between employed and non-employed patients. The differences in treatment perceptions ($F(3, 141) = 4.86$, $p = .029$), control ($F(3, 141) = 5.33$, $p = .022$), and timeline beliefs ($F(3, 141) = 4.65$, $p = .032$) remained significant after adjustments for age and ESRD-SI.

Control beliefs also differed among patients on different income brackets with patients in the higher income brackets (> £30,000) reporting stronger beliefs in the controllability of their condition compared to patients in the lowest income group (< £10,000) ($F(1, 143) = 7.36$, $p = .007$; $F(3, 141) = 9.59$, $p = .02$ after age , ESRD-SI adjustments).

Table 8.7: Correlations between beliefs and sociodemographic and clinical variables in Dialysis

	TEQ	IEQ	Identity†	Timeline†	Control	Conseq
Age	-.041	.157	.013	-.078	-.256**	-.054
Education†	-.075	-.054	-.048	.248**	.22**	-.102
ESRD SI†	.242**	.332****	.223**	-.042	-.414****	.132
DL time†	.046	.020	.166*	.116	.007	.103
RRT time†	.068	.068	.204*	.216**	.020	.129
Kt/V	-.130	-.201*	-.045	.035	.281***	-.264**

Note: TEQ = treatment intrusiveness; IEQ = illness intrusiveness; Conseq = consequences; ESRD = end-stage renal disease severity index; DL time = time on dialysis; RRT time = time on renal replacement therapies

† = Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001

Medical variables were also associated with patients' beliefs. Higher ESRD severity was associated with more 'negative' perceptions, such as higher illness intrusiveness (r_s = 33, p < .000), higher treatment intrusiveness (r_s = 24, p = .003), more symptoms (r_s = .22, p = .007), and lower perceptions of control (r_s = -.41, p = .0001). ESRD severity was also higher in patients reporting particular causal attributions vs. those who did not. This was significant with regard to all causal attributions (i.e. the four beliefs with adequate response spread to allow for comparative analyses), i.e. 'poor medical care' (U = 1545, p = .028), 'chance' (U = 1406, p = .011), 'own behaviour' (U = 589, p = .012) and 'other people' (U = 640, p =.013) except 'hereditary' causal beliefs.

Diabetic status was also significantly associated with illness perceptions. Patients with diabetes, in particular, reported significantly more illness-related disruption (F(1, 143) = 4.302, p = .04) and believed less strongly that their condition is amenable to control (F(1, 143) = 7.164, p = .008). Diabetic status was associated with causal attributions of self-blame (χ^2(145) = 7.983, p = .005). There was also a tendency for patients with diabetes to report more symptoms but this did not reach significance levels (F(1, 143) = 3.741, p = .055).

Significant, albeit weak correlations were also noted between perceived symptoms and RRT duration (r_s = .20, p = .014), and current dialysis duration (r_s = .17, p = .046). Longer time on RRT correlated significantly with stronger chronic timeline beliefs (r_s =

.18, p = .029). Higher dialysis adequacy was significantly associated with stronger control (r = .281, p = .001), lower consequences beliefs (r = -.264, p = .003), and higher IEQ scores (r = -.201, p = .023).

Causal beliefs were associated with primary kidney disease diagnosis. Patients who developed ESRD due to diabetes were more likely to report attributions of self-blame ($\chi^2(145) = 5.552$, p = .018) and those who developed ESRD due to Adult Polycystic Kidney disease were more likely to report hereditary causal beliefs ($\chi^2(145) = 20.553$, p = .0001).

1.6.b Mood measures

Mood measures were associated with patients' illness and treatment beliefs (see Table 8.8). The general pattern of results indicated that higher levels of depression, anxiety, and negative affect are associated with more 'negative' illness and treatment perceptions such as lower control beliefs, more symptoms and higher reports of illness and treatment intrusiveness.

In contrast positive affect appears to be associated with more 'positive' illness and treatment beliefs.

Table 8.8: Correlations between mood measures and beliefs in Dialysis

	TEQ	IEQ	Identity†	Timeline†	Control	Conseq
BDI	.558****	.603****	.481****	.076	-.458****	.503****
CDI	.528****	.54****	.402****	.139	-.424****	.482****
STAI	.388****	.455****	.315****	.003	-.329****	.341****
PNS-PA	-.240**	-.329****	-.205*	.139	.465****	-.249**
PNS-NA†	.445****	.420****	.338****	-.044	-.370****	.389****

Note: CDI = cognitive depression index; STAI = Spielberger state trait anxiety inventory; PNS-PA = PANAS positive affect; PNS-NA = PANAS negative affect; TEQ = treatment effects questionnaire; IEQ = illness effects questionnaire; Conseq = illness consequences

† = Spearman's correlations

p <.05. ** p <.01. *** p <.001. **** p <.0001

1.6.c Cognitive functioning

The next analysis addressed the question of whether the differences in illness and treatment beliefs might be associated with differences in other illness-related variables that have been hypothesised to contribute to the burden of ESRD. NP functioning was hence investigated.

First linear relationships were explored by means of correlations. Three summary NP scores were used:

(1) the mean of overall NP functioning at T1 and T2 (NP-TO).

(2) the mean of number NP impairments at T1 and T2 (number of NP tests in which patients' scores fell more than 1 *SD* below their age respective norms) (NP-Norm)

(3) A summary score reflecting acute change in NP functioning. The latter was expressed as the difference in overall NP functioning between T1 and T2 (NP change). The higher change scores reflect the greater the improvement in NP functioning across the two assessments

Findings indicated that the less efficient the cognitive functioning the more negative patients' illness and treatment beliefs and perceptions.

Results for instance showed significant correlations between average NP performance (NP-TO) and timeline and control beliefs. The more efficient the cognitive functioning the stronger patients believed that their condition is amenable to control ($r = .344$, $p = .0001$) and is of a more chronic nature ($r_s = .183$, $p = .035$). Likewise the more NP impairments observed across the assessed areas of cognition (NP-Norm), the lower the control ($r_s = -.326$, $p = .0001$) and timeline beliefs ($r_s = -.202$, $p = .015$), and the higher patients' perceptions regarding treatment disruptiveness/burden ($r_s = .177$, $p = .034$).

Some significant associations were found between causal beliefs and cognitive functioning. Patients reporting ' poor medical care' causal beliefs had less efficient cognitive functioning (NP-TO; $t(137) = 2.593$, $p = .011$) and more NP impairments (NP-Norm; $U = 1423$, $p = .006$) compared to patients not expressing such causal attributions. Number of NP impairments was also higher in patients blaming other people for their illness ($U = 644.5$, $p = .014$) compared to those who did not hold such causal beliefs.

The composite score of acute changes in NP performance was unrelated to illness and treatment perceptions.

Section 2: Transplantation sample

2.1 Descriptives – beliefs

Internal consistency, means and Standard deviations (*SD*s) of the IPQ sub-scales, the Illness and Treatment Effects Questionnaires (IEQ; TEQ) and the Beliefs about Medicines Questionnaire (BMQ) are presented in Table 8.9.

Table 8.9: Illness and Treatment beliefs in Transplantation

		All TX	CAD	LRD
Identity[a]	α	**.879**		
	M	9.11	9.52	7.48
	Sd	4.41	4.31	4.51
Identity-m[b]	α	**.781**		
	M	8.83	9.22	8.83
	Sd	4.51	4.19	4.63
Identity-tx[c]	α	**.906**		
	M	18.25	18.74	16.30
	Sd	8.04	7.88	8.51
Timeline	α	**.743**		
	M	4.05	4.05	4.02
	Sd	.737	.744	.725
Control	α	**.720**		
	M	3.37	3.35	3.47
	Sd	.600	.625	.481
Consequences	α	**.731**		
	M	.330	3.29	3.31
	Sd	.655	.672	.595
IEQ	α	**.917**		
	M	36.70	39.19	28
	Sd	27.19	28.38	21.58
TEQ	α	**.892**		
	M	29.29	29.48	28.67
	Sd	22.35	22.69	21.58
BMQ necessity	α	**.788**		
	M	4.35	4.32	2.40
	Sd	.719	.571	.775
BMQ concerns	α	**.677**		
	M	2.41	4.51	2.44
	Sd	.719	.561	.569

[a] = Identity score based on 19 items used for dialysis (IPQ core items and renal-specific)

[b] = score based on the 22 symptoms related to side effects of immunosuppressive medication

[c] = identity score based on the 41 items used for TX patients (IPQ core items, renal specific and TX immunosuppression side effects)

Mean scores in the IEQ (*mean* = 36.7; *SD* = 27.19) and the TEQ (*mean* = 29.3; *SD* = 22.36) indicate mild distress associated with perceived disruption caused by illness or treatment compared to other medical patients (Greenberg & Peterson, 1997b). Transplant patients, as a group perceived few areas in their life as being affected by their condition and their treatment. Distribution of scores according to severity of perceived disruption also showed that a large percentage of TX patients had scores lower than 24, signifying minimal disruption/distress due to illness or treatment (see Table 8.10).

Table 8.10: Level of illness and treatment disruption in Transplantation

IEQ	***Minimal (below 24)***	***Mild (24-55)***	***Average (56-88)***	***Moderate (89-120)***	***Extreme (above 120)***
	% (n)	***% (n)***	***% (n)***	***% (n)***	***% (n)***
CAD	32.1% (27)	47.6% (40)	11.9% (10)	8.3% (7)	
LRD	54.2% (13)	37.5% (9)	8.3% (2)		
Total TX	37% (40)	45.4 (49)	11.1% (12)	6.5 (7)	
TEQ	***Minimal***	***Mild***	***Average***	***Moderate***	***Extreme***
	% (n)	***% (n)***	***% (n)***	***% (n)***	***% (n)***
CAD	42.9% (36)	42.9% (36)	13.1% (11)	1.1 (1)	
LRD	54.2% (13)	33.3% (8)	12.5% (3)		
Total TX	45.4% (49)	40.7(44)	13% (14)	.09% (1)	

Note: IEQ = illness intrusiveness; TEQ = treatment intrusiveness; CAD = cadaver transplant patients; LRD = living related donor transplant patients; TX = transplant patients

Inspection of mean IPQ scores (see Table 8.9) indicate that on average TX patients believed strongly that their condition is likely to be chronic as opposed to acute (n = 91; 88.3% had greater than midpoint scores) and that it is likely to be amenable to control or cure (n = 73; 70.9 % had greater than midpoint scores). Mean scores on the 'consequences' IPQ component also suggest that patients as a whole tended to agree that their condition has had significant consequences in their life (n = 61; 59.2% had greater than midpoint scores).

The most frequently cited causes of their condition were 'chance' endorsed by 62.5% (n = 64) of TX recipients, 'heredity' by 23.1% (n = 24), and 'poor medical care' reported by 22.1% (n = 23) of the participants. A lower percentage attributed their condition to 'stress' (16.3%, n = 17) and 'germ/virus' (15.4%, n = 16). The remaining causal items

were dropped from subsequent analyses due to insufficient numbers endorsing the causes.

Transplantation is also accompanied by a variable symptomatology. For the assessment of symptoms in TX patients, an extended questionnaire including generic, renal-specific and transplantation-specific symptoms was used.

Three symptom scores were hence calculated:

- one score based on the 19-items also used for dialysis (identity; including IPQ identity core items and some renal-specific symptoms). This was used for comparisons with dialysis patients
- a score referring to immunosuppressive medication side effects (identity-m; 22 items)
- a total symptom score including all 41 items (identity-tx). This was used in all subsequent analyses involving only TX patients only, unless stated otherwise or comparisons with dialysis patients were performed.

Inspection of total symptom scores (identity-tx) indicates that TX recipients reported a wide range of generic, and 'transplantation or renal specific' symptoms (range 1–38 out a possible score of 41).
With regard to generic symptoms, the majority of them reported fatigue (n = 90, 79.6%), breathlessness (n = 77, 68.1%), and stiff joints (n = 68, 60.7%).
With regard to 'transplantation-specific' symptoms (i.e. symptoms manifested as the result of immunosuppressive medication), weight gain, increased appetite were the most frequently reported side-effects endorsed by 64.3% (n = 72) and 60.7% (n = 68) of the TX recipients respectively, followed by tremor (n = 65; 58.6%) and excessive hair growth (n = 51; 45.1%). Finally, infections were also frequently experienced by TX recipients (n = 69; 61.1%).

Mean BMQ scores suggest that transplant patients expressed very strong beliefs in the necessity of immunosuppressive medication (n = 105; 98.1% of the TX participants had greater than midpoint scores) and that they were unconcerned about the harmful potential of their immunosuppressive drug regime (n =93; 85.3% had equal or lower than midpoint scores).

2.2 Comparisons - CAD vs. LRD TX patients

ANCOVAs were conducted to investigate the effect of transplant type on the patients' beliefs. Casemix differences significantly associated with the outcome in question were used as covariates (see Table 8.11).

Table 8.11: The relationship between casemix differences and beliefs in Transplantation

	BMQ n	BMQ c	IEQ	TEQ	IPQ Identity-tx	IPQ Timeline	IPQ Control	IPQ Conseq
Age	-	-	-	-	-	-	+	-
Education	-	-	-	-	+	-	-	-
Work	-	-	+	+	+	-	+	-
Income	-	-	-	-	-	+	-	-
ESRD-SI	-	-	+	+	+	-	+	-
RRT duration	-	-	-	-	-	-	+	-
DL duration	-	-	-	-	-	-	-	-

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

Note: BMQ-n = beliefs about necessity of medication; BMQ-c = concerns about medication; IEQ = illness intrusiveness; TEQ = treatment intrusiveness; ESRD-SI = end stage renal disease severity index; RRT = renal replacement therapy; DL = dialysis

Group comparisons (ANCOVAs) indicated no significant differences between the two transplant groups in any of the illness or treatment beliefs. Likewise chi-square analysis showed no significant associations between type of transplant and causal beliefs. LRD and CAD transplant recipients were hence collapsed to form one group (i.e. combined transplant) in subsequent analyses.

2.3 Intercorrelations between illness and treatment beliefs

Significant associations were noted between illness and treatment beliefs (see Table 8.12). The strongest correlation was between patients' perceptions of illness and treatment intrusiveness ($r_s = .815$, $p = .0001$).

Illness disruption was also significantly associated with all IPQ components: identity-tx (total symptom score; $r = .52$, $p = .0001$), identity-m (i.e. medication side-effects; $r = .46$, $p = .0001$), consequences ($r = .63$, $p = .0001$), control ($r = -.32$, $p = .001$), timeline ($r = .28$, $p = .005$), and concerns regarding medication ($r = .41$, $p = .0001$). Perceptions

of treatment disruption were similarly associated with all these beliefs albeit correlation coefficients were lower than those observed for illness disruption.

Table 8.12: Correlations between illness and treatment beliefs in Transplantation

	Ident-tx	Ident-m	Timel	Conseq	Control	IEQ	TEQ†	BMQ-c
Ident-m	.925 ****							
Timel	.050	.028						
Conseq	.329 ****	.271 ***	.393 ****					
Control	.05	.028	-.35 ****	-.224*				
IEQ	.522 ****	.457 ****	.277 ***	.635 ****	-.318 ***			
TEQ†	.406 ****	.405 ****	.234*	.538 ****	-.219*	.815 ****		
BMQ-c	.383 ****	.429 ****	-.033	.288***	-.167	.407 ****	.413 ****	
BMQ-n †	-.016	-.019	.308***	.273***	-.002	.110	-.033	-.249**

Note: Ident-tx = extended 42 item version of identity sub-scale (generic, renal and transplant specific symptoms; Ident-m = immunosuppressive medication side effects (23 items); timel = timeline IPQ sub-scale; conseq = consequences IPQ sub-scale; IEQ = illness effects questionnaire; TEQ = treatment effects questionnaire; BMQ-c = medication concerns sub-scale of the beliefs about your medicines questionnaire; BMQ-n = medication necessity sub-scale of the beliefs about your medicines questionnaire

† Spearman's correlations

* p < .05. ** p < .01. *** p <.001. **** p <.0001

Correlational analysis on the IPQ data revealed that timeline and perceived consequences correlated significantly with all other IPQ sub-scales as well as illness and treatment disruption and beliefs regarding medication. Control beliefs were negatively correlated with timeline, consequences and perceptions of illness and treatment intrusiveness.

Finally, beliefs regarding medication were found to be associated with illness beliefs. Concerns regarding medication side-effects was associated with symptom experience (total 41-item symptom score and TX medication-specific 22-item symptom score). Correlation coefficients were higher for the TX specific symptoms as expected with

greater concerns regarding immunosupression side-effects being associated with reports of more TX medication-specific symptoms.

Perceptions of the impact of illness and treatment as expressed by IPQ consequences, IEQ and TEQ scores also correlated with 'concerns' about the effects/harmful potential of immunosuppressive medication. Negative correlations were found between 'necessity' beliefs and 'side-effect concerns' beliefs ($r_s = -.25$, $p = .01$).

The associations between causal attributions and other beliefs were examined in a series of independent group *t*-tests or Mann-Whitney tests (as appropriate) comparing patients endorsing or not 'chance', 'hereditary', 'poor medical care', 'germ/virus' and 'stress'. Between groups comparisons indicated only one significant difference. Patients attributing their conditions to 'chance' had stronger medication necessity beliefs (*mean* = 22.19, *SD* = 2.64) than patients not endorsing chance as a cause for their condition (*mean* = 20.08, *SD* = 3; U = 903.5; $p = .019$).

2.4 Factors associated with beliefs

2.4.a Sociodemographic and medical variables

Significant associations were found between patients' illness and treatment beliefs and several sociodemographic and medical factors (see Table 8.13).

With respect to sociodemographic variables, only a few significant associations were found, with little consistency across the variables.

Age was negatively associated only with control perceptions and gender with medication concerns. Female transplant recipients believed more strongly in the harmful potential effect of immunosuppressive medication (*mean* = 12.98, *SD* = 3.32) relative to male TX patients (*mean* = 11.38, *SD* = 3.66; t(107) = -2.314, $p = .023$).

Education was negatively associated with symptom experience both in terms of overall generic and renal symptomatology as well as symptoms experienced as medication side effects.

Table 8.13: Correlations between sociodemographic, clinical variables and beliefs in Transplantation

	Iden-tx	Iden-m	Timel	Conseq	Control	IEQ	TEQ†	Bmq-c	Bmq-n †
Age	.158	.025	.058	-.063	-.296 **	.065	.108	-.007	.000
Educat†	-.346 ****	-.256 **	.118	.028	.194	-.168	-.102	-.156	.110
Esrd-SI†	.217*	.111	.134	.165	-.286 **	.326 ***	.269 ***	.014	-.017
GFR	-.374 ****	-.320 ***	.034	-.149	.247*	-.438 ****	-.267 ***	-.098	-.048
RRT dr†	.023	-.049	.079	.028	-.227 **	.058	.015	-.091	.065
TX dr†	.121	.086	.212*	.108	-.294 **	.036	.086	-.039	.107
DL dr†	.158	.024	.085	.006	.032	.045	-.005	-.074	-.002

Note: Ident-tx = extended 42 item version of identity sub-scale (generic, renal and transplant specific symptoms; Ident-m = immunosuppressive medication side-effects (23 items); timel = timeline IPQ sub-scale; conseq = consequences IPQ sub-scale; IEQ = illness effects questionnaire; TEQ = treatment effects questionnaire; BMQ-c = medication concerns sub-scale of the beliefs about your medicines questionnaire; BMQ-n = medication necessity sub-scale of the beliefs about your medicines questionnaire ; Educat = educational level; Esrd-SI = end stage renal disease severity index; GFR = glomerular filtration rate; RRT dr = renal replacement therapy duration; TX dr = transplant duration; DL dr = dialysis duration;

† = Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001

Illness and treatment beliefs differed between employed vs. non employed TX recipients. Between groups comparisons revealed that employed patients reported less symptoms (total 41 item score; $F(1, 110) = 6.005$, $p = .016$), illness disruption ($F(1, 106) = 6.954$, $p = .01$) and treatment effects ($F(1, 106) = 7.318$, $p = .008$) and had stronger control beliefs ($F(1, 101) = 5.869$, $p = .017$) compared to non-employed patients. These differences bar IPQ identity-tx (41 item TX extended symptom checklist) remained significant even after the effects of age and ESRD severity were taken into account by means of ANCOVAs.

Clinical risk indicators and medical factors were associated with more negative treatment and illness perceptions (see Table 8.13).

Higher ESRD severity correlated significantly with lower control beliefs (r_s = -.29, p = .003), more symptoms (identity-tx; r_s = .22, p = .021), higher perceptions of illness intrusiveness (r_s = .33, p = .001), and higher perceptions of treatment intrusiveness (r_s = .27, p = .005). With respect to particular comorbid conditions, ANOVA comparisons showed that TX patients suffering from ischaemic heart disease reported lower perceptions of control than patients with no such diagnosis (F(1, 101) = 5.416, p = .022).

Higher Glomerular Filtration Rate, a measure of clearance achieved by the transplanted kidney (with higher scores signifying more efficient functioning) was associated with higher control beliefs (r = .25, p = .013), less symptoms (r = -.37, p = .0001) and less perceived illness (r = -.44, p = .0001) and treatment disruption (r = -.27, p = .006). Finally, a significant association was noted between duration of current functioning graft and timeline beliefs, indicating that the longer TX patients lived with their transplant the more strongly they believed that in the chronic nature of their condition (r_s = .21, p = .032).

There were no significant associations between causal beliefs and sociodemographic or medical variables (data not shown).

2.4.b Immunosuppressive medication

The next analysis compared illness and treatment beliefs between TX patients treated with different immunosuppressive agents, namely cyclosporin (n = 70) and tacrolimus (n = 40). Two sets of comparisons were performed: (a) without casemix adjustments and (b) with casemix adjustments (age, duration of functioning graft, RRT duration, diabetes). Only casemix differences that were significantly associated with the outcomes in question were included as covariates.

Oneway ANOVAs (without adjustments for casemix differences) revealed that patients on cyclosporin had lower control beliefs (F(1, 99) = 5.385, p =.022) and held stronger chronic timeline beliefs than patients on Tacrolimus (F(1, 94) = 11.979, p = .001). These differences however were no longer significant after duration of functioning graft and age were controlled for, hence suggesting that it was these two variables rather than

immunosuppressive regime driving these perceptions. It should be noted that the treatment effect on timeline beliefs approached but did not reach significance ($F(3, 92) = 3.614, p = .06$).

There were no group differences in necessity and concerns medication beliefs. The two groups also did not differ in the reported symptoms. A trend was noted for cyclosporin-treated patients to express stronger 'medication necessity' beliefs than tacrolimus-treated patients ($F(1, 99) = 3.618, p = .06$) but this did not reach significance (no covariates were included as neither age nor duration of TX functioning were associated with medication beliefs).

2.4.c Mood measures

Negative mood as signified by high CDI symptoms and PNS-NA correlated with more negative illness and treatment perceptions such as more illness and treatment disruption and more perceived illness consequences. The opposite pattern (inverse correlations) was observed for positive affect.

Table 8.14: Correlations between mood and beliefs in TX

	Iden-tx	Iden-m	Timel	Conseq	Control	IEQ	TEQ†	Bmq-c	Bmq-n †
BDI	.440 ****	.382 ****	.178	.587 ****	-.402 ****	.628 ****	.508 ****	.321 ***	.188 p <.058
CDI†	.305 **	.246 *	.173	.616 ****	-.321 ***	.469 ****	.419 ****	-.245 *	.248 *
PNS NA	.246 *	.211 *	.135	.295 **	-.09	.294 **	.302 **	.130	-.038
PNS PA	-.243 ****	-.120	-.237 *	-.392 ****	.152	-.566 ****	-.319 **	-.202 p <.055	-.049

Note: BDI = total depression score; CDI = cognitive depression index; PNS PA = PANAS positive affect; PNS NA = PANAS negative affect; Ident-tx = extended 42 item version of identity sub-scale (generic, renal and transplant specific symptoms; Ident-m = immunosuppressive medication side effects (23 items); timel = timeline IPQ sub-scale; conseq = consequences IPQ sub-scale; IEQ = illness effects questionnaire; TEQ = treatment effects questionnaire; BMQ-c = concerns about medication; BMQ-n = beliefs about the necessity of medication

† = Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

2.4.d Cognitive functioning

Two NP scores were used: the mean of overall NP performance (NP-TO) and the mean number of NP tests in which TX patients scored more than 1 *SD* below their respective age norm (NP-Norm). Results showed no significant associations between any of these NP indices and illness and treatment beliefs (data not shown).

Section 3: Dialysis vs. Transplantation

TX patients were not compared separately to HD and PD as previous analysis showed no significant differences in illness nor treatment beliefs between the two dialysis groups. Five group comparisons involving TX vs. hospital HD vs. home HD vs. CAPD vs. APD were performed only in perceptions of treatment intrusiveness (TEQ) as this was the only variable in which the dialysis subgroups differed significantly.

3.1 Sample characteristics: combined dialysis and transplant

As reported earlier, there were significant differences between dialysis and transplant groups in sociodemographic and medical variables: time on RRT; time on current treatment; ESRD severity; diabetes; ischaemic heart disease; income and work status (see Chapter 5; section 2.6.a). Significant associations were found between casemix variables and patients' cognitions, indicating the need to include covariates in subsequent comparative analyses (see Table 8.15 below).

The casemix differences were associated with causal attributions albeit not consistently across the different causal items.

Patients with the lowest yearly income (< £10,000) were more likely to report 'chance' causal attributions ($\chi^2(240) = 5.438$, $p = .020$) compared to those with higher income. A greater percentage of non-employed patients attributed their illness to other people ($\chi^2(249) = 6.359$, $p = .012$) relative to employed patients.

ESRD severity was higher among patients expressing attributions of 'own behaviour', 'other people' (U = 1234.5, p = .01), and 'poor medical care' (U = 4637.5, p = .024) vs. those who did not endorse these beliefs. Diabetes was associated with 'self-blame' and 'poor medical care' attributions in that patients with diabetes were more likely to attribute their illness to their 'own behaviour' ($\chi^2(249) = 13.318$, p = .0001) and 'poor medical care' ($\chi^2(249) = 9.593$, p = .002) compared to non-diabetic participants. Ischaemic heart disease was similarly associated with 'own behaviour' ($\chi^2(249) = 6.413$, p = .011) and 'other people' causal beliefs ($\chi^2(249) = 4.01$, p = .046).

Table 8.15: The associations between casemix differences and beliefs in DL and TX

	Covariates used in DL vs. TX comparisons						
	IEQ	TEQ	IPQ Identity[a]	IPQ Timeline	IPQ Control	IPQ Conseq	IPQ Causes[b]
Work	+	+	+	-	+	+	+
Income	+	+	+	-	+	-	+
ESRD-SI	+	+	+	-	+	+	+
Heart disease	+	+	+	-	+	+	+
Diabetes	+	+	+	-	+	+	+
RRT duration	+	+	-	-	-	-	-
Current treatment duration	-	-	+	-	-	-	-

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

[a] = identity scores used were based on the 19 items also used with dialysis participants

[b] = significant association but no covariate could be used in causal beliefs comparisons

3.2 Comparison results

Two sets of comparisons between dialysis and transplant patients were performed: (1) using simple effects ANOVAs without casemix adjustments, (2) using ANCOVAs with casemix adjustments.

Results of ANOVA comparisons (without casemix covariates) showed significantly more symptoms (i.e. stronger identity beliefs) ($F(1, 256) = 38.728$, p = .0001), stronger chronic timeline beliefs ($F(1, 247) = 11.871$, p = .001), increased treatment disruption ($F(1, 251) = 90.701$, $p < .000$), illness disruption ($F(1, 251) = 116.309$, $p < .000$) and

illness consequences ($F(1, 246) = 6.797$, $p = .01$) and decreased control beliefs ($F(1, 246) = 12.641$, $p = .0001$) voiced by the dialysis group.

These differences persisted even after casemix differences were partialled out. The treatment effect was still significant in IEQ ($F(7, 233) = 71.346$, $p = .0001$); TEQ ($F(7, 233) = 64.367$, $p = .0001$); IPQ identity ($F(7, 233) = 27.065$, $p = .0001$); IPQ timeline ($F(1, 246) = 11.871$, $p = .001$); and IPQ control ($F(6, 229) = 4.169$, $p = .042$). A tendency was noted for transplant patients to perceive less consequences associated with their condition relative to dialysis patients but this difference did not reach significance levels ($F(5, 242) = 3.123$, $p = .078$).

Five group ANCOVAs to compare treatment perceptions between TX and dialysis subgroups (hospital HD; home HD; CAPD; APD) similarly indicated a significant treatment main effect ($F(10, 230) = 18.209$, $p = .0001$). Tukey's post-hoc tests indicated that all four dialysis groups reported significantly higher treatment intrusiveness than transplant recipients.

Group differences in causal beliefs were investigated with chi-square analysis, thereby not allowing for casemix differences adjustments. Results indicated that a greater percentage of dialysis patients endorsed 'chance' ($\chi^2(249) = 5.309$, $p = .021$) and 'own behaviour' causal attributions ($\chi^2(249) = 6.753$, $p = .009$) compared to TX patients. The association between treatment and 'germ-virus' causal beliefs approached but did not reach significance. This trend indicated that more TX patients attributed their condition to 'germ or virus' ($\chi^2(249) = 3.810$, $p = .051$) relative to dialysis participants. Significant differences in causal beliefs are likely to reflect casemix differences, as these cannot be controlled for in chi-square analysis.

Section 4: Summary of Results

- Dialysis and transplant patients hold coherent models of their ESRD consistent with SRM and expressed views regarding their treatment regime.

- Illness and treatment beliefs differed between patients on dialysis and transplant recipients. TX patients held lower chronic timeline beliefs, believed more strongly in the controllability of ESRD, reported less illness and treatment intrusiveness, perceived less consequences and less symptoms associated with their condition relative to dialysis patients

- There were no significant differences in illness and treatment beliefs between patients on different dialysis treatments, with the exception of treatment intrusiveness. CAPD patients perceived their treatment to be significantly more burdensome compared to patients on APD.

- Significant interrelations were noted between the different IPQ components and between illness and treatment beliefs in both dialysis and transplantation

- Significant correlations were found between patients' beliefs and age, ESRD SI, mood and cognitive functioning. The overall pattern of correlations indicated that more negative illness and treatment perceptions were associated with increasing age and ESRD severity, negative-valenced mood and less efficient cognitive functioning.

CHAPTER 9: HQOL RESULTS

Section 1: Dialysis sample

1.1 HQoL Descriptives

Table 9.1: HQoL (*Means, SDs, Cronbach alpha*) in Dialysis

			HD			PD		
		All DL	Hs-HD	Hm-HD	All HD	CAPD	APD	All PD
GH[a]	*a*	**.727**			**.721**			**.736**
	M	30.38	30.06	33.16	31.07	29.01	30.73	29.59
	SD	8.82	8.35	10.45	9.13	8.68	8.07	8.45
PF[a]	*a*	**.923**			**.919**			**.926**
	M	27.20	27.15	31.2	28.46	23.02	31.18	25.78
	SD	16.45	16.64	15.14	16.19	16.02	17.16	16.75
BP[a]	*a*	**.873**			**.866**			**.874**
	M	4.90	42.28	43.78	42.77	35.20	45.84	38.8
	SD	12.03	11.64	11.2	11.45	11.99	10.11	12.4
VT[a]	*a*	**.882**			**.877**			**.871**
	M	40.85	42.68	44.85	43.38	35.81	42.24	37.99
	SD	10.82	10.88	10.98	10.89	10.54	7.65	10.08
RPh[a]	*a*	**.811**			**.788**			**.839**
	M	35.32	35.46	39.03	36.62	29.86	41.66	33.86
	SD	13.06	12.33	13.49	12.74	11.33	13.75	13.34
REm[a]	*a*	**.805**			**.810**			**.798**
	M	45.46	45.89	48.66	46.79	44.18	43.51	43.95
	SD	12.42	12.69	10.39	12.01	12.93	12.78	12.79
SF[a]	*a*	**.711**			**.741**			**.677**
	M	35.74	37.58	38.65	37.93	30.52	38.61	33.26
	SD	13.73	12.42	14.08	12.90	14.7	12.09	14.31
MH[a]	*a*	**.827**			**.823**			**.827**
	M	45.37	45.49	48.60	46.50	42.68	46.85	44.09
	SD	10.70	10.33	10.39	10.39	11.30	9.97	10.97
MCS								
	M	47.24	48.17	50.22	48.84	45.08	46.10	45.42
	SD	10.37	9.75	9.90	9.79	11.01	10.51	10.77
PCS								
	M	28.87	29.3	32.32	30.28	23.49	34.64	27.27
	SD	13.19	12.23	13.13	12.52	12.59	13.4	13.84

Note: Hs-HD = hospital haemodialysis; Hm-HD = home haemodialysis; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

[a] = normative based scoring (population mean = 50 and *SD* = 10)

In keeping with previous research, observed mean scores in PCS, PF, GH, RPh and SF were more than 1 *SD*s below general population norms (Normative Based Scoring population mean = 50, *Sd* = 10) while mean scores reflecting emotional well-being (e.g. MCS, MH, REm) tended to be closer (i.e. within 1 *SD*) to population mean (see Table 9.1).

There were also obvious differences in the SF-36 profile of the four dialysis groups. For instance, CAPD patients had markedly lower SF-36 scores than the other dialysis groups, with average scores in 8 out of the 10 SF-36 sub-scales falling more than 1 *SD* below those of general population norms.

The number of individuals who could be considered to have severely impaired HQoL, defined as a score on PCS or MCS of 2 or more *SD*s below the general population mean (corresponding to the lowest 2.5% scoring of the general population), was calculated.

Table 9.2: Prevalence of MCS and PCS impairment in Dialysis

	HD			PD			All DL
	Hs-HD	Hm-HD	All HD	CAPD	APD	All PD	
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
PCS	51.9%	48%	50.6%	64.4%	39.1%	55.9%	53.1%
< 2 SD	(27)	(12)	(39)	(29)	(9)	(38)	(77)
MCS	1.9%	4%	2.6%	11.1%	13%	11.8%	6.9%
< 2 SD	(1)	(1)	(2)	(5)	(3)	(8)	(10)

Note: Hs-HD = hospital haemodialysis; Hm-HD = home haemodialysis

Using this criterion, 53.1% (n = 77) of the total dialysis sample were found to be severely impaired on the PCS and 6.9%, of dialysis respondents (n = 10), had MCS scores that were similarly impaired.

1.2 HQoL comparisons among dialysis treatments

To investigate the effect of treatment modality after accounting for casemix differences two sets of comparisons (ANOVAs or ANCOVAs as appropriate) were performed:

- HD vs. PD patients
- Hospital HD vs. Home HD vs. CAPD vs. APD patients

1.2.a Two group comparisons: HD vs. PD

i. *Sample characteristics*

To identify which of the casemix differences between PD and HD (gender, diabetes, dialysis duration, RRT duration, Albumin and Hb) might require statistical control in subsequent comparative analyses, their univariate associations with SF-36 scores were examined (see Table 9.3 for summary of results).

Table 9.3: The associations between casemix differences and HQoL in dialysis (HD; PD)

	Covariates used in HD vs. PD comparisons									
	PF	**GH**	**BP**	**RPh**	**REm**	**MH**	**SF**	**VT**	**PCS**	**MCS**
Gender	-	-	-	-	-	+	-	-	-	+
Diabetes	+	-	+	+	-	+	+	+	+	-
RRT time	-	-	-	-	-	-	-	-	-	-
Time on dialysis	-	-	-	-	-	-	-	-	-	-
Albumin	+	+	+	+	-	-	+	+	+	-

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

ii. *Absolute HQoL scores*

In the first set of analyses ANCOVAs (controlling for casemix differences) were performed on HQoL between patients on HD (hospital and home) and patients on PD treatments (CAPD and APD).

Results indicated that at T1, HD patients had significantly higher scores in vitality ($F(2, 142) = 4.911$, $p = .028$) and MCS ($F(2, 142) = 6.146$, $p = .014$) compared to PD patients. The treatment effect on vitality was no longer significant after albumin levels were included as covariates in the analysis ($F(3, 140) = .114$, $p = .736$).

iii. *Prevalence of HQoL impairments*

The association between dialysis modality and the prevalence of severe PCS and MCS impairments was examined with chi-square analysis. None were detected for PCS

($\chi^2(145) = .397$, $p = .53$). The prevalence of severe MCS impairment was significantly greater in the PD group compared to HD (Fisher's exact test $p = .046$).

1.2.b Four groups comparisons: Hospital HD vs. home HD vs. CAPD vs. APD

i. *Sample characteristics*

Significant group differences between the four dialysis groups were noted in work status, income, diabetes, RRT duration and time on current treatment requiring statistical control in subsequent group comparisons. Table 9.4 lists the casemix differences that were used as covariates when comparing SF-36 scores between the four dialysis groups, on the condition that they were also significantly associated with the particular SF-36 score.

Table 9.4: The associations between casemix differences and HQoL in dialysis (hospital HD; home HD; CAPD; APD)

	Covariates used in Hosp HD vs. Home HD vs. CAPD vs. APD comparisons									
	PF	**GH**	**BP**	**RPh**	**REm**	**MH**	**SF**	**VT**	**PCS**	**MCS**
Work status	+	+	+	+	-	+	+	+	+	-
Income	+	-	+	+	-	-	-	-	+	-
Diabetes	+	-	+	+	-	+	+	+	+	-
RRT duration	-	-	-	-	-	-	-	-	-	-
Duration of current treatment	-	-	-	-	-	-	-	-	-	-
Albumin	+	+	+	+	-	-	+	+	+	-

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

As evident from this table income and work status were strongly associated with the physical dimensions of SF-36. Although there is no clear consensus as to whether work and income ought to be controlled for in HQoL comparisons, these were nevertheless included as covariates as it was thought that this would provide a much stronger test of any treatment effects on HQoL over and above socio-economic considerations.

It is also arguable whether to control for biochemical differences (i.e. albumin) given that these reflect treatment differences. Comparative analyses were hence conducted with and without the inclusion of albumin.

ii. *Absolute HQoL scores*

HQoL differences between all four groups were examined using a series of ANCOVAs controlling for casemix differences if appropriate (see Table 9.1 for SF-36 mean scores). Significant main effects were followed with Tukey's HSD post-hoc tests.
To account for casemix differences in post-hoc comparisons, residualised scores were obtained for the SF-36 sub-scales and summary scores. These were obtained by regressing each of the SF-36 sub-scales on casemix differences in order to obtain the unstandardised regression coefficient, a value that reflects the observed SF-36 scores minus the effect of diabetes, work status and/or income (as appropriate; see Table 9.4). This procedure was not necessary when comparing the four groups on GH, REm and MCS as no significant associations were found between casemix differences and these SF-36 scores.

ANCOVAs controlling for all casemix differences except albumin indicated a significant treatment effect on BP ($F(6, 138) = 2.769$, $p = .044$) and VT ($F(5, 139) = 2.748$, $p = .045$).
Post-hoc tests using residualised scores showed no significant differences between the four dialysis groups. A trend was noted for CAPD to report more bodily pain relative to hospital HD patients but this did not reach significance ($p = .081$). Post-hoc tests on absolute scores however indicated that CAPD patients reported significantly more bodily pain than the other three dialysis groups.
With regard to VT scores, significant differences were noted only between CAPD and hospital HD and Home HD patients. After controlling for albumin (in addition to diabetic status) however, the treatment effect in vitality and bodily pain ceased to be significant.

It is also of note that by excluding income, and work status from the list of covariates significant differences were found in all physical dimensions of SF-36 (PCS; BP; RPh; VT), with CAPD patients faring significantly worse than APD patients in these sub-scales.

iii. *Prevalence of HQoL impairments*

Chi-square analyses showed no significant differences in the prevalence of severe PCS ($\chi^2(145) = .4.418, p = .22$) and MCS impairments ($\chi^2(145) = 4.928, p = .152$) among the four groups.

1.3 Factors associated with HQoL in dialysis

The associations between the sociodemographic, clinical, psychological variables and HQoL were examined using univariate and multivariate analyses.

1.3.a Sociodemographic and medical variables

Univariate analyses showed several significant relationships between HQoL and sociodemographic, medical and psychological variables (see Table 9.5) in addition to those described earlier (see sub-sections 1.2.a and 1.2.b)

The physical dimensions of SF-36 were strongly associated with age of dialysis patients, with scores deteriorating as a function of age (correlation coefficients ranging from r = -.24 to r = -.41) but no significant correlations were observed between age and the emotional SF-36 sub-scales.
Gender (Female) was associated with lower scores in MCS ($F(1, 144) = 5.2387, p = .0236$) and MH ($F(1, 144) = 7.2487, p = .0079$).

ANOVAs (with Tukey's HSD post-hoc tests) indicated that dialysis patients on the lower income brackets (i.e. earning less than £10,000 per year) had significantly lower physical well-being (PCS $F(3, 141) = 7.654, p = .0001$; PF $F(3, 141) = 4.724, p = .004$; BP $F(3, 141) = 7.805, p = .0001$; RPh $F(3, 141) = 7.603, p = .0001$) than patients with higher income.

ANOVAs (without casemix adjustments) indicated that employed patients had higher scores in most SF-36 sub-scales, exceptions being MCS and REm. Adjustments for age and ESRD severity did not alter the observed group differences in physical SF-36 dimensions: PCS ($F(3, 141) = 4.272, p = .041$); PF ($F(3, 141) = 17.319, p = .0001$); RPh

($F(3, 141) = 12.061$, $p = .001$). Differences in VT approached but did not reach significance ($F(3, 141) = 3.538$, $p = .062$), whereas the effect on MH was no longer significant after casemix adjustments.

Table 9.5: Correlations between HQoL and sociodemographic and medical variables in Dialysis

	PF†	GH	BP	RPh †	Rem †	MH	SF†	VT	PCS	MCS
Age	-.415 ****	-.121	-.268 ***	-.239 **	.090	.004	-.150	-.314 ****	-.405 ****	.109
Education †	.210 *	.206 *	.233 *	.141	.020	.074	.146	.233 *	.258 **	.034
DL time duration†	-.040	-.048	.038	.026	.097	-.006	.056	.078	-.007	.082
RRT time	-.040	-.099	.025	.027	.056	-.030	.080	.080	.003	.055
No comb†	-.519 ****	-.384 ****	-.313 ***	-.371 ****	-.009	-.144	-.253 **	-.381 ****	-.535 ****	-.019
ESRD SI†	-.635 ****	-.382 ****	-.424 ****	-.370 ****	-.131	-.293 ****	-.313 ****	-.470 ****	-.594 ****	-.131
Kt/V	.312 ****	.212 *	.254 **	.217 *	-.050	-.048	.220 *	-.157	-.078	-.099
Albumin	.222 **	.170 *	.259 **	.191 *	.044	.096	.223 **	.314 ****	.241 **	.078
Hb	-.027	-.030	-.222 **	-.031	-.110	-.048	-.067	-.157	-.078	-.099

Note: DL = dialysis; RRT = renal replacement therapy; ESRD-SI = end-stage renal disease severity index; Kt/V = dialysis adequacy measure; Hb = haemoglobin GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

With respect to clinical characteristics, an increasing number of comorbid conditions (ESRD severity) correlated with decreasing HQoL scores in 8 of 10 SF-36 sub-scales. Correlation coefficients ranged from r = -.31 to r = -.63, signifying moderate-sized correlations.

In addition to diabetes, ischaemic heart disease was similarly associated with lower SF-36 scores (i.e. poorer HQoL) in PCS ($F(1, 144) = 26.347$, $p = .0001$), PF ($F(1, 144) =$

25.540, p = .0001), RPh (F(1, 144) = 10.706, p = .001), BP (F(1, 144) = 11.531, p = .0009), SF (F(1, 144) = 8.981, p = .003), VT (F(1, 144) = 15.925, p = .0001), and GH (F(1, 144) = 17.493, p = .0001). Of particular note are the observed significant correlations with mental health, suggesting that increased disease burden as indexed by comorbidities may adversely affect both physical and emotional well-being.

Significant associations were noted between dialysis adequacy and HQoL predominantly with respect to physical parameters: PCS (r =.37, p = .0001), GH (r = .21, p = .017), VT (r = .25, p = .004), PF (r_s = .31, p = .0001), RPh (r_s = .22, p = .017), BP (r_s = .25, p = .004) and SF (r_s = .22, p = .013). Correlation coefficients indicated concomitant changes in HQoL with increases in dialysis adequacy levels. These analyses were performed on standardised z-scores as the absolute Kt/V values of peritoneal and haemodialysis dialysis adequacy measures are not equivalent.

It was intended to examine the associations between critical levels of dialysis delivery and HQoL, but as there were insufficient numbers in the 'poor/inadequate dialysis' groups (n = 6 in CAPD, n =1 in APD group n = 2 in Home HD and n = 10 in Hospital HD group), these comparisons were not feasible and were therefore abandoned.

1.3.b Beliefs

Correlational analysis on the total dialysis sample also showed that illness and treatment beliefs were consistently associated with all SF-36 scores (see Table 9.6).

Correlation coefficients indicated moderate-sized associations in the expected direction. Better HQoL was associated with higher IPQ control beliefs, lower illness and treatment effect perceptions, lower perceived IPQ consequences, and less perceived symptoms.

Timeline beliefs were found to be inversely correlated with general health perceptions. The stronger the beliefs on the chronicity of the illness the more negative patients' evaluations of general health.

Table 9.6: Correlations between beliefs and HQoL in Dialysis

	PF†	GH	BP	RPh †	Rem †	MH	SF†	VT	PCS	MCS
IPQ time†	.025	-.162 p<.051	.097	.014	.020	-.036	-.083	.127	.028	-.028
IPQ Control	.491 ****	.502 ****	.386 ****	.317 ****	.210 *	.393 ****	.399 ****	.514 ****	.486 ****	.308 ****
IPQ Conseq	-.271 ***	-.504 ****	-.334 ****	-.234 **	-.228 **	-.43 ***	-.342 ****	-.430 ****	-.336 ****	-.359 ****
IPQ identity†	-.381 ****	-.403 ****	-.431 ****	-.296 ****	-.223 **	-.406 ****	-.439 ****	-.469 ****	-.408 ****	-.364 ****
IEQ	-.524 ****	-.535 ****	-.480 ****	-.405 ****	-.273 ***	-.515 ****	-.51 ****	-.555 ****	-.537 ****	-.395 ****
TEQ	-.400 ****	-.421 ****	-.410 ****	-.336 ****	-.336 ****	-.550 ****	-.401 ****	-.429 ****	-.407 ****	-.436 ****

Note: Conseq = consequences; IEQ; illness intrusiveness; TEQ = treatment intrusiveness; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

As treatment perceptions were strongly associated with illness perceptions, particularly beliefs about illness intrusiveness (r = .73, p = .0001), it is possible that the observed significant correlations between treatment beliefs and HQoL would be due to effects of illness perceptions rather than an indication of a direct association between the two of them.

Partial correlations were therefore conducted to re-examine the associations between treatment beliefs and HQoL after taking into account the effect of illness intrusiveness. Results demonstrated that beliefs about treatment intrusiveness were still significantly correlated with psychological dimensions of SF-36, namely MH (r = -.30, p = .0001), REm (r = -.28, p = .005), and MCS (r = -.23, p = .005) but not with remaining sub-scales and PCS (ps <.1).

Independent group t-tests and Mann-Whitney tests (as appropriate) comparing SF-36 scores between patients endorsing or not particular causal beliefs (i.e. 'chance'; 'poor medical care'; 'hereditary; 'own behaviour'; 'other people') showed no significant group differences.

1.3.c Mood variables

Significant correlations were noted between mood and HQoL. Negative mood indicators were associated with compromised emotional and physical well-being with correlation coefficients ranging from r = .26 to r = .67. As anticipated the strongest correlations were found between mood measures and emotional well-being on the SF-36, with correlations between mood and physical indicators of HQoL being somewhat lower, i.e. in the range of low to moderate associations.

Table 9.7: Correlations between mood and HQoL in Dialysis

	PF†	GH	BP	RPh †	REm †	MH	SF†	VT	PCS	MCS
BDI	-.619 ****	-590 ****	-.517 ****	-.444 ****	-.512 ****	-.669 ****	-.570 ****	-.624 ****	-.599 ****	-.547 ****
CDI	-.570 ****	-.578 ****	-.466 ****	-.452 ****	-.419 ****	-.666 ****	-.556 ****	-.557 ****	-.535 ****	-.543 ****
STAI	-.403 ****	-.349 ****	-.411 ****	-.257 **	-.383 ****	-.564 ****	-.388 ****	-.447 ****	-.355 ****	-.466 ****
PNS NA†	-.425 ****	-.333 ****	-.417 ****	-.260 **	-.405 ****	-.570 ****	-.386 ****	-.493 ****	-.361 ****	-.482 ****
PNS PA	.478 ****	.377 ****	.421 ****	.287 ****	.314 ****	.470 ****	.506 ****	.476 ****	.339 ****	.420 ****

Note: BDI = total beck depression scores; CDI = cognitive depression index; STAI = state anxiety; PNS NA = PANAS negative affect; PNS PA = PANAS positive affect; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlation coefficient

p <.05. ** p <.01. *** p <.001. **** p <.0001

1.3.d Cognitive functioning

To examine the association between cognitive functioning and HQoL, correlations were performed between SF-36 scores and indices of NP performance. For these analyses, three summary scores reflecting patients' overall cognitive functioning (see earlier section 1.6.c) were used in preference to the individual NP scores to reduce the number of correlations and thereby the chance of type I error.

These included the number of NP impairments relative to age respective norms (NP-Norm), the mean of the two derived NP summary scores across the two assessments (NP-TO) and the change score in overall NP performance from T1 to T2 (acute NP-change).

Table 9.8: Correlations between cognitive functioning and HQoL in Dialysis

	NP-TO		NP-change		NP-Norm	
	Full	**Partial**	**Full**	**Partial**	**Full**	**Partial**
PCS	.396****	.146	.019	-.022	-.429****	-.235**
MCS	.085	.137	.163*	.202*	-.131	-.081
GH	.129	-.0001	.225**	.259**	-.173*	-.013
PF†	.558****	.238**	-.002	-.096	-.458****	-.284***
BP	.292****	.131	.045	.028	-.338****	-.223**
RPh†	.360****	.151	.078	.024	-.314****	-.200*
REm†	.176*	.232**	.093	.078	-.193*	-.187*
MH	.194*	.181*	.121	.155 p<.064	-.230**	-.161p<.054
SF†	.257**	.066	.112	.112	-.208*	-.063
VT	.317****	.109	.157 p<.06	.153 p<.068	-.339****	-.119

Note: GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlations

* p <.05. ** p <.01. ***. p <.001. **** p <.0001.

Results showed several significant associations, primarily in relation to physical dimensions of SF-36. Cognitive functioning correlated significantly with PCS, PF, RPh, BP, VT, BP and MH. Correlations ranged from .17 to .41 (see Table 9.8).

Correlational analyses were repeated using a series of partial correlations taking into account two variables: age and ESRD-SI, a weighed index of comorbidity and renal complications (see Table 9.8). Partialling out the effect of these two variables rendered some of the previous (significant) correlations between overall cognitive functioning or acute NP change and SF-36 scores (PCS, BP, SF, VT) non-significant, with only the associations between physical functioning, role limitations-emotional and mental health and NP summary scores remaining significant.

With respect to NP Impairments (NP-Norm), partial correlations produced a similar pattern of results. It should be noted that only ESRD-SI was partialled out in the case of NP impairments as classification of individual NP performance as impaired or not (i.e. within or lower than norms) was based on age respective normative data. ESRD-SI adjustments reduced the strength of observed correlations but did not completely remove their significance.

A separate correlational analysis was performed on the HD sample alone to examine whether acute changes in overall cognitive functioning for pre- to 24-hours post-dialysis (NP-change) were associated with HQoL levels. Results indicated that changes in overall NP performance from T1 to T2 (HD group only) was unrelated to SF-36 scores (*p*s <.1; data not shown).

1.3.e Subjective cognition

The associations between subjective cognition and HQoL were examined using two subjective cognition indices: Overall cognitive decline since initiation of dialysis (SCS-TO) and overall acute subjective cognitive change from T1 and T2 (acute SCS-TO). Higher scores in both summary scores signified perceptions of greater cognitive decline.

Table 9.9: Correlations between indices of subjective cognition and HQoL in dialysis

	SCS-TO		**Acute SCS-TO**	
	Full	**Partial**	**Full**	**Partial**
PCS	-.346 ****	-.209 *	.040	.046
MCS	-.350 ****	-.307 ****	-.027	-.130
GH	-.323 ****	-.244 **	-.011	-.019
PF†	-.358 ****	-.331 ****	.082	.089
RPh†	-.438 ****	.009	.082	.008
REm†	-.267 ****	-.231 **	-.013	-.082
MH	-.423 ****	-.352 ****	-.026	-.093
SF†	-.376 ****	-.298 ****	-.027	-.096
VT	-.440 ****	-.316 ****	.026	-.008

Note: GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlations

* p <.05. ** p <.01. *** p <.001 **** p <.0001.

Results indicated that perceptions of greater cognitive decline since dialysis onset were associated with poorer HQoL. Significant correlations ranging from r = -.13 to r = -.44. were evident in both physical and emotional SF-36 dimensions (see table 9.9). These associations remained significant even after the effect of age and ESRD was controlled for with partial correlations.
In contrast, acute subjective cognition was unrelated to SF-36 scores.

1.3.f Multivariate analysis

Subsequently, all variables univariately associated either with physical (PCS) and mental (MCS) component scores were presented stepwise to hierarchical multiple regressions to assess their independent prognostic value for HQoL in dialysis patients.

Predictors were entered in a specified order. On the first step sociodemographic variables (age; education; gender; income; work status) were entered to control for their relationship with HQoL. Medical variables (dialysis modality; ESRD SI; dialysis adequacy; dialysis duration; albumin; diabetic status) were entered on the second step. Indices of cognitive functioning and cognitive complaints followed at step 3. Patients' illness and treatment beliefs entered at step 4. As there was no specific hypothesis regarding their primacy, illness and treatment beliefs were entered together rather than as separate blocks. In the last block, cognitive depression scores were entered.
To evaluate the contributions of patients' beliefs over and above attributed to mood, regression analyses were repeated entering mood indicators before patients' beliefs .

In each of the blocks described only the variables significantly associated with PCS or MCS were included. Variables that were significantly associated with the individual sub-scales but not the summary scores were also included on the grounds that PCS and MCS reflect a weighted summary of the eight SF-36 sub-scales. The only exceptions were education, gender (Block 1) and time on dialysis (Block 2) that were entered under forced entry despite the lack of significant correlations with either summary component or individual SF-36 scores, so as to control for their potential influence.

Finally in order to create a more favourable case to variables ratio, certain variables were excluded from regression analyses. Neither diabetes nor ischaemic heart disease

status entered the regression equation as separate variables as these were included in the total disease severity and comorbidity weighted index score (ESRD-SI).
Mood measures assessing daily affective state (PANAS, STAI) were also left out given their acute time frame ('at the moment') that made them inappropriate predictors of HQoL over the previous 4 weeks preceding measurement. Cognitive depression (rated over a longer time frame) was retained. The significant intercorrelations noted between CDI and other mood measures (see chapter 6; sub-section 1.6) suggests that little will be lost by this strategy.

It should be noted that regressions included variables with non-normal distribution (e.g. education, ESRD-SI). This was deemed essential, as there was no alternative way of conducting analyses of similar type.

Multivariate analyses results indicated that a large proportion of the variance in PCS (R^2 = 58.7%; adj.R^2 = 56.3%) was explained by a combination of sociodemographic, medical and psychological variables.
Significant predictors (as in the last step of regression) were: work status, age, ESRD severity, dialysis adequacy (Kt/V), illness intrusiveness and cognitive depression. As presented in Table 9.10, sociodemographic and medical variables accounted for R^2 = 45.8% (Adj. R^2 = 43.9%) of the total variance indicating a medium effect size (f^2 = .845). Perceptions of illness intrusiveness independently contributed an additional ΔR^2 = 8.5% (ΔAdj.R^2 = 7.6%) in the explained variance (*F*change (1, 137) = 26.542, p = .0001) and depression added ΔR^2 = 2.8% (ΔAdj.R^2 = 2.6) in the total variance explained (*F*change (1, 136) = 8.861, p = .003).
Subjective cognitive complaints, a significant PCS predictor at steps 6 and 7 of the regression model, was no longer significant with the entry of depression in the equation, suggesting a mediating effect for depression.

The entry of mood measures before patients' cognitions did not alter the results. The overall variance explained was still R^2 = 58.7% (Adj. R^2 = 56.3%) and significant PCS predictors as in the last step were again: work status (R^2 = 20.6%), age (ΔR^2 = 8.4%), ESRD severity (ΔR^2 = 11.2%), dialysis adequacy (ΔR^2 = 3%), cognitive depression (ΔR^2 = 7.4%) and illness intrusiveness (ΔR^2 = 4.1%). The only, minor difference was that illness intrusiveness had a smaller independent yet significant contribution to the overall variance explained (*F*change (1, 137) = 13.539, p = .0001) (see Appendix J).

Table 9.10: Multiple regressions to predict PCS and MCS in dialysis: standardised regression coefficients, cumulative variance explained

	PCS			MCS		
	β	Cum R^2	Cum Adj.R^2	β	Cum R^2	Cum Adj.R^2
Block 1						
Work Status	.140*	.212 f^2 =.513	.206 f^2 =.471			
Age	-.165*	.295 f^2 =.201	.285 f^2 =.181			
Gender				.105 ns	.035 f^2 =.055	.029 f^2 =.044
Education						
Income						
Block 2						
Dialysis group				.162*	.075 f^2 =.063	.062 f^2 =.051
ESRD severity	-.248***	.408 f^2 =.274	.395 f^2 =.252			
Kt/V	.125*	.438 f^2 =.073	.422 f^2 =.062			
Albumin	.076 ns	.458 f^2 =.048	.439 f^2 =.039			
Haemoglobin						
Block 3						
NP functioning						
NP impairments						
SCS TO	-.010 ns	.475 f^2 =.041	.452 f^2 =.030	-.141 ns	.194 f^2 =.189	.177 f^2 =.176
Block 4						
IEQ	-.245***	.560 f^2 =.206	.538 f^2 =.197			
TEQ				-.181*	.287 f^2 =.148	.266 f^2 =.136
IPQ conseq						
IPQ control						
IPQ identity						
Block 5						
CDI	-.218**	.587 f^2 =.065	.563 f^2 =.057	-.356 ****	.370 f^2 =.132	.347 f^2 =.124

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; cum = cumulative variance; Kt/V = dialysis adequacy; NP= neurospychological; IEQ = illness intrusiveness; TEQ = treatment intrusiveness; conseq =consequences; CDI = cognitive depression index

p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

Hierarchical regression analysis to predict MCS were performed with and without the inclusion of CDI in the last step. The reason being that there is a significant overlap between CDI and MCS as both are essentially measuring or reflecting the same underlying concept, i.e. emotional well-being.

The resulting regression model explained R^2 = 28.7% (Adj.R^2 = 26.6%) of the MCS variance with treatment group, treatment perceptions and illness consequences being significant multivariate correlates at the last step of the regression (see Table 9.10).
Gender and treatment group explained R^2 = 6.2% of the total variance, with male gender and HD status being associated with higher MCS scores. Perceptions of cognitive decline adversely impacted upon emotional well-being (ΔR^2 = 11.9%; *F*change (1, 141) = 20.766, p = .0001). Among the psychological variables, beliefs about treatment intrusiveness made the strongest independent contribution explaining ΔR^2 = 9.3% of the variance explained (*F*change (1, 141) = 3..408, p = .0001).
Inclusion of mood measures in the last block of the regression (see Table 9.10) changed final results, by rendering the contribution of gender, and cognitive complaints no longer significant. The resulting model explained a total of R^2 = 37% (Adj.R^2 = 34.7%), significant predictors as in the last step being dialysis modality, perceptions of treatment intrusiveness, and depressive mood. Gender and subjective cognitive complaints ceased to be significant predictors in the last stage of entry (CDI). The changes in beta weights suggest a mediation effect for cognitive depression.

Reversing the order of entry for mood and cognitions produced similar results with treatment group, CDI and treatment intrusiveness explaining R^2 = 37% (Adj.R^2 = 34.7%) of the MCS variance (see Appendix J).

Section 2: Transplantation sample

The bulk of the findings reported below are based on the sample from the Middlesex Hospital used in the main (full protocol) study. Where equivalent data was available on the large sample recruited from Royal Free Hospital, then additional analyses were performed.

2.1 Sample Characteristics

Sociodemographic and clinical characteristics of the TX sample recruited from MIDDX have been reported earlier (Chapter 5; section 1.1). Observed casemix between CAD and LRD TX participants are also detailed in previous sections (see Chapter 6; section 2.4).

2.2 Descriptives - HQoL in Transplantation

HQoL levels as measured by the eight SF-36 sub-scales were found to be similar in both LRD and CAD transplant recipients. Group mean scores in all SF-36 sub-scales were all within 1 *Sd* of those reported for general population and so were the physical and mental component scores (PCS and MCS).

Table 9.11: HQoL in TX patients

		All TX	CAD TX	LRD TX
GH[a]	*a*	**.828**	**.836**	**.823**
	M (SD)	45.22 (11.48)	44.23 (11.77)	49.05 (9.51)
PF[a]	*a*	**.935**	**.937**	**.856**
	M (SD)	41.97 (14.80)	39.99 (15.36)	49.81 (8.61)
BP[a]	*a*	**.903**	**.913**	**.77**
	M (SD)	48.88 (12.56)	47.58 (13.14)	53.96 (8.35)
VT[a]	*a*	**.665**	**.614**	**.856**
	M (SD)	52.09 (16.24)	52.18 (17.75)	51.72 (8.08)
RPh[a]	*a*	**.948**	**.952**	**.869**
	M (SD)	43.67 (14.23)	41.69 (14.83)	50.39 (8.85)
REm[a]	*a*	**.927**	**.931**	**.846**
	M (SD)	47.17 (12.42)	46.01 (13.19)	51.77 (7.23)
SF[a]	*a*	**.70**	**.683**	**.776**
	M (SD)	47.69 (10.34)	47.01 (10.72)	50.40 (8.34)
MH[a]	*a*	**.759**	**.775**	**.644**
	M (SD)	49.91 (9.42)	49.67 (9.96)	50.86 (6.92)
MCS				
	M (SD)	51.40 (9.04)	51.50 (9.39)	51.02 (7.67)
PCS				
	M (SD)	42.96 (14.96)	40.96 (15.39)	50.81 (10.04)

Note: CAD TX = cadaver transplant recipients; LRD TX = living related donor transplant recipients PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

[a] = normative based scoring (population mean = 50 and *SD* = 10)

2.3 HQoL comparisons – LRD vs. CAD Transplantation

2.3.a Prevalence of HQoL impairments

The number of individuals who could be considered to have severely impaired HQoL, defined as a component HQoL score (PCS or MCS) of 2 or more *SD*s below the general population mean (*mean* = 50, *SD* = 10) corresponding to the lowest 2.5% scoring of the general population, was calculated. Using this criterion, 19.8% (n = 22) of the total transplant sample (n = 20, 21.7% of CAD and 8.7% of LRD, n = 2) were found to be severely impaired on the PCS. In contrast only 2.7% (n =3) of TX respondents (4.3% of LRD, n = 1 and 2.3% of CAD, n = 2) had MCS scores that were similarly impaired. No association was found between type of transplant and prevalence of severe impairments in PCS (Fisher's exact test significance = .156) and in MCS (Fisher's Exact test significance = 1.00).

When however scores were classified as falling within 1 *SD* of the population mean (a less stringent criterion of impairment) or not, transplant-type differences were detected. Chi square analysis showed that significantly more CAD patients (n = 35, 30.1%) had PCS scores lower (> 1 *SD*) than norms, relative to LRD patients (n = 3, 7.9%) ($\chi^2(111) = 5.786, p < .017$).

As however the sample size of LRD TX patients recruited in the main study from the Middlesex hospital was fairly small (n = 25), it was decided to repeat this analysis in the combined TX population including both participants from Middlesex Hospital and from the Royal Free Hospital totalling n = 347 (of whom n = 75 had received a LRD transplant) (see Chapter 5; Table 5.7).

A similar pattern of results emerged. Of the combined Middlesex and Royal Free Hospital transplant sample recruited, 22.6% (n = 79) patients (24.5% of CAD, n = 67 and 15.8% of LRD, n = 12) were found to be severely impaired on the PCS. In contrast, only 10% of TX respondents (11.8% of LRD, n = 9 and 9.5% of CAD, n = 26) had MCS scores that were similarly impaired. Chi-square analysis showed that the prevalence of physical HQoL impairment (PCS) was greater in CAD than LRD patients (χ^2 (337) = 7.627, p = .022). MCS impairment prevalence was similar between the two transplant groups.

2.3.b Absolute HQoL scores

Group comparisons were performed without the casemix adjustments by using independent *t*-tests or Mann-Whitney tests (as appropriate). These showed significant group differences only in the physical dimensions of SF-36. LRD TX patients had higher scores, i.e. better HQoL than CAD TX patients in PCS (U = 599, p =.002); PF (U = 599, p = .001); BP (U = 732.5, p = .02); and RPh (U = 647.5, p = .005).

Analyses of covariance, ANCOVAs (see Table 9.12 for covariates used) were then used to investigate the effect of transplant type on the HQoL domains after casemix differences were taken into account (with p values, uncorrected for multiple comparisons, considered significant if $p < .05$).

Table 9.12: The associations between casemix differences and HQoL in TX

	Covariates used in CAD vs. LRD TX comparisons									
	PF	**GH**	**BP**	**RPh**	**Rem**	**MH**	**SF**	**VT**	**PCS**	**MCS**
Age	+	-	+	+	-	-	-	-	+	+
Education	+	-	+	+	-	-	-	-	+	-
Work status	+	+	+	+	+	-	+	-	+	-
Income	+	+	+	+	+	-	-	-	+	-
ESRD-SI	+	+	+	+	+	-	+	+	+	-
RRT duration	-	-	-	-	-	-	-	-	-	-
DL duration	-	-	-	-	-	-	-	-	-	

Note: ESRD-SI = end –stage renal severity index; RRT = renal replacement therapy; DL = dialysis; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

There were no significant group differences in any of the SF-36 sub-scale scores or the two component scores. LRD and CAD TX patients reported equivalent levels of HQoL after casemix adjustments.

An identical analysis of the HQoL data in the combined TX sample recruited from both the Middlesex and Royal Free Hospital similarly failed to find significant HQoL

differences between LRD (n = 75) and CAD (n = 271) patients after adjustments for age, income and dialysis duration differences (see Appendix K).

2.3. Factors associated with HQoL in Transplantation

2.3.a Sociodemographic and medical variables

Univariate analyses showed several significant relationships between HQoL and sociodemographic and medical variables in the TX sample (see Table 9.13).

Table 9.13: Correlations between HQoL and sociodemographic and medical variables in Transplantation

	PF†	GH	BP†	RPh†	REm†	MH	SF†	VT†	PCS†	MCS
Age	-.482 ****	-.179	-.316 ***	-.236 *	-.045	.148	-.015	.008	-.479 ****	.277 **
Education†	.372 ****	.131	.307 ***	.226 *	.171	-.022	.133	.035	.342 ****	-.106
TX time†	.004	.054	-.055	.131	-.008	.045	.110	-.042	.034	.061
DL time †	-.045	.009	.013	-.090	-.145	-.015	-.134	.059	-.052	-.016
RRT time †	.029	.026	-.010	.052	-.096	-.025	.024	.048	-.043	-.30
No comrb†	-.324 ****	-.184	-.348 ****	-.204*	-.053	.019	-.095	-.123	-.366 ****	.082
ESRD SI†	-.518 ****	-.397 ****	-.499 ****	-.421 ****	-.260 **	-.062	-.203 *	-.299 ***	-.571 ****	-.047
GFR	.375 ****	.38 ***	.416 ****	.317 ***	.292 **	.192 *	.316 ***	.269 **	.393 ****	.175
Hb	.309 ***	.412 ***	.25 **	.327 ***	.231 *	.205 *	.224 *	.20*	.321 ***	.143
Albumin	.248 **	.162	.21*	.143	.165	-.004	.175	.155	.272 **	.119

Note: TX-time = time elapsed since transplantation; RRT = renal replacement therapy; DL = dialysis; ESRD-SI = end–stage renal severity index; No comrb = number of comorbidities; GFR = glomerular filtration rate; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

The physical dimensions of SF-36 were strongly associated with age, with scores in BP, GH, PF, RPh, PCS deteriorating as a function of age (correlations ranging from r_s = -.24 to r_s = -.48). Interestingly age was positively associated with emotional well-being, i.e. higher MCS scores (r = .276, p = .003).

The only significant HQoL difference between male and female transplant patients was found in physical functioning in favour of male patients ($F(1, 112) = 3.985$, p = .048). This difference was however not significant when adjustments were made for casemix differences (age and ESRD-SI) ($F(3, 110) = 2.666$, p = .105).

Higher education correlated significantly with better physical HQoL as indexed by higher scores in BP, RPh, PF and PCS but these significant associations were again due to age. Partial correlations controlling for age showed no significant associations between education and HQoL (r = .157, p = .062 for PCS; r = .181, p = .062 for PF; r = .138, p = .138 for RPh; r = .143, p = .144 for BP).

Annual income was also associated with the HQoL, particularly physical well-being. ANOVA comparisons between patients on the four different income groups indicated that transplant patients on the lower income brackets (i.e. earning less than £10,000 per year) had significantly poorer HQoL, as indexed by lower scores in PCS ($F(3, 96)$ = 7.378, p = .0002), PF ($F(3, 97) = 7.988$, p = .0001), BP ($F(3, 97) = 5.714$, p = .0012), RPh ($F(3, 96) = 5.518$, p = .0016), and REm ($F(3, 97) = 3.386$, p = .0213) than patients with higher incomes. No systematic differences were found between the other three income groups.

ANOVA comparisons between employed and non-employed TX patients indicated significant group differences, favouring employed patients, primarily in physical SF-36 dimensions. These remained significant even after adjustments for age and ESRD severity differences using ANCOVAs: PCS ($F(3, 108) = 9.446$, p = .003); GH ($F(3, 108) = 10.673$, p = .001); BP ($F(3, 109) = 5.005$, p = .027); PF ($F(3, 109) = 8.623$, p = .004); RPh ($F(3, 108) = 9.889$, p =.002); REm ($F(3, 109) = 18.999$, p = .0001); and SF ($F(3, 109) = 8.445$, p = .004).

With respect to clinical characteristics, increased ESRD severity correlated significantly with decreasing HQoL scores in 8 of 10 SF-36 sub-scales. Spearman's correlation

coefficients ranged from r_s = -.20 to r_s = -.57, signifying moderate- to strong-sized correlations (see Table 9.12). Ischaemic heart disease, in particular was associated with lower scores (i.e. poorer HQoL) in PCS (U = 672, p = .0001), PF (U = 731.5, p = .001), RPh (U = 848.5, p = .008), GH (F(1, 111) = 9.678, p = .002), BP (U = 832, p = .004) and SF (U = 954, p = .042).

Higher GFR values, signifying better kidney function were associated with better HQoL as indexed by higher SF-36 scores. Correlation coefficients ranged from r = .191 to r_s = .416, with the strongest correlations being observed for the physical sub-scales of SF-36 (e.g. PCS, BP). The association GFR and MCS approached but did not reach significance (r = .175, p = .067).

Neither time spent on dialysis and RRT prior to transplantation, number and duration of previous transplants (if any), nor time with their current transplant (duration of functioning graft) were associated with SF-36 scores.

2.4.b Immunosuppressive medication

The impact of immunosuppressive treatment on HQoL for TX patients was also examined.

Firstly HQoL comparisons were performed between TX patients on tacrolimus (n = 40) vs. those on cyclosporin (n = 70; see Appendix I) using Mann-Whitney or Independent t-tests (as appropriate). There was no need to control for TX duration (the only significant casemix difference between the two groups), as it had no association with SF-36 scores.

No significant group differences were found, hence suggesting that immunosuppressive regimen appears to be unrelated to HQoL or that the two treatments are comparable in their HQoL effects.

Secondly, correlations between serum levels of cyclosporin and tacrolimus and SF-36 scores were performed and again no significant associations were found (ps < .1).

1.3.c Beliefs

Correlations were performed to examine the relationship between patients' beliefs (IPQ; TEQ; IEQ; BMQ) and HQoL (see Table 9.14).

Table 9.14: Correlations between beliefs and HQoL in TX

	PF†	GH	BP†	RPh†	REm†	MH	SF†	VT†	PCS†	MCS
IPQ time	.029	-.204 *	-.033	.072	.037	-.103	.004	-.197 *	.005	-.034
IPQ control	.271 **	.319 ****	.202 *	.207*	.252*	.199 *	.088	.242 *	.224*	.049
IPQ Consequences	-.255 **	-.506 ****	-.231 *	-.329 ***	-.402 ****	-.374 ****	-.451 ****	-.458 ****	-.223*	-.363 ****
IPQ identity	-.563 ****	-.432 ****	-.495 ****	-.517 ****	-402 ****	-.286 ****	-.351 ****	-410 ****	-.534 ****	-.131
IPQ ident-tx	-.494 ****	-.414 ****	-.472 ****	-.456 ****	-.409 ****	-.29 **	-.34 ****	-.406 ****	-.469 ****	-.161
IPQ ident-m	-.348 ****	-.336 ****	-.37 ****	-.326 ****	-.334 ****	-.252 **	-.28 **	-.324 ***	-.335 ****	-.169
IEQ	-.489 ****	-.675 ****	-.458 ****	-.492 ****	-.422 ****	-.467 ****	-.524 ****	-.524 ****	-.463 ****	-.292 ***
TEQ†	-.442 ****	-.501 ****	-.389 ****	-.395 ****	-.374 ****	-.369 ****	-.473 ****	-.42 ****	-.394 ****	-.32 ***
BMQ-n	-.112	-.093	-.112	-.084	-.034	-.094	-.074	-.159	-.059	-.072
BMQ-c	-.274 **	-.321 ***	-.164	-.138	-.284 **	-.306 ***	-.312 ***	-.255 **	-.154	-.305 ***

Note: ident-tx = extended 42 item version of identity sub-scale (generic, renal and transplant specific symptoms; ident-m = immunosuppressive medication side-effects (23 items); IEQ = illness effects questionnaire; TEQ = treatment effects questionnaire; BMQ-n = beliefs about the necessity of medication; BMQ-c = concerns about medication; GH = general health; PF = physical functioning; BP = bodily pain; VT = vitality; RPh = role limitations due to physical problems; REm = role limitations due to emotional problems; SF = social functioning; MH = mental health; MCS = mental component score; PCS = physical component score

† = Spearman's correlations

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Results showed significant associations between cognitions and both the physical and psychological SF-36 dimensions, with more negative beliefs being associated with poorer HQoL. Correlation coefficients ranged from r_s = .29 to r_s = .49 for identity-tx (expanded 41-item symptom checklist) and from r_s = .23 to r_s = .46 for IPQ consequences. Stronger control beliefs were associated with higher SF-36 scores, i.e. better HQoL (r_s = .20 to r =.32).

Consistent with previous work, strong correlations were also observed between illness intrusiveness, treatment intrusiveness and SF-36 scores, indicating that higher scores in

illness and treatment intrusiveness were associated with poorer HQoL. Correlation coefficients ranged from r = -.29 to r = -.67 for illness intrusiveness and from r = -.32 to r = -.50 for treatment intrusiveness. The latter associations (i.e. TEQ) however ceased to be significant when the effect of illness intrusiveness was partialled out, clearly suggesting a minimal effect of treatment perceptions on HQoL in TX patients. When partial correlation analysis was reversed (i.e. partialling out treatment intrusiveness in correlations between IEQ and SF-36), illness intrusiveness remained a significant correlate of HQoL, albeit the strength of observed associations was lower.

Medication beliefs were also significantly correlated with HQoL. Concerns regarding the effects of immunosuppressive medication had a negative effect on physical and psychosocial dimensions of HQoL (MCS, GH, MH, PF, REm, SF, VT) (r = -.26 to r = -.32). 'Timeline' and 'medication necessity' beliefs appeared to be largely unrelated to HQoL in transplant patients although this is likely to be due to insufficient range of values in these two variables. The vast majority of patients believed strongly in the chronic nature of their condition and expressed strong beliefs regarding the necessity of their prescribed immunosuppressive medication.

1.3.d TxEQ Sub-scales

Higher levels of worry regarding TX viability from the TxEQ were associated with more compromised HQoL, particularly with respect to emotional well-being sub-scales. As seen in Table 9.14 below TX worry was inversely correlated with MCS (r = -.314, p = .001); MH (r = -.404, p = .0001); GH (r = -.231, p = .017); SF (r_s = -29, p = .003); and VT (r_s = -.356, p = .0001). Perceived responsibility correlated significantly only with physical functioning (r_s = -.198, p = .04).

1.3.e Mood variables

Significant associations were also found between mood measures (CDI; PANAS-PA; PANAS-NA) and HQoL. As anticipated higher cognitive depression and negative affect correlated with poorer HQoL whereas the opposite was true for positive affect. It is also of note that cognitive depression and positive affect were associated with the physical dimensions of SF-36 (PCS; PF; BP; RPh; GH) as well as the psychological SF-36 sub-scales (as anticipated).

Table 9.15: Correlations between mood and HQoL in Transplantation

	PF†	GH	BP†	RPh†	REm†	MH	SF†	VT†	PCS†	MCS
BDI	-.425 ****	-.473 ****	-.364 ****	-.468 ****	-.516 ****	-.492 ****	-.465 ****	-.515 ***	-.326 ****	-.349 ****
CDI	-.309 ****	-.381 ****	-.281 **	-.376 ****	-.508 ****	-.503 ****	-.396 ****	-.449 ****	-.212 *	-.453 ****
PNS-NA	-.152	-.252 *	-.092	-.208*	-.281 *	-.391 ****	-.343 ***	-.208 *	-.077	-.219 *
PNS-PA	.314 **	-.391 ****	.319 **	.445 ****	.327 ****	.491 ****	.505 ****	.435 ****	.278 **	.385 ****

† Spearman's correlation coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

1.3.f Cognitive functioning

Correlations were used to test the associations between cognitive functioning and HQoL in transplantation. As before two NP indices were used: a composite score of NP performance (summary of standardised individual NP test scores; NP-TO) and count of NP impairments (NP-Norm: number of NP tests in which TX patients performed worse than age-respective norms). Significant associations were found between NP functioning and HQoL, primarily with respect to physical dimensions of SF-36 (see Table 9.16). The more NP impairments experienced and the less efficient the cognitive functioning the more compromised the HQoL.

Table 9.16: Correlations between indices of cognitive functioning and HQoL in TX

	NP-TO		NP-Norm	
SF-36 sub-scales	**Full**	**Partial**	**Full**	**Partial**
PCS†	.346***	.102	-.339****	-.202*
MCS	-.209	.001	-.046	.116
General Health	.185	.134	-.233*	-.194*
Bodily Pain†	.183	-.127	-.285**	-.140
Physical Functioning†	.334****	.122	-.311***	-.210*
Role Physical†	.24*	.174	-.315***	-.262**
Role Emotional†	.054	.034	-.197*	-.179 p<.058
Mental Health	-.168	-.043	-.124	-.219*
Social Functioning†	-.084	.127	-.202*	-.105
Vitality†	-.010	.009	-.112	-.029

Note: NP-TO = composite score of NP performance; NP-Norm = count of NP impairments

† Spearman's correlations coefficient

* p <.05. ** p <.01. *** p <.001. **** p <.0001.

Partial correlations however (partialling out the effect of age and ESRD-SI) altered the findings.

Overall NP performance (NP-TO) for instance was no longer significantly associated with SF-36 scores. In contrast most of the associations between the number of NP impairments and HQoL remained significant even after the effect of ESRD-SI was partialled out (there was no need to include age as NP impairments were defined relative to age norms). However observed correlation coefficients were lower. It is also of note that partialling out ESRD-SI, the correlations between mental health and NP impairments became significant ($r = -.219$, $p = .02$).

1.3.g Subjective Cognition

Correlational analysis showed significant associations between SF-36 and indices of subjective cognition in TX. Perceptions of greater cognitive decline since transplantation (SCS-TO) correlated with lower SF-36 scores except for mental health and MCS (correlational coefficients ranged between $r_s = -.20$ to $r_s = -.23$).

Partial correlations adjusting for the effect of age and renal severity and comorbidity removed some of the significant associations with PF, BP, VT, RPh and SF. Only the associations with GH and RPh retained their significance (see Table 9.17).

Table 9.17: Correlations between indices of subjective cognition and HQoL in TX

	SCS-TO	
SF-36 Sub-scale	**Full**	**Partial**
PCS†	-.232 *	-.205 *
MCS	-.064	-.112
General health	-.229 *	-.208*
Bodily pain†	-.208 *	-.160
Physical functioning†	-.217 *	-.146
Role physical†	-.256 **	-.272**
Role emotional†	-.193 *	-.150
Mental Health	-.125	-.158
Social Functioning†	-.196 *	-.146
Vitality†	-.220 *	-.039

† Spearman's correlations coefficient

* p <.05; ** p <.01

1.3.h Multivariate analysis

To examine which variables accounted for the variance in HQoL, hierarchical multiple regression analyses using the stepwise method were subsequently conducted. Physical and mental component scores (PCS; MCS) were regressed on the sociodemographic, clinical, neuropsychological and psychological variables. The variables selected for these analyses were those significantly associated with the outcome in question in the univariate analyses. Regressions were performed on the combined TX sample as the small number of LRD patients made running the regressions separately for CAD and LRD patients inappropriate.

Predictors used in the PCS regression included: age, education, work status, income (Block 1); ESRD severity, GFR, albumin and haemoglobin (Block 2); Overall cognitive functioning, number of NP impairments, subjective cognitive complaints (Block 3); IEQ, TEQ, IPQ consequences, IPQ control, IPQ identity-tx (extended 41-item symptom list) (Block 4); and cognitive depression (Block 5).

The results (as in the last step of regression) indicated that age, income, ESRD severity, haemoglobin, perceptions of illness disruption and identity beliefs were significant multivariate predictors of PCS in transplant patients, accounting for 65.8% (Adj.R^2 = 63.6%) of the variance (see Table 9.18). Sociodemographic and clinical variables jointly explained the largest amount of PCS variance (R^2 = 53.5%; ΔR^2 = 51.4%) with measures of variance-based effect sizes indicating a large effect size (f^2 = 1.56 jointly).

Among the patients' beliefs only perceptions of illness intrusiveness and perceived symptoms appeared to impact on physical HQoL explaining ΔR^2 = 12.3% of the total variance (f^2 = .36 indicative of small effect size). Mood, added in the last step did not contribute significantly in the PCS prediction.

Multiple regressions in which the order of beliefs and mood was reversed (i.e. mood was entered before patients cognitions) revealed a similar pattern of results (see Appendix L). A total of 65.8% (Adj.R^2 = 63.6%) of the variance was explained by work status, age, income, ESRD severity, haemoglobin, cognitive depression, illness intrusiveness and identity beliefs.

Table 9.18: Hierarchical multiple regressions to predict PCS and MCS in TX: standardised regression coefficients and cumulative variance explained

	PCS			MCS		
	β	Cum R^2	Cum Adj.R^2	β	Cum R^2	Cum Adj.R^2
Block 1						
Work Status	.040 ns	.204 f^2 = .596	.197			
Age	-.200**	.270 f^2 = .193	.257	.289***	.073 f^2 =.102	.065
Income	.182**	.302 f^2 =.094	.283			
Education						
Block 2						
ESRD severity	-.342****	.462 f^2 = .471	.443			
GFR				.144 ns	.124 f^2 =.071	.109
Haemoglobin	.151*	.535 f^2 = .211	.514			
Albumin						
Block 3						
NP functioning						
NP impairments						
Block 4		f^2 = .360		f^2 = .184		
IEQ	-.254****	.630 f^2 =.278	.610			
TEQ						
IPQ conseq				-.144	.212 f^2 =.121	191
IPQ control						
IPQ identity-tx	-.199**	.658 f^2= .0819	.636			
BMQ-concerns				-.196*	.257 f^2 =.063	.230
TxEQ worry						
Block 5						
CDI				-.200*	.284 f^2 =.038	252

Note: f^2= variance-based measure of effect size calculated as $f^2 = \Delta R^2 / (1- R^2_{Total})$; cum = cumulative; GFR = glomerular filtration index; NP = neuropsychological; IEQ = illness intrusiveness; TEQ = treatment intrusiveness; conseq = consequences; identity-tx = identity score based on the 41 items used for TX patients (IPQ core items, renal specific and TX immunosuppression side effects); TxEQ = worry about transplant from the Transplant Effects Questionnaire; CDI = cognitive depression index

* p <.05. ** p <.01. *** p <.001. **** p <.0001. ns = non significant

In the multiple regression to explain MCS, age (Block 1); ESRD severity, GFR levels, Haemoglobin (Block 2); NP deficits (Block 3); IEQ, TEQ, IPQ consequences, BMQ concerns (Block 4); worry about TX viability (Block 5); CDI (Block 6) were used.
It should be noted that even though Block 2 variables were not directly related with MCS scores, they were still entered in the regression as they correlated significantly with more than half of the SF sub-scale scores that contribute to the calculation of MCS scores. It was also thought that their inclusion would provide a more stringent test for the effect of patients' beliefs on emotional well-being over and above the effect of medical indicators.
To reduce the cases-to-variables ratio, only cognitive depression, the stronger univariate MCS correlate, was included in preference to PANAS sub-scales for these regression analyses. Three sets of regressions were performed: without the inclusion of mood, with mood entering last after patients cognitions, and finally with mood entering before patients' beliefs.

When mood was not included in the analysis, the final regression indicated that age (β = .289; R^2 = 7.3%), glomerular filtration rate (β = .171; ΔR^2 = 5.1%) illness consequences (β = -.244; ΔR^2 = 8.7%) and concerns about medication (β = -.220; ΔR^2 = 4.5%) explained R^2 = 25.7% (Adj.R^2 = 23%) of the MCS variance.

Inclusion of mood improved model prediction but also rendered the effect of GFR and consequences beliefs non significant. The resulting regression model to predict MCS in the combined TX sample explained R^2 = 28.4% (Adj.R^2 = 25.2%) of the variance with only age, concerns about medication side-effects and cognitive depression being significant predictors at the last stage of entry (Table 4). The effect of perceived consequences (IPQ), which was significant at step 3 and 4, was not found to be significant at the last stage of entry (CDI), suggesting a mediating effect for cognitive depression. F^2 values indicated small effect sizes for all significant predictors.

Reversing the order of entry so that mood entered before patients' cognitions did not considerably alter the results. The resulting regression model explained R^2 = 26.9% (adj.R^2 = 24.3%) of the variance in MCS scores. Significant predictors (last step) were age, cognitive depression, and BMQ concerns. Perceived illness consequences did not emerge as a significant predictor (see Appendix L).

Section 3: HQoL comparisons – Dialysis vs. Transplantation

HQoL levels reported by transplant recipients were compared to those reported by dialysis patients. These analyses were performed using (a) the combined dialysis sample (hence collapsing across all four dialysis groups) in order to evaluate how dialysis treatment in general compared to transplantation and (b) the HD and PD groups separately. In all comparisons, casemix differences between transplant and dialysis patients were statistically controlled for using ANCOVAs, providing that they were also significantly associated with HQoL.

3.1 Two group comparisons: combined dialysis vs. TX

3.1.a Sample characteristics

Casemix differences between TX and dialysis patients were found (see chapter 6; section 2.6.a). There were also significant group differences between transplant and dialysis patients in biochemistry. Of them, only the differences in serum albumin and haemoglobin levels will be discussed as being more relevant, i.e. empirically linked to HQoL (Lowrie *et al.*, 2000). As expected, transplant patients had significantly higher albumin (U = 2268, p = .0001) and Hb (t(220,55) = -9.22, p = .0001) than dialysis patients. Variables were used as covariates in subsequent comparisons providing that they were significantly associated with the outcome in question (Table 9.19).

Table 9.19: The associations between casemix differences and HQoL in the combined dialysis and TX sample

	Covariates used in dialysis vs. TX comparisons									
	PF	**GH**	**BP**	**RPh**	**Rem**	**MH**	**SF**	**VT**	**PCS**	**MCS**
Work status	+	+	+	+	+	+	+	+	+	-
Income	+	+	+	+	+	+	+	+	+	-
ESRD SI	+	+	+	+	+	+	+	+	+	-
Diabetes	+	+	+	+	-	+	+	+	+	-
Heart disease	+	+	+	+	+	+	+	+	+	-
RRT time	+	+	+	+	-	-	+	+	+	-
Time on treatment	-	+	-	+	-	-	+	+	-	+
Haemoglobin	+	+	+	+	+	+	+	+	+	-
Albumin	+	+	+	+	+	+	+	+	+	+

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

3.1.b HQoL absolute scores

ANCOVAs between transplant and the combined dialysis sample (covarying for work status, income, ESRD severity, time on RRT, time on current treatment modality, diabetes and ischaemic heart disease as appropriate) showed that HQoL was superior in transplant patients.

In the first set of comparisons, no adjustments were made for biochemistry casemix differences. Transplant patients scored significantly higher in 8 of the 10 SF-36 sub-scales: PCS ($F(7, 234) = 36.359$, $p = .0001$), PF ($F(7, 235) = 28.431$, $p = .0001$), RPh ($F(8, 233) = 6.057$, $p = .015$), BP ($F(7, 235) = 6.734$, $p = .01$), GH ($F(8, 233) = 92.635$, $p = .0001$), VT ($F(6, 236) = 16.887$, $p = .0001$), SF ($F(8, 234) = 24.286$, $p = .0001$), and MCS ($F(2, 255) = 7.561$, $p = .006$). A tendency for higher MH scores in TX patients was noted but did not reach significance ($F(6, 236) = 3.599$, $p = .059$).

In the second set of comparisons haemoglobin and albumin were also included as covariates. These ANCOVAs indicated that transplant patients' scores were still significantly higher in PCS ($F(9, 227) = 12.261$, $p = .001$), PF ($F(9, 228) = 11.047$, $p = .001$), GH ($F(10, 226) = 34.534$, $p < .000$), VT ($F(10, 227) = 12.129$, $p = .002$) and SF ($F(10, 227) = 7.372$, $p = .007$).

3.1.c Prevalence of severe HQoL impairments

Chi-square analysis of the observed prevalence of HQoL impairment in dialysis and transplant patients confirmed the ANCOVAs results in that HQoL impairments were more prevalent in dialysis patients particularly with respect to physical well-being.

When HQoL impairment were defined as more than 1 *SD* below norms (indicative of mild-moderate impairment), chi-square analysis indicated that a significant treatment effect in both MCS and PCS classification. Significantly more dialysis patients ($n = 113$, 77.9%) had lower than average PCS scores (1 *Sd* or more lower than norms) than did transplant patients ($n = 22$, 19.8%; $\chi^2(256) = 49.621$, $p = .0001$). A larger proportion for the dialysis patients ($n = 39$, 26.9%) had MCS scores lower than 1 or more *SD*s than

those of general population compared to transplant patients (n =10, 9%; $\chi^2(256)$ = 12.998, p = .0001).

Chi square analysis was also used to compare the prevalence of severe (i.e. more than 2 *SD*s below norms) HQoL impairments. Differences in the prevalence rates of PCS severe impairments persisted when using this criterion, with significantly more dialysis patients (n = 77, 53.1%) scoring in the range of severe PCS impairments relative to transplant patients (n = 22, 19.8%; χ^2 (256) = 29.367, p = .0001).
No differences were noted in the prevalence rates of severe MCS impairment between dialysis (n = 10, 6.9%) and TX patients (n = 3, 2.6%; $\chi^2(256)$ = 2.294, p = .13).

3.2 Three groups comparisons: HD vs. PD vs. TX

3.2.a Sample characteristics

Three group comparisons (HD; PD; TX) indicated significant group differences in sociodemographic and medical variables: income, perceived work ability, time on current treatment, time on RRT in general, ESRD severity index and diabetic status. These casemix differences were controlled for in subsequent comparisons, providing that they were significantly associated with the particular SF-36 score.

Table 9.20: The associations between casemix differences and HQoL in HD vs. PD TX comparisons

	Covariates used in PD vs. HD vs. TX comparisons									
	PF	**GH**	**BP**	**RPh**	**REm**	**MH**	**SF**	**VT**	**PCS**	**MCS**
Income (2 groups)	+	+	+	+	+	+	+	+	+	-
ESRD SI	+	+	+	+	+	+	+	+	+	-
Diabetes	+	+	+	+	-	+	+	+	+	-
RRT time	+	+	+	+	-	-	+	+	+	-
Current treatment	-	+	-	+	-	-	+	+	-	+
Haemoglobin	+	+	+	+	+	+	+	+	+	-
Albumin	+	+	+	+	+	+	+	+	+	+

+ = significant association / used as a covariate

- = non significant association / not used as a covariate

3.2.b Absolute HQoL scores

As significant HQoL differences were noted between HD and PD patients (see sub-section 1.2.a) three group comparisons (HD vs. PD vs. TX) were undertaken using ANCOVAs covarying for group casemix differences (see Table 9.19).
These were followed by Tukey's HSD post-hoc tests if the main effect of the omnibus ANOVAS was significant at $p < .05$. Residualised SF-36 scores, in which the effect of casemix differences (diabetes, ESRD severity, time on RRT, time on current treatment and income) has been partialled out (as appropriate, i.e. only if significant with the SF-36 score in question), were used as dependent variables in post-hoc analyses.

In the first set of comparisons no adjustments were made for biochemical differences as these were seen as a reflection of treatment differences. Covariates used were thereby chosen among the remaining sociodemographic and clinical variables.
Results indicated a significant treatment effect on: PCS ($F(6, 235) = 17.835$, $p = .0001$); PF ($F(6, 236) = 12.834$, $p = .0001$); BP ($F(6, 236) = 5.375$, $p = .005$); GH ($F(7, 234) = 45.917$, $p = .0001$); SF ($F(7, 235) = 13.775$, $p = .0001$); VT ($F(7, 235) = 9.312$, $p = .0001$), RPh ($F(7, 234) = 3.315$, $p = .038$); and MCS ($F(3, 254) = 5.321$, $p = .005$). Despite the significant effect on MCS, no differences were found in REm, MH suggesting that when casemix differences are accounted for, HD, PD and TX patients report equivalent levels of emotional well-being.
Post-hoc tests revealed that TX patients had higher scores than both HD and PD patients in PCS ($ps = .0001$); PF ($ps = .001$); GH ($ps = .0001$); SF ($ps < .001$); and VT ($ps < .01$). Differences in BP and MCS were only significant between TX and PD patients and not between TX and HD patients, with transplant patients reporting higher emotional well-being (MCS) and less pain (BP) compared to PD patients.

After adjustment for laboratory values (albumin and haemoglobin), group differences were still evident in PCS ($F(8, 228) = 6.253$, $p = .002$), PF ($F(8, 229) = 4.491$, $p = .012$); GH ($F(9, 227) = 17.849$, $p = .0001$); SF ($F(9, 228) = 4.267$, $p = .015$); and VT ($F(9, 228) = 5.636$, $p = .004$). The previously observed differences in BP and MCS failed to reach significance in these comparisons.
Subsequent post-hoc tests were performed on the residualised scores, i.e. absolute scores regressed to casemix differences as described above including albumin and Hb levels. These revealed only two significant differences. One in GH with PD and HD

patients having significantly lower GH scores than TX patients and another in PCS. The latter was only significantly different between PD and TX patients (p = .046). When casemix differences were accounted for, no other post-hoc tests revealed significant differences

It should be noted that post-hoc tests with no casemix adjustments (i.e. using absolute SF-36 scores rather than the residualised SF-36 scores) showed more significant group differences always in favour of transplantation over both PD and HD groups: PCS; PF; BP; GH; RPh; SF; VT.

3.2.c Prevalence of HQoL impairments

Chi-square analysis showed that HQoL impairments were more prevalent in HD and PD patients compared to TX patients. Results indicated that relative to HD and PD patients, significantly less TX patients had PCS scores lower than 1 *SD* ($\chi^2(254) = 50.082$, p = .0001) or 2 *SDs* ($\chi^2(254) = 29.784$, p = .0001) below population mean.
The HQoL advantage of transplantation was also evident in MCS score classification ($\chi^2(254) = 14.312$, p = .001 for MCS more than 1 *SD* below norm; $\chi^2(254) = 8.59$, p = .014 for MCS more than 2 *SDs* below norm)

Section 4: Summary of results

- Physical HQoL is substantially impaired in dialysis patients relative to the general population. Emotional well-being (HQoL) on the other hand remains within normal limits.

- Comparisons between different dialysis treatments indicated that PD patients have lower scores in MCS and vitality compared to HD. Four group comparisons have similarly shown that CAPD patients scored significantly worse on vitality than the two HD groups. Vitality differences in both cases ceased to be significant after adjustments for albumin levels.

- Regression analysis indicated that age, employment status, dialysis adequacy, perceptions of illness intrusiveness and cognitive depression explained 58.7% of the variance in PCS scores in dialysis.

- The regression model to predict MCS scores explained 35.8% of the variance with dialysis treatment, treatment intrusiveness and cognitive depression being significant at the last step of the regression.

- HQoL in TX patients is comparable to that of the general population and superior to that of dialysis patients, particularly with respect to physical well-being.

- A range of factors was associated with HQoL in TX patients. Age, income, haemoglobin, illness intrusiveness and identity accounted for 65.8% of variance in PCS whereas age, medication concerns and cognitive depression explained 28.4% in MCS.

CHAPTER 10:
DISCUSSION OF PATIENTS' BELIEFS AND HQOL FINDINGS

This chapter presents a discussion of the study and related findings on HQoL and illness and treatment beliefs in ESRD. It is organised in three sections: section one focuses on patients' beliefs, section 2 discusses HQoL, and section 3 discusses determinants of HQoL in dialysis and TX.

Section 1: Illness and treatment beliefs

One of the aims of the present study was to examine the content and nature of illness and treatment cognitions in ESRD patients and to examine their interrelationships and their explanatory role in outcomes such as HQoL. The present study used Leventhal's SRM as an explanatory and predictive tool. The model's scope was expanded to include perceptions of illness intrusiveness and perceptions of treatment (Horne, 1997; 2003b). Treatment cognitions assessed comprised perceptions of treatment intrusiveness (Greenberg & Peterson, 1997b), and medication beliefs (Horne *et al.*, 1999).

1.1 Dialysis

Dialysis patients have a dominant view of their illness, comprised of a strong illness identity, mainly external attributions for their condition and pessimistic beliefs about controllability, consequences and timeline of their illness. Consistently high scores on the identity, consequences and timeline beliefs (and the high percentage of above midpoint scores) suggest that dialysis patients believe their illness has a wide range of symptoms, a profound impact on their lives and is likely to last a long time. Illness and treatment intrusiveness scores indicated moderate levels of distress compared to other medical patients (Greenberg & Peterson, 1997b) and are comparable to those reported in other dialysis samples (Eitel *et al.*, 1995; Kimmel *et al.*, 1998b; 2000; Patel *et al.*, 2002; Sacks *et al.*, 1991). These negative illness beliefs do not appear to be just a

consequence of having a chronic physical illness. When compared to patients with rheumatoid arthritis, diabetes and chronic back pain on the IPQ (Weinman *et al.*, 1996), dialysis patients in this study had lower control beliefs; consequences beliefs were however similar across groups. The lack of variance on beliefs about the timeline of their illness reflects these patients' accurate understanding of their illness.

Investigation of patients' causal beliefs regarding their illness revealed that the vast majority of dialysis patients held a causal model which featured prominently attributions to chance, poor medical care and heredity. Genetically inherited disorders such Adult Polycystic Kidney disease that may be diagnosed quite early on before renal implications manifest, are some of the commonest causes of ESRD. Heredity beliefs reflecting patients' knowledge were anticipated at least for a subgroup of patients. The results indeed showed that heredity beliefs are more likely to be reported by dialysis patients with family predisposition to kidney disorders, such as polycystic kidney disease.

The largest percentage of patients attributed ESRD to chance. This finding may reflect cases of medical uncertainty in establishing primary kidney disease diagnosis, and /or patients' uncertainty or poor understanding or lack of knowledge about their medical history. In cases of non-established aetiology for ESRD, chance attributions may be regarded as realistic as well as self-protective.

Perhaps even more intriguing is the finding that a substantial number of dialysis patients attributed ESRD to poor medical care in the past. Attributions related to medical mismanagement were also found in qualitative investigations of dialysis patients (Krespi *et al.*, 2003). In our study, such attributions were more frequent in PD and diabetic patients. Whether this implied 'poor medical care' as in poor self-management by the patients themselves (e.g. poorly controlled diabetes leading to ESRD; uncontrolled hypertension) or poor medical care within the context of the health services and health care delivery as in misdiagnosis, late diagnosis or lack of timely or effective treatment, could not be determined in this study. Both interpretations are equally plausible. Nevertheless in both cases such causal attributions appear to echo patients' relative dissatisfaction with medical care either before or after entering the system as ESRD patients.

1.2 Transplantation

TX patients' illness model consisted of chronic timeline beliefs, causal attributions of chance, hereditary and poor medical care, and reports of few symptoms associated with their condition. TX patients also expressed more positive views regarding the impact of illness and treatment on their lives and the controllability of their condition in comparison to patients on dialysis. Illness and treatment intrusiveness were in the mild range and IPQ consequences scores indicated ambivalence regarding the severity of illness consequences on their lives.

TX patients were relatively unconcerned about the side effects of immunosuppression and expressed strong beliefs in the necessity of their prescribed medication. 'Necessity' scores are comparable with those reported by other patient groups (e.g. asthma and diabetes) whereas 'concern' scores were somewhat lower especially in comparison with cardiac, asthma and psychiatric patients (Horne *et al.*, 1999). These low concern scores may reflect uncertainty about the impact of medication rather than an unconcerned attitude. Alternatively low worry scores may be due to the fact that patients tend to receive detailed information regarding potential side effects of anti-rejection medication early post-TX or even before the operation.

Lower control and more chronic timeline beliefs were found for patients on Cyclosporin compared to those on Tacrolimus but these effects disappeared when time since TX and age were controlled for. The decline in graft function with the resultant increase in physical symptoms, and the manifestation of more immunosuppressive side-effects over time might explain why patients who have had their TX for a long time expressed stronger views that ESRD is chronic and less amenable to control.

1.3 Intercorrelations between beliefs

Illness and treatment cognitions showed logical interrelations in both dialysis and TX. For example, TX patients were more likely to regard their immunosuppressive medication to be necessary if they viewed their illness as chronic, with negative consequences. This replicates findings in other patient groups (Horne & Weinman, 2002). Strong concerns regarding immunosuppressive medication were related to

patients' symptoms, more negative evaluation of treatment burden and more negative perceptions regarding the intrusiveness and consequences associated with illness.

Perceptions of treatment intrusiveness, a construct that refers to the impact of treatment on patients' lives was significantly associated with all SRM components except timeline. Of note are also the high correlations between illness and treatment intrusiveness as measured by the Illness Effects Questionnaire and the Treatment Effects Questionnaire. These are more likely than not to reflect the conceptual similarities and substantial item overlap across the two measures, and may also indicate how patients attempt to mirror their responses to the two questionnaires.

There are however other likely interpretations. For instance, the observed significant associations may also imply that the distinction between the illness and treatment may become more blurred in ESRD than perhaps in other illness groups. In ESRD medical treatment is very prescriptive (dialysis is chronic and ongoing procedure), the impact of treatment and that of illness may become less easily differentiated that may explain patients' responses. This distinction may be particularly difficult to make in TX reflecting in addition patients' ambivalence as to whether transplantation constitutes a treatment for an underlying condition or a new state of health, a new condition or a new illness (Johnson, 1990).
Although specific instructions were written detailing the intended meaning of the terms 'illness' and 'treatment', namely directing patients to think of their ESRD as their illness and their RRT (including associated medication and diet and fluid intake as applicable) as their treatment, it is possible that questionnaire items may be perceived and interpreted very differently by respondents (Mallinson, 2002).

The study findings also showed that illness cognitions (and the SRM components) were also related in a logically consistent way. The pattern of interrelations exhibited is consistent with those observed by studies on various other illnesses (e.g. Moss-Morris *et al.*, 1996; Petrie *et al.*, 1996; Weinman *et al.*, 1996), a recent metanalytical review (Hagger & Orbell, 2003), and with Leventhal's model (1980). Correlations were strong and significant but did not exhibit associations of a magnitude that was indicative of conceptual overlap. Identity beliefs were negatively associated with control but positively related to serious consequence beliefs and illness intrusiveness. Control beliefs were inversely related to illness intrusiveness, illness consequences and

symptom (identity) beliefs and the more negative beliefs of illness intrusiveness and illness consequences were also inter-correlated. Causal attributions were also associated with other illness cognitions (Shiloh *et al.*, 2002). Attributing illness to own behaviour or medical care was associated with heightened perceptions of illness symptoms, consequences and illness intrusiveness, although these associations could be explained by differences in diabetic status between patients endorsing or not these causal beliefs.

1.4 Treatment modality and beliefs

It has been suggested that illness representations are based on factual information, personal experience and a variety of cultural beliefs. It is reasonable to assume that illness and treatment beliefs develop and change over the course of an illness and hence the experience of different treatments is likely to influence them. As described earlier, treatment exigencies vary greatly in different dialysis treatments and between dialysis and transplantation. The differential treatment demands placed upon patients should affect beliefs about illness and treatment intrusiveness, perceptions of control, consequences and timeline beliefs. The data reported here provide modest support that illness representations and cognitions appear to be formed at least in part as a function of personal treatment experience.

Comparisons involving transplant vs. dialysis patients revealed significant group differences consistently across the various beliefs assessed. Transplant patients believed less strongly that their condition is chronic, reported less symptoms and perceived more control and less disruption associated with either their illness or their treatment relative to their dialysis counterparts. These findings are consistent with previous studies (Devins *et al.*, 1990a) and with the prediction that the less intrusive and demanding nature of transplantation should lead to more positive illness and treatment representations. Constraints can be extensive, for example when renal replacement involves maintenance dialysis that must be administered repeatedly. CAPD for example typically involved four daily 30- to 60-minute dialysate fluid exchanges; HD requires thrice 3-5 hour long sessions for which the vast majority of patients have to attend a hospital or satellite centre. Successful transplantation in contrast, involves little more than daily ingestion of immunosuppressive medications. As all casemix differences were statistically controlled, the observed differences in illness and treatment beliefs

should reflect the effect of differential treatments experienced by the two groups rather than other sociodemographic and medical variables.

A word of caution is however warranted regarding the interpretation of illness and treatment perceptions in TX and the meaning attributed in the terms illness and treatment by transplant patients although specific instructions were used to clarify the intended meaning of the terms. It is unclear for instance whether transplantation, immunosuppression or both were construed as the treatment by TX patients.

Illness beliefs appeared to be largely unrelated to dialysis modality, although inspection of group mean scores revealed a consistent pattern across all illness cognitions: APD patients held more positive illness beliefs. For example, they had the strongest perceptions of control and the lowest perceived consequences, followed by hospital HD, home HD with the CAPD patients last. Comparative analysis (with casemix adjustments) however failed to reveal systematic significant differences in illness cognitions between any of the dialysis modalities. In keeping with previous research (Devins *et al.*, 1983; 1990; 1994; Sacks *et al.*, 1990), our findings indicate that ESRD patients on dialysis hold similar beliefs regarding their illness despite the experience of different treatments. The only exceptions to this were the observed significant associations between PD treatment and causal attributions of 'self-blame' and 'poor medical care'. These are however more likely to reflect the differential proportion of patients with diabetes between dialysis treatments. Significant associations were found between prevalence of diabetes (and IDDM as primary kidney disease diagnosis) and attributions of 'self-blame' but not with poor medical care causal beliefs. As chi-square analysis does not permit casemix adjustments it was not possible to determine whether dialysis modality or alternatively diabetes might be driving/affecting patients' causal attributions.

The latter explanation is however favoured on several grounds. Firstly, comparative analysis on the other illness beliefs demonstrated that the effect of casemix variables (including diabetes) outweighed that of dialysis modality. For instance casemix adjustments (including diabetes) muted the effect of dialysis treatment on control beliefs, which was significant in uncontrolled comparisons. It is also a more plausible explanation; as ESRD is a common diabetic complication, perhaps one should also expect that living with diabetes might fuel stronger attributions of poor medical care or

internal attributions (i.e. 'own behaviour') as diabetic control is so dependent on personal behaviour (Norris *et al.*, 2002).

The only significant difference between patients on different dialysis modalities was in perceptions of treatment burden. Patients on CAPD perceived significantly more treatment-related disruption compared to APD patients, a finding that substantiates the differential objective demands and procedural differences of CAPD vs. APD. In contrast to APD that is automatically performed overnight, CAPD involves repeated daily administrations (three or four exchanges a day). It hence requires more patient' input, takes up more of patients' waking time and is more likely to interfere more with everyday activities and patients' lifestyle. Bro *et al.* (1999) reported that significantly more time for work, family, and social activities was available to patients on APD compared those on CAPD. This is the first report to document significant differences in treatment perceptions between the two PD groups. Maiorca *et al.* (1995a; 1996c) for instance commented that after a number of years there may be burnout of either the CAPD patient and their caregiver but no comparisons with other dialysis treatment groups were undertaken. From a methodological point of view, this treatment effect provides some support the discriminant validity of the TEQ.

The mean difference between APD and Home HD patients' TEQ scores approached but did not reach significance. There was a tendency for home HD patients to perceive more treatment disruption compared to APD patients. The relatively low numbers of APD and home HD patients assessed, might have undermined the power to detect significant differences between the two home based treatments.

Contrary to previous studies (Wolcott & Nissenson, 1988a) patients on HD treatments did not perceive more treatment burden relative to PD patients. The lack of significant differences in treatment perceptions between patients on HD and those on PD is noteworthy. PD has been advocated as the treatment that potentially allows more control and increased independence in patients' lives (Ronco & La Greca, 1997), in that it avoids repeated visits to dialysis units, is pain free, quick to perform, thereby minimising disruption to patients' lives. HD, on the other hand, albeit more common treatment, is often described as time-consuming, invasive, and painful (Binik *et al.*, 1989; Levy, 2000; 2003). Patients' perceptions of treatment intrusiveness did not echo these notions as both dialysis groups (HD and PD) perceived their respective treatments

as imposing the same level of disruption on physical, social and personal life and behaviours.

Four group comparisons also did not indicate a more favourable evaluation of the home treatments (APD; CAPD; home HD). They were on the whole perceived equally burdensome or disruptive as hospital-based HD. Although this may at first glance seem counterintuitive, especially if one considers the logistics of hospital vs. home care, there are some, perhaps less obvious, advantages associated with hospital HD, such as closer medical supervision and more opportunities for social support among patients. Regular contact with hospital staff and other patients enables the creation and maintenance of strong social networks and resources as well as the reassurance of repeated, often 3 times per week, health care professional involvement in care. The reassuring nature of this may mitigate against the impact of the time disruption of hospital- based HD. It is possible that these factors, not measured in this study, might affect at least indirectly patients' treatment evaluation, and hence explain the lack of significant differences in TEQ perceptions.

In conclusion study findings suggest that ESRD patients on different dialysis modalities expressed different beliefs regarding the burden of treatment albeit not always significantly so. As however study assessments focused solely on perceptions of treatment intrusiveness, this might have lead to a rather perfunctory measure or assessment of treatment perceptions. Therefore, it remains unclear whether other treatment cognitions (e.g. treatment effectiveness) might also differ between groups. Recent research in cardiac disease (Hirani *et al.* 2003) showed that treatment representations comprise beliefs about 'treatment value', 'emotional impact of treatment', 'decision dissatisfaction', and 'treatment pessimism'.

Section 2: HQoL

One of the principle outcomes assessed in this study was HQoL. The objectives were to examine HQoL levels in ESRD patients, to compare HQoL across all form of RRTs and to identify the sociodemographic, clinical, cognitive and psychological variables that determine HQoL in ESRD. Although HQoL has been extensively studied in ESRD, this study was the first to include patients on four dialysis modalities and two groups of kidney TX patients.

2.1 Dialysis

In accordance with previous research (Lamping *et al.*, 2000; Merkus *et al.*, 1999b; Mingardi *et al.*, 1999) results showed that dialysis has a significant impact on patients' physical aspects of HQoL whereas mental health and emotional well-being is generally similar to normative data.

Lower scores in the dialysis patients were found in all SF-36 domains that reflect discomfort by physical impairment such as physical functioning, pain, role performance and general health. The severely reduced physical HQoL of dialysis patients in comparison to the general population has been reported in many other studies (reviewed in Merkus, & Krediet, 2000). A substantially high number of dialysis patients (53%) were found to have a physical component score on the SF-36 (PCS) which was severely impaired (more than 2 *SD*s below general population mean). Such a score corresponds to the 2.5^{th} percentile of the distribution of HQoL scores in the general population. This finding indicates that over half of those assessed reported significant limitations in all physical activities, such as walking or climbing stairs, were severely bothered by pain and rated their health as poor. This finding may have clinical implications as poor HQoL (poor physical performance assessed by PCS) has been found to be independently associated with poorer outcomes such as increased mortality and hospitalisation rate (De Oreo, 1997; Lopes *et al.* 2003; Mapes *et al.*, 1999; 2003).

In contrast, mean scores of dialysis patients on the SF-36 sub-scales that reflected emotional HQoL were close to those expected in the general population. The prevalence

of impaired emotional well-being was what would be expected from a normal distribution, with 6.9% (n = 10) of dialysis patients scoring 2 *SD*s below norms. This finding is in agreement with previous reports (De Oreo, 1997; Devins *et al.*, 1990a; Groothoff *et al.*, 2003; Mittal *et al.*, 2001a; 2001b).

A greater effect on self-assessed physical, compared to mental, health has also been found in other chronic diseases (Hays *et al.*, 1995). It may be that with chronic disease the impact on aspects of mental or emotional well-being becomes blunted over time as psychological adaptation takes place (Andrykowski *et al.*, 1993), consistent with Taylor's theory of cognitive adaptation to life-threatening events (Taylor, 1983).

The finding of uncompromised emotional well-being is remarkable when the number of physical, psychological and even economic hardships these dialysis patients face, is considered.

A possible explanation is the fact that any type of dialysis is lifesaving. Without treatment all patients would be dead and this simple fact causes dialysis patients to rank their HQoL as high or higher than observers (Seedat *et al.*, 1987). Patients are also likely to change their internal standards, values, or conceptualisation of quality of life and therefore assess it differently as they adapt to their situation. This phenomenon of internal adaptation that results from recalibration of internal standards and reconceptualisation of the frame of references used to produce HQoL judgements is often referred to in the psychological literature as "response shift" and may explain these apparently paradoxical HQoL.

A reverse response shift is demonstrated by the finding that patients awaiting a kidney transplant had a mean HQoL of 5.23 on a 10 point scale; this rose to 7 after transplantation. However, when at 5 months, 12 months, and 18 months after transplantation these patients were asked to rate what their HQoL had been before surgery the mean retrospective scores were 3.27, 3.14, and 3.05, respectively (Adang *et al.*, 1998). Before transplantation these patients had relatively successfully adapted to their condition, and thus had rated their HQoL more highly than when they later re-evaluated it from the advantage point of improved health after TX. The process of denial may also play a role in mediating these perceptions (i.e. HQoL evaluation) (Devins *et al.*, 1986-87), a reaction that may ultimately be adaptive as suggested by Binik *et al.* (1989).

2.2 HQoL comparisons between different dialysis treatments

The issue of HQoL advantages or outcomes associated with different treatment modalities is important to both the decision making process for patients and in evaluating available treatments. From a healthcare policy point of view, considering HQoL levels afforded by ESRD patients on different treatment could potentially inform policy makers and influence the allocation of the existing constrained resources.

To evaluate the effect of treatment modality on HQoL comparisons between all available treatment options for ESRD, hospital HD, home HD, CAPD, APD, CAD TX and LRD TX recipients were performed. This enabled two, three and four group comparisons to be undertaken, such as between dialysis and transplant patients and between patients on different dialysis modalities either in terms of PD vs. HD regimens or in the four dialysis groups. Furthermore all comparative analyses were undertaken with methodological rigour as suggested by Cameron *et al.* (2000) and Greenfield *et al.* (1994). Since many variables differ significantly between RRT groups and may hence introduce biases and confounders in group comparisons, this research has addressed the problem of casemix by undertaking a careful identification, and measurement of relevant case-mix variables and followed this by appropriate statistical adjustments. Furthermore, residualised scores were computed and used in post-hoc comparisons in preference to absolute scores to allow for statistical adjustments.

The findings showed dialysis patients on different modalities had equivalent scores in most SF-36 sub-scales after casemix adjustments. The equivalence of HQoL in patients on different dialysis treatments found in the present study is in accordance with previous research (De Wit *et al.*, 2002; Gudex, 1995; Moreno *et al.*, 1996a; 1996b), but could also be related to the inadequate power to detect differences between groups. The number of patients on home HD and APD in particular, was relatively small ($n < 30$) and this might account for the lack of significant differences between the four dialysis groups despite a significant main effect on pain and vitality in the omnibus ANCOVAs. This suggests that the hypothesised effect of dialysis treatment on HQoL may be subtle and it will hence be important to replicate these findings with larger samples.

From a methodological point of view it is of note that the results of post-hoc comparisons differed between residualised and absolute scores. For instance, post-hoc

tests on pain absolute scores indicated that CAPD patients reported significantly more pain than all other dialysis groups but no two groups were different when residualised pain scores were used. This highlights the importance of adequate statistical adjustment for casemix differences in all omnibus and post-hoc comparisons.

Comparisons between patients on HD and PD regimes showed that energy levels and emotional well-being might be better preserved in HD than in PD. HD patients had higher MCS scores and a lower prevalence of severe MCS impairments. Treatment status was also found to be a significant multivariate predictor of MCS in multiple regression analyses.

Vitality scores were likewise higher in HD compared to PD although adjustments for albumin negated this effect. Controlling for albumin had also removed the significant main effect on pain and vitality when the four dialysis groups were compared. Other studies have also found that PD patients, particularly those on CAPD had lower physical HQoL relative to HD (Julius *et al.*, 1989a; Merkus *et al.*, 1999; Mittal *et al.*, 2001b) but as in this study, lower albumin in the PD group explained to some extent the observed differences (Mittal *et al.*, 2001b). This highlights the importance of albumin to patients' physical functioning and well-being (Lowrie *et al.*, 2000), in addition to clinical outcomes such as survival (Maiorca *et al.*, 1995b; Pifer *et al.*, 2002). One might speculate whether the lower serum albumin levels observed for the PD patients in this study was an indication that these were 'sicker' patients and thus had lower vitality scores. It is interesting to note that the PD patients were not different from HD patients on comorbid disease and renal severity. The dialysis groups also were not different in haemoglobin levels, which would be expected to affect energy levels.

The finding of higher emotional well-being in HD patients contrasts previous claims of more opportunities for psychological adjustments afforded by PD treatments (Cameron *et al.*, 2000; Diaz-Buxo *et al.*, 2000; Merkus *et al.*, 1997; Simmons & Abress, 1990; Wolcott & Nissenson, 1988a). The difference in findings may be attributable to methodological issues, including use of different instruments and other variations in the metrics and tools (Deniston *et al.*, 1989), random sample variability and differences in relative statistical power, which are common problems in naturalistic research (McClelland & Judd, 1993; Tunnell, 1977).

The findings also contradict the commonly held view in the medical community that CAPD, by allowing more flexibility and control over treatment, might be psychologically beneficial. There is however only limited support for these clinical impressions. Research has found little or no difference in psychosocial outcomes based on differences in control over treatments (Devins *et al.*, 1981; Levenson & Glocheski 1991; Sacks *et al.*, 1990). Devins *et al.*, (1981) for instance examined depression in three group patients: low control (hospital HD), medium control (hospital self-administered HD) and high control (CAPD). No relationship was found between the amount of behavioural control and depression.

A study by Eitel *et al.*, (1995) showed that this relationship might be moderated by clinical variables. Their findings indicate that with increases in disease severity a relationship between behavioural control over treatment and depression becomes evident. In particular, as severity of illness increases and possibly less amenable to control, high-control (CAPD) patients have significantly higher depression than do low control (HD) patients. Their findings imply that as illness becomes more severe, control over treatment might become an added burden to the patient resulting in poorer adjustment. The psychological costs of control have been noted previously in the literature (Brownell, 1991).

Findings of better emotional outcomes in HD compared to PD are by no means unprecedented. For instance, Maiorca *et al.* (1998) showed that although CAPD and APD patients had a greater degree of independence and more positive attitudes than Hospital hemodialysis, they were also found to be more anxious and insecure. Griffin *et al.*, (1994) also found better psychological adjustment in HD patients relative to PD although group differences in time on treatment limit the validity of these effects. HD patients in that study had been treated for longer and consequently there might have had more time to adjust. However a longer time on RRT is unlikely to lead to more favourable HQoL as there is evidence to suggest that HQoL decreases over time in dialysis patients (Merkus *et al.*, 1999a).

Study findings showed no relationship between HQoL and treatment duration (total interval since dialysis onset irrespective of dialysis modality and time on current dialysis treatment) in keeping with previous findings (Evans *et al.*, 1985; Wolcott *et al.*, 1988a). In this study HD and PD groups also differed with regard to time on RRT and on their current dialysis modality but these variables as well as other sociodemographic

and clinical casemix differences that could introduce biases were controlled for in all the comparisons.

Several potential explanations can be suggested to account for the observed MCS and vitality differences in PD and HD.

First the continuous burden of PD compared with the intermittent nature of HD and peritonitis may place patients at risk for emotional distress. PD may be stressful on a more sustained basis due to the responsibility that a patient must take for their health and well-being (Mittal *et al.*, 2001b). Emotional well-being might also be expected to be lower for PD patients whose continuous nature of their treatment might make the boundaries between treatment and non treatment less distinct than for HD patients (especially in relation to hospital HD). It might be more difficult for PD patients to suppress or inhibit distressing aspects of their illness given the daily treatment routine whereas HD being an intermittent treatment taking place within distinct blocks every week might be intruding less in daily activities and thoughts. Hospital HD in particular has the added advantages of being completely separated from patients' home environment and might discourage the spill-over of treatment related stress in other aspects of patients' lives.

MCS differences may also result from differences in the demands associated with PD and HD. HD whether performed at hospital or at home, typically entails 3 sessions a week, hence allowing perhaps more dialysis free days to pursue valued social, leisure and other daily activities without treatment interruption. Time requirements have been found to be greater in CAPD patients compared to HD but this was not been measured in the current study (Devins *et al.*, 1990a; De Vecchi *et al.*, 1994). Another study comparing home HD patients to CAPD has indeed found that home HD reported less adverse effect of kidney disease on lifestyle, better cognitive functioning, sleep and treatment satisfaction than did PD patients (Carmichael *et al.*, 2000).

Yet another potential reason for this finding may be that PD patients experience greater distress, and isolation due to a lack of social support from similar others (i.e. fellow patients) and medical staff in comparison to HD patients. HD, especially when delivered at hospital offers more opportunities for regular social interaction amongst patients and with medical staff. Home HD necessitates a trained assistant, typically the patients'

partner or other family member that might also create a more favourable environment for supportive social interactions between patients and the designated assistant. There is a vast literature attesting to the psychological benefits of social support on physical and emotional well-being (Christensen *et al.*, 1989; 1992; 1994; Cohen & Wills, 1983; Wallston *et al.*, 1983). The more regular contact of HD patients with health care staff might also mean that patients medical needs or emergencies are more promptly taken care of or addressed, and it might also serve to alleviate treatment- or illness-related worries and concerns and hence contribute to patients' well-being. It is possible that fewer opportunities for such social interactions and for the establishment of supportive networks are present in PD patients. The sense of isolation, (which was not measured in the current study) might be greater among some PD (CAPD) patients, especially the elderly or those living alone (Eitel *et al.*, 1995). A study by McLaughlin *et al.* (2003) showed that hospital HD patients were reluctant to change to self-care PD regimes because of fear of social isolation (McLaughlin *et al.*, 2003) but no PD patients were assessed.

An alternative explanation for the differences in MCS between HD and PD patients is that these differences are due to variations in interpersonal expectancies placed upon and experienced by the patients (Ditto & Hilton, 1990).

Previous literature suggest that medical staff assume that CAPD patients are healthier and better adjusted than HD patients (Levy, 1988; Witenberg *et al.*, 1983). PD advocates have also promoted PD as the treatment that allows more control over patients' lives (Ronco & La Greca, 1997). These assumptions on the part of medical staff, significant others or patients may lead to increased expectations of self-sufficiency and expectations to maintain or resume normal life style. However if inappropriate, these may come to be perceived as burdensome, undermine patients' sense of control and prevent them from getting the support they need. Patients' perceived inability to meet others' expectations has been shown to lead to poorer psychological adjustment (Hatchett *et al.*, 1997). Placing such expectations of control or empowerment on patients who do not feel they can successfully accept the responsibility associated with them is another example of the negative costs of control (Thompson *et al.*, 1988). Such expectations may not be placed on HD patients or maybe not to the same extent. Lower interpersonal expectations on the other hand may be associated with less burden and more support for these patients, resulting in better emotional adjustment and well-being.

Differences in patients' personal expectations rather than interpersonal expectation might also account for the HQoL differences. Unmet expectations (discrepancy between health expectations and health experiences) are thought to adversely impact HQoL (Carr *et al.*, 2001). HD patients may have lower expectations than PD. Consequently their lives would probably be more likely to meet their expectations despite their physical disabilities. Further research is needed to examine personal and interpersonal expectations across the different ESRD treatments and to explore their role in determining HQoL in ESRD.

Finally, it is also possible that treatment selection might have played a role. Patients with poorer emotional well-being may not have chosen or been chosen for HD. Because this study is based on cross-sectional data it is difficult to differentiate a treatment effect from treatment selection. A longitudinal study assessing patients prior to and post dialysis onset, and controlling for MCS levels pre- dialysis onset, would be required to determine the influence of treatment modality on HQoL outcomes.

Although the question of which dialysis treatment confers the best HQoL outcomes is an important one it is also likely that each form of therapy (i.e. HD, PD) may have a role to play during the lifetime of patients with renal failure. Perhaps a move to identify ways in which the differing modalities complement each other is required. In this respect it is interesting to note the recent report by Van Biesen *et al.* (1998) suggesting that patients starting on PD and then switched to HD had better survival than those remaining on their initial treatment of either type.

This study confirmed previous studies regarding the HQoL advantage of TX relative to dialysis (Evans *et al.*, 1985; Jofre *et al.*, 1998; Wight *et al.*, 1998). Casemix adjusted comparisons indicated that TX patients scored significantly higher than their dialysis counterparts in almost all SF-36 sub-scales except for MH and REm. Physical HQoL differences persisted even after adjustments for casemix differences and biochemistry. A literature review has similarly concluded that the TX HQoL advantages over comparison groups such as dialysis are less apparent in mental health and emotional well-being (Dew 2000a; Dew *et al.*, 1997). The uncertainty related to graft viability is thought to account for the lack of superiority of kidney TX in terms of psychosocial adjustment and emotional well-being (Kalman *et al.*, 1983). Study findings showed that

TX worry was prominent in TX recipients and that it correlated with emotional well-being.

Alternatively lack of significant differences in emotional well-being might be related to the use of a generic HQoL measure, namely the SF-36 which by definition is less sensitive to specific emotional concerns of the ESRD patients than disease specific QoL measures. The SF-36 emotional sub-scales in other words may have failed to capture ESRD-specific aspects of emotional well-being. The combined use of disease specific and generic HQoL measures would be recommended for future research. Nevertheless it is important to recognise that as study findings indicate, global emotional well-being indicators are not related to dialysis vs. transplantation status.

It is also important to note that the observed SF-36 scores in TX showed comparable HQoL relative to general population norms (Dew *et al.*,. 2000b). These mean values however mask the fact that a substantially high number of TX patients (n = 79, 22.6%) have very low PCS scores (being more than 2 *SD*s below population mean) which indicate severe impairments in physical function. Such a score corresponds to the 2.5th percentile of the distribution of HQoL scores in the general population. Patients were on average 70.7 months from TX suggesting that these findings are not simply a residual of pre-transplantation physical dysfunction associated with uraemia and dialysis (Dew *et al.*, 2000b; Julius *et al.*, 1989b).

Only a fraction of TX had severe MCS impairments despite PCS impairments. These findings suggest that for a proportion of individuals emotional well-being remains uncompromised despite the severely affected physical HQoL. The magnitude of physical well-being impairments highlights the significant functional limitations post-TX for some patients (Hathaway *et al.*, 2003) and reinforces the importance of efforts to affect HQoL favourably and complete advance directives in this group of patients.

The findings on HQoL in CAD and LRD TX were consistent with those reported by Evans *et al.* (1984) and Julius *et al.* (1989b) in that HQoL appears to be unaffected by transplant type. Both living-related and cadaver transplant recipients reported equivalent HQoL levels in all SF-36 sub-scales with mean scores for both groups being within one standard deviation of the mean of a normal population. This finding is reassuring and

further documents the attraction of renal transplantation as a mode of treatment that largely restores individuals' HQoL.

The inability to detect significant HQoL differences between the two transplant groups in the SF-36 sub-scales may have several possible explanations. The primary reason may be that the transplant procedure itself accounts for such large HQoL improvements that the detection of additional incremental differences in HQoL between LRD and CAD treatments is very difficult to detect. If this explanation is correct then the clinical benefits observed with LRD continue to be the most important factors in distinguishing between these two transplant options.

Section 3: HQoL determinants in ESRD

One of the aims of this study was to identify the combination of illness and patient variables that best predicts HQoL in dialysis and transplantation. Although this has been the subject of intense investigation, this study adds to previous research by examining multifactorial models of HQoL that included sociodemographic, medical, neuropsychological, mood variables, and patients' cognitions. Previous studies have predominantly focused on the first two sets of variables overlooking the role of illness and treatment cognitions and mood (Mingardi *et al.*, 1999; Mittal *et al.*, 2001a; Moreno *et al.*, 1996a; Wolcott *et al.*, 1988b).

Although a few studies (see review by Hagger & Orbell, 2003) have evaluated the separate roles of illness and treatment beliefs, and mood in HQoL, no published studies have evaluated their relative contribution as well as their synergistic effect on HQoL. Moreover assessing treatment beliefs alongside illness perceptions has allowed us to evaluate the relative contribution of these two sets of beliefs to HQoL.
Results indicated that several different factors including sociodemographic, medical and psychological variables were associated with HQoL, although specific predictors and the strength of the observed associations differed in physical and emotional well-being as indexed by PCS and MCS (SF-36). The contributions of each set of variables will be separately discussed in the following four sections.

3.1. Sociodemographics

The overall pattern of results indicates that sociodemographic and medical variables were mainly associated with the physical HQoL and less consistently so with the emotional HQoL.

Age was the key demographic factor that was independently associated with both physical and emotional dimensions of HQoL. Observed associations indicated that physical function deteriorated as a linear function of age (in both dialysis and TX) whereas the opposite pattern of results was evident for emotional well-being. Increasing age in TX patients was associated with higher MCS. These findings confirm previous research in which older age is consistently related to worse physical HQoL (Merkus *et al.*, 1997; Mittal *et al.*, 2001a; 2001b; Moreno *et al.*, 1996a), and also findings of others (Horina *et al.*, 1992; Kimmel *et al.*, 1998b; Lowrie *et al.*, 1997; 2000) who report that elderly patients frequently show greater satisfaction with some aspects of their life than younger patients. The relationship of age with mental health/emotional well-being has often been described as 'non-linear' (with "middle age" respondents often having relatively low mental health scores and "older age" having higher or better emotional well-being), in that the emotional impact of illness is attenuated with advanced age (De Oreo, 1997; Kutner, 1994; Kutner & Jassal, 2002). Older persons appear to use different reference points to evaluate their HQoL than do younger persons. Older respondents tend to downplay the negative aspects of situations giving them neutral meaning compared to younger adults (Diehl *et al.*, 1996). Also, changes in expectations about health and well-being across the life span may explain the association between age and emotional well-being in TX (Kutner, 1994).

Significant associations were also found in this study between gender and MCS (only in the dialysis sample), in line with other studies using the SF-36 (Mingardi *et al.*, 1999; Moreno *et al.*, 1996a). The gender effect on emotional well-being is consistent with previous research (see reviews Bebbington, 1996; Harris, 2003) and may reflect the tendency for women to be more willing to report negative emotional states (Sack *et al.*, 1990; Newman, 1984). It is interesting that this relationship was not found in the TX sample that had generally high scores in emotional well-being sub-scales.

Lack of paid-employment (including retirement) and lower income were both associated poorer HQoL, mainly physical well-being confirming previous findings (Blake *et al.*, 2000; Curtin *et al.*, 1996; Harris *et al.*, 1993; Hathaway *et al.*, 1998). Multiple regressions indicated that both employment and income were independent predictors of physical function, with variance explained being over and above the effect of various other sociodemographic, clinical psychological variables. It is also noteworthy that dialysis modality did not affect likelihood of working and that the effect of work and income outweighed that of dialysis modality on HQoL. Controlling for work and income negated all the significant differences between dialysis groups on physical dimensions of HQoL.

The direction of these relationships needs further investigation as these findings beg the question as to whether better physical well-being may lead to work rehabilitation or facilitate maintaining work activity while on dialysis, thus ensuring better income despite illness and treatment constraints or vice versa in that employment and income confer better physical HQoL.

Each of these non-illness variables has been found to be related to HQoL among the general population in exactly the same way as observed in the current study and so the fact that they are involved similarly in ESRD is not surprising. These findings serve as an important reminder, however that the HQoL in ESRD is very much dependent on several contextual variables (such as socio-economic status) that are to a great extent independent of ESRD and RRTs (Greenfield *et al.*, 1994; Valderrabano *et al.*, 2001).

3.2 Clinical/medical variables

Among clinical variables, ESRD severity, albumin, haemoglobin and GFR were associated with HQoL although observed associations were not consistently found across dialysis and TX. Importantly, in multivariate analyses their contribution was small and not always significant, especially with regard to MCS scores.

ESRD severity, a weighted index of comorbidity and renal complications, was found to be consistently associated with physical HQoL scores in univariate analyses and was the strongest clinical predictor of PCS in both dialysis and TX patients (in multivariate analyses). The observed association point to the detrimental effect of comorbid factors superimposed on ESRD in reducing patients' HQoL. The role of comorbidity in ESRD

has repeatedly been demonstrated in previous research (Jofre *et al.*, 1998; Valderrabano *et al.*, 2001; Merkus *et al.*, 1999b; Mittal *et al.*, 2001a).

The associations of other clinical markers and biochemical values with HQoL were found less consistently across dialysis and transplantation. For instance, albumin predicted HQoL in dialysis but not in TX. The serum albumin remains a powerful yet enigmatic predictor of poor outcomes in ESRD (Leavey *et al.*, 1998; Mapes *et al.*, 2003). In recent years a body of evidence has accumulated suggesting that a low serum albumin concentration reflects the presence of inflammation and malnutrition (Bistrian, 1998). The observed associations between SF-36 scores and albumin (in dialysis) particularly with respect to physical dimensions of SF-36 is consistent with previous research (Mittal *et al.*, 2001a; 2001b) and the general perception that low serum albumin levels may reflect poor overall general health.

Haemoglobin on the other hand predicted HQoL in TX but not in dialysis. Although, the lack of significant associations between haemoglobin and HQoL in dialysis is in contrast with studies carried out over a decade ago, it is in keeping with more recent studies (Bakewell *et al.*, 2002; Merkus *et al.*, 1999b; Mingardi *et al.*, 1999). Treatment and prevention of anaemia in renal dialysis patients using erythropoietin is now standard practice in many renal clinics and was routinely used in the participating units. The low haemoglobin levels typically associated with poor physical function were not present in this study and therefore it is not surprising that no association was found between haemoglobin and HQoL.

The findings also indicated that as glomerular filtration rate decreased the physical HQoL deteriorated in TX. Similar associations have been reported in patients with renal insufficiency or on dialysis (Merkus *et al.*, 2000; Shidler *et al.*, 1998) but this is the first report in TX patients. The symptomatology that accompanies diminishing kidney function (e.g. fatigue, loss of energy, weakness) may mediate the association between GFR and well-being (Rocco *et al.*, 1997).

The observed significant associations between dialysis adequacy and physical well-being are consistent with some reports (Chen *et al.*, 2000; Manns *et al.*, 2002; Merkus *et al.*, 2000) but are in contrast with other studies (De Oreo 1997; Merkus *et al.*, 1999b; Mittal *et al.*, 2001; Morton *et al.*, 1996).

3.3 Beliefs and mood

On a multivariate level, sociodemographic and clinical factors did not explain a large amount of the variation in HQoL. Although study findings support their explanatory value for PCS scores, they only explained a small percentage of variance in the MCS scores. The indications are that factors other than sociodemographic and medical variables are also important in explaining HQoL. Within this study, illness and treatment beliefs were postulated to have significant effects on HQoL and were hence included in the models built to predict HQoL in ESRD.
Both univariate and multivariate analyses showed that illness and treatment beliefs were significantly associated with HQoL in both dialysis and transplantation.

Correlations showed that more negative illness and treatment beliefs, i.e. perceptions of illness and treatment disruptiveness, perceptions of high illness consequences and low control, and strong identity beliefs were associated with poorer HQoL in both dialysis and TX patients. Similar findings have been reported for various other illness groups (Moss-Morris *et al.*, 1996; Murphy *et al.*, 1999; Scharloo *et al.*, 1998; Steed *et al.*, 1999) and for ESRD (Eitel *et al.*, 1995; Patel *et al.*, 2002). Some of these univariate associations remained significant even after statistical adjustments for sociodemographic (age, income), illness (e.g. albumin, ESRD severity) and treatment variables (e.g. mode of renal replacement), demonstrating that the impact of patients' cognitions cannot be accounted for by these factors.

Regression analyses showed that patients' cognitions are predictive of both physical and emotional HQoL and that individual differences in illness and treatment beliefs account for more variance than individual differences in sociodemographic and clinical variables in predicting HQoL, particularly emotional well-being (MCS). The size of the effects for illness and treatment beliefs were not large but were obtained using a conservative strategy in which the effects of several demographic and medical history variables were controlled. Regression analyses also indicated that the specific beliefs that predicted HQoL outcomes differed between the two groups (dialysis and TX) and between the physical and emotional HQoL dimensions. The overall pattern of results indicated that

illness beliefs were primarily associated with physical HQoL and treatment perceptions with emotional HQoL.

Multiple regression analysis on PCS revealed that illness intrusiveness was the only cognitive variable that was multivariately associated with physical well-being in dialysis. Illness intrusiveness and identity also predicted physical HQoL in TX.
Illness intrusiveness has previously been found to contribute to psychosocial impact of ESRD on outcomes such as depression rather than physical well-being (Devins 1994; Devins *et al.*, 1990a; 1990c; 1997; Sacks *et al.*, 1990; Eitel *et al.*, 1995).

The contribution of timeline, consequences, control, and identity components of SRM, despite being significantly correlated with SF-36 scores in univariate analyses, failed to reach significance in PCS regressions.
Although lack of sufficient range in some of these variables (i.e. timeline) and multicollinearity (as indexed by the moderated interrelations among predictors, especially between IPQ consequences with illness intrusiveness) could explain the absence of significant multivariate associations, methodological considerations regarding the ratio of cases to number of variables in the regression analysis also need to be kept in mind when interpreting results.

Nevertheless, the observed multivariate associations between illness intrusiveness and PCS provide indirect support for the role of perceived consequences in HQoL due to their conceptual overlap (as both illness intrusiveness and perceived consequences reflect the same underlying concept, patients perceptions of the effect of their illness on their lives). The IEQ measures a patient's perception of the extent to which illness interferes with or modifies personal and social behaviour, i.e. is intrusive in patient's life. It therefore reflects a concept similar to that assessed by the 'IPQ-consequences' sub-scale (observed intercorrelations were high r = .635 and r = .555 for TX and dialysis respectively). When regressions were performed without IEQ, IPQ consequences emerged as a significant predictor (data not shown).

There are however measurement differences in the length of scales and the response categories that could explain why IEQ rather than IPQ consequences predicted PCS. The 20-item IEQ allows a greater specificity in the measurement of illness impact than the substantially shorter IPQ sub-scale, by detailing a range of life domains and

behaviours likely to be affected by ESRD. These are implied but not directly assessed by the IPQ consequences items. One would expect therefore that if an association between perceptions of illness impact and HQoL exists, IEQ would be a more powerful determinant of HQoL because of its greater specificity. IEQ items are also scored on an 8-point Likert scale ensuring a wider range of responses as opposed to IPQ consequence items, which rated on a 5-point Likert scale. An alternative way to evaluate beliefs regarding the impact of illness would have been to construct a combined score for the two measures or use only one of the two. Further work is warranted to examine the degree of similarity between these IEQ and IPQ consequences and the value of IEQ as a HQoL measure as advocated by some investigators (Kimmel, 2000a; 2000b).

Finally some of the IPQ consequences items (e.g. 'my illness has had major consequences in my life', 'my illness has strongly affected the way other people see me' or 'my illness has affected the way I see myself as a person') may have both positive and negative connotations and therefore be interpreted in both a positive and a negative fashion. For instance, the phrasing of 'my illness has had major consequences on my life' item creates the potential for both a positive and negative change as illness may bring a family closer together or add stress to family life. Their ambiguous meaning might have led to different interpretations, which further might explain why IPQ consequences were not a significant predictor in the multivariate analyses performed. The recent move towards 'positive' psychology demonstrates that as paradoxical as it may seem even within the context of chronic illness, positive consequences/outcomes may occur (Affleck & Tennen, 1996; Andrykowski *et al.*, 1993; Antoni *et al.*, 2001). Many different terms have been used including 'benefit finding', 'growth', 'meaning making' and more to describe a range of positive outcomes in this growing area of research.

Greater symptom burden, a score reflecting the occurrence of generic, renal and medication-related symptoms explained an additional amount of HQoL (PCS) variance in TX. These associations are consistent with previous findings on the adverse effects of symptomatology and immunosuppression side-effects on HQoL (Hathaway *et al.*, 2003; Merkus *et al.*, 1999a; De Geest & Philip, 2000; Keown, 2001).

Study findings showed no direct influence of perceived symptoms on HQoL in dialysis when background variables were adjusted for. The lack of multivariate associations contrasts with previous findings (Curtin *et al.*, 2002; Weisbord *et al.*, 2003). There

might however be an indirect effect on HQoL in that symptom beliefs affect perceptions of illness intrusiveness compromising HQoL as a result (Devins *et al.*, 1990c). Observed correlations indicate that as symptom frequency increases there is an increase in the impact the illness has on patients' lives (increased illness intrusiveness) and that in turn affects HQoL.

Methodological issues related to scoring may have also compromised power to detect significant associations between identity and HQoL. In this study, identity scores were estimated as the number/count of symptoms associated with ESRD, which is in agreement with the authors' recommendations and previous research (Weinman *et al.*, 1996). An advantage of combining individual items is that random error that occurs with respect to individual symptoms is averaged out. A disadvantage of summation is that one is not able to distinguish the number of symptoms from the extent of their occurrence. For example, a patient who reports 4 symptoms as occurring very often obtains the same total score of 4 as a patient who reports four symptoms occurring rarely. The various ways that the same symptom score can be arrived at may be partly attributed to the lack of multivariate associations between identity and PCS in dialysis.

Specific symptoms might also have a greater impact on HQoL rather than aggregate scores. Employing individual/separate scores would additionally examine if each symptom differentially affected HQoL. For instance, itchiness or dry skin albeit frequently reported by dialysis patients, might have less grave HQoL implications compared to fatigue, breathlessness or pain. There is some evidence that this must be the case in ESRD. Devins *et al.* (1990c) for instance, found that muscle pain was associated with QoL but not headaches. Pain in particular, a pervasive medical problem, has been found to account for substantial levels of disability and to contribute greatly to the overall burden of illness (Kimmel *et al.*, 2003; Turk & Melzack, 2001). Inextricably linked to depression and other negative moods, pain can increase disease severity and mortality (Staats, 1998). Additionally, pain may disrupt many aspects of physical, mental, and social functioning (Leventhal *et al.*, 1998). Identifying those symptoms more likely to impinge upon HQoL and assessing their relative contribution of different symptoms in patients' HQoL has not been addressed in the present study.

In addition to specific symptoms, symptom variability may also be pertinent in HQoL especially for dialysis patients. It is possible that the fluctuating nature of symptoms may also have obscured meaningful associations in dialysis. Analyses comparing HD

and PD groups on symptoms reporting across the two assessments (pre- to 24-hours post-dialysis) indicated a significant dialysis treatment by time interaction effect, a finding consistent with the finding of low intra-observed reliability for symptoms assessed within 1-week interval (Parfrey *et al.*, 1989). This may have implications when retrospective evaluations of symptoms associated with ESRD are made. Therefore future studies should consider symptom variability, the number of symptoms endorsed, and the degree of burden of each individual symptom as well as frequency and duration of symptom occurrence.

Finally although there is some work on symptom appraisal and related processes (Pennebaker, 1982; Petrie & Weinman, 2003), little is also known about how patients judge the relative contribution of underlying illness and treatment on their symptoms. This is an important area of research as mistaken attributions may effect outcomes such as distress, HQoL or may trigger non-adherence (Nerenz *et al.*, 1984; Thune-Boyle *et al.*, 2003).

Regression analyses on MCS indicated that the effect of treatment beliefs outweighed that of illness beliefs. Treatment intrusiveness was the most powerful predictor of MCS in dialysis accounting for 9.3% (ΔR^2 = 8.9%) of the total variance explained. Although this signifies a small effect size, it is noteworthy that treatment perceptions added to the variance explained by dialysis modality as it highlights the independent contributions of objective treatment and subjective treatment appraisals in predicting emotional well-being.

In contrast to the significant univariate associations, the resulting regression model did not demonstrate a substantial impact of illness beliefs on emotional well-being in dialysis patients. Again the effect of multicollinearity between the IVs may cause some of these variables to lose statistical significance when entered simultaneously as one regression block. The decision to enter illness and treatment beliefs in one block was justified, as there appeared to be no a priori hypothesis regarding their primacy.

In TX, perceived consequences and medication beliefs reflecting concerns about medication side-effects accounted for almost half of the total MCS variance explained (ΔR^2 = 13.3%). These findings suggest that the power of Leventhal's SRM (Leventhal *et al.*, 1996; 1998) to explain variation in emotional well-being in TX was enhanced by

taking into account beliefs about medication. Only medication beliefs however were found to have a direct effect on HQoL adding a small albeit significant (4.5%) percentage in variance explained. Perceived consequences were no longer significant when CDI scores entered the regression equation, suggesting a mediating effect for the latter. Patients' beliefs about the consequences of their illness influence their mood (i.e. depressive affect), which in turn adversely impact upon emotional HQoL. The observation that treatment beliefs were substantially and independently related to MCS is consistent with previous findings about treatment effectiveness (Hampson *et al.*, 2000) and substantiate the role of treatment beliefs in adherence (Horne & Weinman, 2002).

Treatment intrusiveness was not a significant predictor of MCS in TX. This could be attributed to insufficient variance on TEQ scores, which were uniformly very low among TX recipients.

Previous research has demonstrated the importance of illness beliefs in ESRD but evidence on the role of treatment perceptions in this patient population was lacking. The independent contribution of treatment beliefs in the prediction of HQoL provide some evidence for the theoretical predictions that treatment beliefs add to the explanatory power of SRM (Horne & Weinman, 2002), although these relations need to be re-investigated with path analysis or structural equation modelling procedures. This type of analysis would advance knowledge of the structure and interactions between illness and treatment beliefs/representations within the self-regulatory framework and would also reveal the direct or indirect links between these variables and HQoL by testing mediational hypotheses. For instance, regression analysis showed no direct associations between control beliefs and HQoL unlike previous research (Jopson & Moss Morris, 2003). Although this might mean that control beliefs are less relevant in ESRD outcomes, it is more plausible that these beliefs may be indirectly linked to outcomes, in that their influence on MCS might be mediated by illness intrusiveness or treatment perceptions. In particular, patients who view their illness as uncontrollable are more likely to perceive more illness or treatment related disruption, which may in turn adversely affect HQoL. Mediating effects have indeed been demonstrated for IPQ consequences and beliefs regarding treatment necessity in studies of other patient groups (Horne & Weinman, 2002). Control beliefs may also be implicit in illness and treatment intrusiveness ratings as exemplified by respective IEQ and TEQ items 'my illness is difficult to control' and 'treatment side effects are difficult to control'.

Path analyses would also have the added advantage of providing further supportive evidence of the predictive ability of illness and treatment cognitions as the correlational and regression analyses in this study do not provide evidence to support a causal relationship.

The specificity of beliefs and behaviour links and the fact than they can be easily identified early on in ERSD is important. Unlike other factors, such as personality or sociodemographic variables, these links provide considerable potential for developing cognitively based interventions. Thus if negative thinking can be identified and an intervention instituted to foster more adaptive models and expectations, then improved levels of functioning and well-being could be expected. Recent work by Petrie *et al.*, (2002) have demonstrated an earlier return to work for MI patients in an illness perception changing intervention. An important implication of this study is that attempts to improve HQoL in dialysis and TX patients should not focus only on illness beliefs but also address treatment perceptions. The latter may also produce changes in HQoL. On the whole study findings provide moderate support for the extended self-regulatory theory that includes illness and treatment perceptions.

Mood variables (patients' depression scores) showed a significant inverse association with physical and emotional indicators of HQoL. Previous research has shown similar associations (Franke *et al.*, 2003; Iliescu *et al.*, 2003; Kimmel *et al.*, 1993; 1996; Maor *et al.*, 2001; Steele *et al.*, 1996; Walters *et al.*, 2002; Watnick *et al.*, 2003).

In accordance with previous findings depression was found to be a much stronger determinant of HQoL than clinical measures such as dialysis adequacy (Martin *et al.*, 2000; Steele *et al.*, 1996). As proposed by Benito-Leon *et al* (2002) there are three possible explanations for these results. Firstly depression could. affect patients HQoL through an influence on psychological variables, such as perceived support and self-esteem. Secondly, depression may impact directly upon HQoL by causing fatigue, sleep difficulties, and memory and concentration disturbances. Thirdly, patients with previous poor HQoL may be at greater risk for depression.

The amount of variance explained by depression was smaller than that of patients' cognitions although this may be related to the specificity of measurement. General feelings of depression may be more distal and hence less powerful determinants of

ESRD outcomes than the most proximal social cognitions assessed by SRM components and treatment perceptions. Prediction may be enhanced when more specific emotions or mood predictors having direct relevance to illness are used. The revised version of IPQ (Moss-Morris *et al.*, 2002) allows the assessment of emotional responses generated by illness rather than general mood so its use is strongly recommended in future research. A greater understanding of the emotional representation of illness and the emotional processing component of self-regulation is needed and future studies ought to reflect this perspective using more appropriate methodology.

A final word of caution is warranted in interpreting the observed associations between depression and MCS scores, as there is some conceptual overlap between the two measures. MCS and MH scores correlate with validated measures of depression (Beusterien *et al.*, 1996b) and have even been used as a first stage screening for depression in previous studies (Lopes *et al.* 2002; Mittal *et al.*, 2001a; 2001b; Ware *et al.*, 1994).

3.4 Neuropsychological functioning

The hypothesis that NP functioning would be associated with HQoL, particularly emotional well-being, received very modest support. Although significant correlations were noted in the predicted direction when univariate analyses were performed, NP functioning failed to predict HQoL in the regression analyses even when entered into the regression model before patients' cognitions and mood.

Several factors may have limited the predictive validity of NP indices in the multivariate analyses. In previous studies where significant associations were documented, simple regression models including only age, education and NP scores were tested (Bremer *et al.*, 1997; McSweeny *et al.*, 1985).

In this study the constructed regression models incorporated several background variables to ensure that observed associations are not confounded by the influence of factors such as age, education employment, clinical severity, or dialysis delivery. It may be that the independent contribution of NP functioning on HQoL becomes less apparent when a range of sociodemographic and clinical variables (including treatment modality) are controlled for in the first steps of the model. Secondly, the use of a summary NP score rather than individual NP scores, albeit in accordance with previous studies

(Shifren *et al.*, 1999) might have obscured significant associations between specific cognitive abilities (e.g. memory) and HQoL. There is indeed evidence that specific NP tests served as better predictors of specific life functions. McSweeny *et al.* (1985) for instance found that the Aphasia Screening Test (Reitan & Wolfson, 1993) was the best predictor of communication skills. The associations of different cognitive functions to HQoL have not been explored in this study.

It is also possible that cognitive functioning might be more closely associated with mental health outcomes such as depression (Honn & Bornstein, 2002; LaRue *et al.*, 1995; Shifren *et al.*, 1999) or with performance-type of outcomes such as daily activities or employment rather than more global outcomes such as HQoL (Bremer *et al.*, 1997; Putzke *et al.*, 2000). The correlations between physical functioning and NP performance indices were higher than those observed for the summary component scores in keeping with previous research (Harder *et al.*, 2002) and significant associations were also found between depression and NP scores. It is however unclear whether NP abilities/functioning amplify emotional distress or whether emotional distress influences NP performance. In the analysis, only linear associations between NP performance and HQoL were tested but it is possible that associations may only become evident when NP performance is severely impaired.

Cognitive functions may indirectly impact upon HQoL. For instance compromised memory or speed of information processing may directly influence most of daily activities and indirectly affect well-being. On the whole study findings suggest that NP functioning is relevant to HQoL outcomes, but further research is needed to test the pathways involved.

The present results also demonstrated that subjective cognitive complaints were more strongly associated with HQoL than objective indices of NP performance. Observed correlations were higher and more consistent across the SF-36 sub-scale scores. Cognitive complaints predicted a small albeit significant proportion of the explained variance in PCS and MCS scores in dialysis.

It is likely that these associations were mediated by depression. In other samples significant associations have also been found between depressive symptoms and reports of subjective cognitive complaints (Brickman *et al.*, 1996; Khatri *et al.*, 1999; Newman *et al.*, 1989). Although the observed association with HQoL may be related to method

variance across measures, subjective cognition scores reflect patients' appraisals of their cognitive capacity or disability triggered by their illness or treatment and hence have particular relevance to HQoL evaluations. The inclusion of cognitive sub-scales in some generic and kidney specific QoL measures exemplifies this point (Begner *et al.*, 1981; Hays *et al.*, 1994).

Section 4: Conclusion

The present study expands our understanding of the role of treatment modality on HQoL and also provides a first step toward unravelling the complex associations between HQoL and cognitive and psychological variables in ESRD patients. Although only a controlled randomised study can be definite about treatment effects, the convergence of study findings with previous research and the careful adjustment of casemix differences together suggest real differences between PD and HD patients, and between TX and dialysis. The findings of this study emphasise the need to examine multifactorial models of HQoL in ESRD, and to consider both medical and psychological factors if we are to understand physical and emotional well-being in dialysis and transplant populations.

CHAPTER 11:
CLINICAL IMPLICATIONS STUDY LIMITATIONS AND AVENUES FOR FUTURE RESEARCH

Section 1: Clinical implications of study findings

The study has several clinical implications:

- Dialysis patients present with HQoL impairments. This suggests that there is still room for improvement in treatment delivery and in the clinical management. Physicians/nephrologists need to be aware that even well-dialysed ambulatory may feel pronounced physical functioning limitations and severe pain that disrupt role performance and adjustment.

- Findings also suggest that particular attention should be given on the emotional well-being of PD patients as this group is faring worse than their HD counterparts. PD patients' worries and concerns as well as emotional needs should be given consideration in the health care practice. Given that they spend much time away from the hospital the ability to be in contact and be contacted by the health care professionals should be considered.

- Health care professionals need to become aware that patients have their own ideas about their condition and their treatment and that these sets of beliefs and perceptions affect broader outcomes such as emotional and physical HQoL/well-being. More importantly, beliefs and cognitions are potentially amenable to change and could hence be targeted by appropriate interventions. Addressing illness and treatment misconceptions has the potential to produce changes in patients' HQoL.

- The finding that patients hold beliefs about treatment, which may conflict with the medical views yet, influence emotional wellbeing has implications for clinical practice. Eliciting and alleviating concerns regarding the impact of treatment may enhance the therapeutic partnership between clinician and patients and facilitate patients' emotional adjustment and potentially adherence to treatment.

- Findings can also be used to develop paradigms for doctor patient interaction that will generate 'adaptive' shared perceptions of disease and treatment congruent with respect to symptom formation, timelines and consequences for both illness and treatment that may contribute to overall sense of patients' well-being.

- It is also important to recognise that the gross and pronounced NP impairments reported in early studies on dialysis population were not found in this study. Although there is some evidence for mild NP impairments relative to norms, a substantial number of dialysis patients present with uncompromised cognitive abilities. This attests to the medical advances in the delivery and techniques of dialysis, as well as the continuing efforts to improve renal replacement therapies and patient outcomes. The findings also highlight the importance of adequate dialysis delivery so achieving these clinical goals should be the aim for all patients on dialysis.

Section 2: Limitations of the study

Several limitations require qualifications of the conclusions drawn.

2.1 Shortcomings in applying the theoretical framework

Even though the theoretical model/framework proved useful, a number of problems exist in translating theoretical premises into study designs and subsequent execution.

The self-regulatory framework describes a circular feedback system engaging and linking complex cognitive and emotional processes, coping and outcomes through a series of constant appraisal processes. The cognitive and emotional representations of illness are constantly changing in light of changing coping efforts, changing environmental factors such as (perceived) changes in disease and treatment characteristics. It should be clear that fully testing this self-regulatory system is virtually impossible. Not only is the complexity of this framework hard to research but also it is only possible to capture the dynamics of the changes that influence outcomes and

feedback loops using frequent measurements. Due to the lack of resources in this project this has not been done.

In this thesis only one basic principle derived from the self regulatory theory is used, namely the relationship between illness representations and HQoL; the study in other words was not intended to fully test the SRM theory although designing the model of HQoL determinants and explaining results relied on the self-regulatory theory.

2.2 Study design

The first and foremost methodological limitation relates to the cross sectional design of this study, which negates the ability to make any judgements regarding causality from these data. Drawing conclusions regarding causality can be problematic with cross sectional designs and correlational and regression analyses. The cross-sectional nature of the data provides a snapshot of the interrelations between key variables but precludes making firm causal conclusions as to whether beliefs and mood drive or determine HQoL.

2.3 Sample

The second methodological issue relates to the sample size and representativeness. The recruited ESRD sample, albeit one of the largest in studies involving NP assessments, was still relatively small for particular types of analyses such as comparing all four dialysis groups, and inadequate for testing structural equation models (Loehlen, 1998; Ullman, 2001). The small sample sizes of certain subgroups such as APD and home HD patients or patients with LRD transplants may also have prevented detecting significant differences when for instance, the four dialysis groups were compared, or when LRD patients were compared to CAD TX patients.

Moreover, study eligibility criteria and the resulting study sample characteristics limits the generalisability of observed findings on the broader ESRD population in the UK. The strict inclusion criteria for the dialysis sample on one hand and the rigorous research protocol on the other hand meant that conclusions are based on a highly

selective sample of ESRD patients, that may not therefore be representative of the general ESRD population. The study selection criteria, which are unavoidable requirements for studies involving NP assessments were deliberately chosen to exclude patients in very poor medical and psychological health and thus it is not known whether the observed results would be generalisable to other dialysis populations, particularly patients that are not adequately dialysed, or those with certain co-morbid conditions and medical complications. Similarly study findings may not be generalisable to non-English speaking populations, or more ethnically diverse groups. This highlights an important area of concern in psychological assessments and the need for cross-cultural versions of the measures to meet the needs, linguistically and culturally, of different ethnic groups.

Conducting further studies on the broader ESRD population, not represented in this study would hence be a fruitful endeavour and recruiting even larger samples to enable effective multigroup analysis should be pursued in future research.

2.4 Materials

Study findings are also highly dependent upon the measures used for assessing the variables in question.

Study measures for illness cognitions, mood, and HQoL have been subject to validation and standardisation and as they are widely used in the international research community it was possible to compare study results with many other studies. The only shortcomings regarding study assessment is the lack of disease-specific measures and reliance on exclusively self-report measures. The generic instruments used for study assessment may not have been sufficiently sensitive to detect differences among the subgroups. SF-36 for instance, is a generic measure that assesses broad concepts and may not be sensitive to disease or treatment specific issues as would a disease-specific instrument (Hays *et al.* 1994). The observed differences among the two TX groups in the TxEQ sub-scales (i.e. 'guilt') in absence of HQoL differences illustrate this point.

Specific problems/issues with certain sub-scales and measures are discussed below.

The Illness Perception Questionnaire and the Illness Effects Questionnaire have been used to assess illness cognitions. As discussed earlier (see Chapter 10; section 1.3) it is

not clear how questionnaire items were perceived and interpreted by transplant recipients. Clearly more work is needed in this area to unravel the complexities of illness and treatment cognitions particularly in TX and to determine the meaning that these carry within the TX population and the best or most appropriate methods to measure these cognitions in the TX population.

The assessment of illness and treatment cognitions is complicated in ESRD patients due to comorbidity. ESRD is often the consequence of diabetes or hypertension or may result in the development of other comorbid conditions typically referred to as renal complications (e.g. bone disease; hypertension; anaemia). Renal patients present a spectrum of coincident diseases, which have their time courses, secondary complications and other disturbances. It could be maintained that these conditions would obscure the effect of ESRD and associated treatments on cognition and HQoL. It is important to consider the effect of comorbidities and other conditions when interpreting the results of any study. To minimise the impact of comorbid conditions respondents were instructed to respond to the questionnaires keeping their ESRD or specific treatment modality in mind (as appropriate) and adjustments for ESRD severity and comorbidities were made in statistical analyses. One issue to keep in mind when adjusting for "comorbid" conditions is that one investigator's "comorbid" condition may be another investigator's definition of a more severe level of a primary condition, e.g., bone disease among those with ESRD. In that case, for instance it must be kept in mind that the "adjustment" for bone disease takes away from the estimate of the burden of ESRD.

Finally there were several variables that were not assessed in the current protocol, yet may have been related to the ESRD outcomes examined in this work. Assessments that would have been interesting include personality, social support, interpersonal and personal expectations, coping and treatment adherence.

2.5 Questionnaire administration method

Participants' responses to questionnaire items may be subject to experimental demand and social desirability, especially in interview-based assessment. Although only in a handful of cases the study questionnaire was read out to the participants, it is possible

that the mere presence of the researcher during questionnaire completion/while patients filled in the measures might have biased their responses. On the other hand the inclusion/use of interviewer-administered questionnaires ensured that study participation would not be restricted only on patients who can complete measures on their own and hence the risk of selection bias against patients with older age, minority status and higher level of comorbidity would be lower (Unruh *et al.*, 2003)

Section 3: Additional recommendations for future research

A summary of research recommendations presented previously and a number of yet unaddressed issues are presented below. The following issues could inform the future research agenda and greatly advance the field of psychonephrology.

3.1 Study design issues

An avenue for future research is to adopt longitudinal designs with long-term follow up data and repeated assessments to test the direction of causality in the relationships, and dynamic interactions between illness and treatment cognitions and HQoL, and to delineate how these variables change over time in the course of ESRD, or when patient switch from one treatment modality to another, such as pre- and post- transplantation or after a transplant failure.

From a statistical point of view a useful addition to the present analyses would have been to subject (correlational) data/matrices to path analyses to test mediational hypotheses and to determine the role of treatment cognitions within the self regulatory framework and the interrelations between the illness representation components and between illness and treatment beliefs (see Chapter 10; section 3.3).
Future research will therefore need to focus not only on longitudinal designs but also on elaborate statistical procedures to unravel the complex, dynamic interactions and model predictions. A longitudinal design coupled with such 'advanced' statistical techniques and procedures may provide a more powerful way of assessing the true relationships between cognitions and HQoL outcomes.

3.2 Measures

Future studies would benefit by the use of both generic and disease-specific measures for the assessment of HQoL. Future studies are also encouraged to pursue assessments of individualised QoL to unravel the life domains or aspects that each individual regarded as crucial in determining his or her overall QoL, rather than baseing assessment solely on generic HQoL measures. HQoL instruments may also well require modification and refinements to address the key longer-term HQoL issues (Jamieson & Jamieson, 2003). In addition, qualitative approaches also have their place in ESRD research as they may offer more insight and a greater understanding in the issues that are likely to be of particular relevance and importance in ESRD patients, and in the different treatment groups.

Finally more work needs to be done in the area of treatment perceptions among the RRT groups. A study of how treatment is perceived and evaluated by patients and the implications of such appraisals deserves more attention, and the use of both quantitative and qualitative methodologies is strongly recommended.

3.3 Medication

In evaluating how the impact of treatment modality on ESRD outcomes, more attention should be given to other aspects of treatment regime such as prescribed medication and their HQoL and neuropsychological implications.

Dialysis and TX patients are typically taking numerous medications. Little is known about the effects of these medications on NP outcomes and HQoL and there appears to be great variation among hospital units in physicians' prescription practices and in patients' prescribed medication regime as well as in patients' adherence. Antihypertensive medication for instance may seriously affect cognitive outcomes and physical well-being indicators (i.e. sexual function). While it may not be possible to directly control for medication effects, strategies for evaluating and minimising their confounding effect should be adopted in future research.

3.4 Response Shift

Response shift is a change in the meaning of one's self evaluation of a target construct as a result of (a) a change in one's internal standards of measurements; (b) a change in one's values (i.e. the importance of component domains constituting the target construct); or (c) reconceptualisation of the target construct (Sparngers & Schwartz 1999). As a consequence of response shift, HQoL may remain within acceptable levels or improve even in the light of deteriorating physical conditions. Response shift is therefore a HQoL predictor and may be explained in terms of the self-regulatory theory. Measuring response shift would have been a valuable addition to this study. Information on changes in internal standards, values and conceptualisation could provide information on the dynamic changes in the illness and treatment beliefs/representations and HQoL.

3.5 Research priorities

In addition to the above generic recommendations for future research, several key themes emerge from the data with respect to priorities for future research.

- Biochemical – physiological mechanisms underlying the acute NP changes in HD. This study failed to explain why NP performance improved pre to 24 post-dialysis. Future work is needed to test alternative physiological pathways and the role of different molecules in predicting NP outcomes in ESRD

- More work is also needed to explore the links between dialysis adequacy and cognitive functioning. Whether there is a continuous dose-response relationship demonstrating progressive resolution of NP deficits as a function of increased dialysis delivery at values of Kt/V in excess of clinical minimum standards or whether most NP deficits resolve at some threshold value of dialysis adequacy and there is little improvement with further increases, short of restoring renal function with transplantation remains to be determined.

- The clinical significance of acute NP changes and NP impairments should be the focus of future investigations. Studies are needed to examine how, if and the extent

to which the observed NP changes and the mild NP deficits observed in this study impact upon patients' functioning and performance in the 'real world'.

- Subjective cognition is an intriguing area for future research. Work is needed in a number of research fronts.

1. There is need for laboratory work on how people appraise and respond to (experimentally induced) cognitive failures or successes.

2. There is also the need to work with illness populations especially patients with condition such as ESRD that can potentially affect cognitive functioning to understand how illness and treatment shape patients perceptions of cognitive abilities and if or how these subjective judgements change over time and in response to disease progression or treatment changes.

An understanding of the key processes involved in perceiving, interpreting cognitive changes or rating cognitive abilities and their related behavioural, emotional or other consequences has the potential to inform and improve understanding of patients' personal model of their illness and also provide a greater insight in their experience.

- The longitudinal effects of end-stage renal disease and associated treatments (dialysis; transplantation) on illness and treatment representations, cognitive functioning and quality of life. The important question that needs to get addressed is the progression of cognitive functioning and HQoL over time in both dialysis and transplantation and as patients switch from one form of treatment to another, for instance pre to post-kidney transplantation or following rejection of transplant and return on to dialysis treatment.

- Studies ideally should examine neuropsychological functioning in the broader context of psychological health and sense of well-being. Further interdisciplinary research that crosses the boundaries of neuropsychology and health psychology is strongly recommended to unravel the complex interactions between cognitive, emotional, neurospychological and behavioural processes and outcomes.

- Potential interventions to assist patients in dealing with the complexities of treatment and the course of ESRD and with a view to favourably influencing HQoL and adjustment. These studies could potentially guided by the illness and treatment beliefs identified as important in this study or alternatively be more tied to a particular model. Although this work has identified potential targets for intervention, this research could explore methods for producing adaptive changes in patient undergoing renal replacement therapy.

- As illness and treatment models evolve within the belief systems, social networks and are subject of culture influences exploring socio-cultural or ethnic differences in illness and treatment representations should lead to a greater understanding of their impact on ESRD outcomes. Future investigation would benefit form diversifying the research ESRD population to include different ethnic and cultural groups.

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APPENDICES

Appendix A:

Index of NP tests used in previous ESRD studies

DOMAINS	NEUROPSYCHOLOGICAL TESTS
Intelligence	1. WAIS 2. Quick Test 3. Weschler Bellevue Intelligence test 4. Shipley-Hartford IQ scale
Non-verbal/visual memory	5. Weschler Memory Scale (WMS) 6. Memory for designs test 7. Visual Retention test 8. Rey Osterich complex figure test 9. Taylor's complex figure test 10. Recurring Figures test 11. Benton visual retention test 12. WMS:Visual reproduction 13. Tactual performance test 14. Facial recognition memory task 15. Unspecified visual memory tasks
Verbal memory	16. Auditory short term memory task 17. WMS: Mental control 18. WMS: Logical 19. Story recall / short story recall 20. Digit span / digit retention 21. Rey Auditory Verbal Learning Test 22. Word span 23. Serial digit learning test 24. Free verbal learning task 25. Buschke selective reminder recall test 26. WMS: Paired associates 27. Enhanced cued recall 28. Whalton-Black modified word learning test 29. Contitnuous memory test 30. Unspecified verbal memory tasks
Verbal functions and language skills (e.g. reading verbal expression fluency)	31. WAIS Vocabulary WAIS Information 32. Alexia test 33. National Adult Reading Test (NART) 34. Schonell graded word reading test 35. Agraphia (writing verbal academic skills) 36. Visual naming test 37. Token test 38. Conttolled Oral Word Association (COWA) 39. Aphasia test/aphasia screening test 40. Repetition tasks (aphasia syllable words phrases) 41. Animal naming 42. Graded difficulty naming test 43. Color naming 44. Borkowski verbal fluency test 45. FAS 46. Word fluency (by Thurstone 1938)

	47. Set test of verbal fluency (by Newcombe 1969) 48. Boston Naming test 49. Speech-Sound perception test 50. Reading comprehension task 51. Unreferenced naming tasks (by Churchill 1991) 52. Unreferenced writing tasks (by Churchill 1991)
Attention concentration	53. Stroop word/color test 54. TMT A 55. TMT B 56. SDMT 57. Symbol digit paired associate learning task 58. Choice reaction time 59. Visual reaction time measure 60. Number cancellation protocol 61. Corsi block tapping test 62. Digit symbol 63. PASAT 64. Gordon diagnostic system vigilance test 65. Continuous performance test 66. Vigilance continous performance test computerised 67. Digit vigilance test 68. Barrage test (by Diller 1974) 69. Digits forward 70. Digits backward 71. Letter cancellation test counting As 72. Critical reaction time 73. Critical flicker fusion 74. Unspecified attention tasks
Orientation	75. Spatial relations (spatial orientation) 76. Finger agnosia (body orientation) 77. R-L confusion (body orientation) 78. time place age
Perceptual function	79. Hopper visual organisation test 80. Rhythm test
Motor function/ Performance	81. Luria motor sequences 82. Grip strength 83. Gibson's spiral maze 84. Purdue Pegboard 85. Grooved Pegbgoard 86. Finger tapping 87. Apraxia 88. Mirror test 89. Unspecified motor tasks
Concept formation and reasoning	90. Proverbs test (by Gorham 1956) 91. Category test/computerised category test 92. Raven's advanced progressive matrices 93. WAIS: Similarities 94. WAIS: Opposites

	95. WAIS: Synonymes 96. Graded difficulty arithmetic test 97. WAIS: Arithmetic/mathematics 98. Answer recognition test 99. WAIS: Comprehension 100. Picture completion 101. Unspecified conceptual ability tests
Construction (-al function) combines perceptual ability with motor response	102. WAIS: Digit block 103. WAIS: Object assemply 104. Clock drawing 105. Necker cube 106. Unspecified construction tasks
Dementia evaluation	107. Matis dementia rating scale 108. Mini mental state examination
Neuropsychological batteries for assessment of brain function	109. Luria nebraska neuropsychological battery 110. Halstead-reitan battery 111. Neurobehavioral Evaluation System 112. Bexley Maudsley automated psychological tests

Appendix B :

Review of studies examing the effects of erythropoietin anaemia corrective tretament on neuropsychological outcomes

Study	N	Hct pre-EPO	Hct Post-EPO	Method	Measures
Wolcott 1989	HD=15	22.8	36.1	NP tests	TMT-A, TMT-B, SDMT,-NCP, RAVLT, COWAT, WAIS
Grimm 1990	HD=15 Ctl=6	22.7	30.6	BAEP P3 NP tests	Auditory Oddball TMTA, MMSE
Brown 1991	HD=14	24.6	36	N1 P2 P300 NP tests	Auditory oddball; TMT-B; SDMT; COWAT; RAVLT
Marsh 1991	HD=24	23.7	36.5	N1 P2 P300 NP tests	Auditory oddball TMT-B; SDMT; COWAT; RAVLT
Horina 1991	HD=13	18-35	20-39	NP tests	WAIS Digit Symbol WAIS Digit Span
Temple 1992	HD=9 Ctl=9	Hb 5.8	Hb = 9.3	NP tests	NART; WAIS; PASAT; RAVLT; COWAT
Sagales 1993	HD=43 Cttl=8	N/s	>30	QEEG P3 NP tests	Visual oddball WAIS subscales
Temple 1995	CAPD=	N/s	Hb >10	NP tests	TMT-A; PASAT; WAIS; RAVLT; NART
Pickett 1999	HD=20	31.6	42.9	QEEG ERP/BA EP	Auditory oddball CPT

Abbreviations: HD = hemodialysis; Ctl = controls; CAPD = continuous ambulatory peritoneal dialysis; Hct = hematocrit; Hb = haemoglobin; n/s = not stated QEEG = qualitative electroencaphalogram; ERP = event related potentials; CPT = continuous performance test; TMT-A = Trail Making test part A; TMT-B = Trail Making test part B; COWAT = Controlled Oral Word Association Test; RAVLT = Rey Auditory Verbal Learning test

Appendix C:

Study questionnaires

ST. PETER'S HOSPITAL
THE MIDDLESEX HOSPITAL

The Impact of Kidney Transplantation and Dialysis on People's Lives

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Questionnaires Part I

In this part of our survey we would like to obtain some information about you and your experience with your kidney transplant and finally we would like you to ask you for your views about your health and how you feel.

Your responses are confidential and the completed questionnaires will not be seen by any of the staff involved in your care.

Date:_____ **Code:** _____

The Impact of Kidney Transplantation and Dialysis on People's Lives

CONSENT FORM

(please delete as necessary)

1.	I have read the information sheet about this study	Yes / No
2.	I have had a chance to ask questions and discuss this study	Yes / No
3.	I have received satisfactory answers to my questions	Yes / No
4.	I understand that I am free to withdraw from this study: - at any time - without giving a reason	Yes / No
5.	Do you agree to take part in this study?	Yes / No

SIGNED:._____ DATE: _____

NAME (in block letters): _____

RESEARCHER:
I confirm that I have explained the nature and purpose of the study to the participant:

SIGNED: _____

Some Details About You

Your response to the following questions about yourself (e.g. age, employment status) would be very helpful. Please circle one number for each question or write in the answer on the lines provided.

[1] **What is your date of birth?** *(please write in)* _____

[2] **What is your first language?** *(please write in)* _____

[3] **How would you describe your ethnic background?** *(please circle one number)*

1	Black-Caribbean	2	Black-African
3	Black-other	4	Indian
5	Pakistani	6	Bangladeshi
7	Chinese	8	Asian Other
9	Arabic	10	White
11	Other	12	Do not wish to answer

[4] **How would you describe your relationship status?** *(please circle one number)*

1	married	*4*	single
2	widowed	*5*	living with partner
3	divorced		

[5] **How old were you when you left full-time education?** _____years old

[6] **What is your highest educational qualification?** *(please write in)*

_____

[7] **Are you now able to work for pay full-time, part-time not at all?**
(please circle one number)

1 I am able to work for pay full-time
2 I am able to work for pay part-time
3 I am *unable* to work for pay

[8a] **Which of the following responses best characterises your *current* work activity or employment status?** *(please circle one number)*

1	employed full-time	*5*	retired
2	employed part-time	*6*	looking after home and family
3	self-employed	*7*	student
4	unemployed	*8*	other

[8b] **Which of the following responses best characterises your work activity or employment status *before you received your transplant/or started dialysis*?**
(please circle one number)

1	employed full-time	*5*	retired
2	employed part-time	*6*	looking after home and family
3	self-employed	*7*	student
4	unemployed	*8*	other

[9] **What approximately is the current estimated annual income of your *overall* family?** *(please circle one number)*

1 £ 0 - £ 10,000
2 £ 10,001 - £ 20,000
3 £ 20,001 - £ 30,000
4 £ 30,001 - above
5 don't wish to answer

[10] **Which of the following best describes your living arrangements:** *(please circle one number)*

1 rent from local authority
2 rent from private landlord
3 own home
4 live with parents
5 other

[11] **Do you have any long standing illness, disability or infirmity?** *(If yes please give details)*

_____

[12a] **How old were you when you have been diagnosed with kidney failure?** *(please write in)* _____ years old

[12b] **Have you been on dialysis before you received your transplant?** *(please circle one number/write in)*

1 I have never been on dialysis
2 I have been on CAPD .....How long have you been on CAPD? _____
3 I have been on hemodialysis . How long have you been on HD?_____

[12c] **When have you received your transplant?** *(please write in the date)* _____

[12d] **Where have you received your transplant?** *(please circle one number/write in)*

1 at the Middlesex Hospital
2 other hospital *(please give details)* _____

[12e] **Where does your transplant come from?** *(please circle one number/write in)*

1 from a *non*-living donor
2 from a living donor

If your transplant is from a *living donor*, please give details about your relationship to your donor *(eg. sister, father, friend)* and tell us if this person is still alive:

_____

[12f] **Did you have any previous transplants?** *(please circle one number/write in)*

1 no, this is my first transplant
2 I have had a transplant before

If you had *more than one* transplant please give details:

- *Which organ was transplanted?*
- *Was the transplant from a living donor or from a non-living donor?*
- *When was the transplantation?*

_____

_____

SYMPTOM QUESTIONNAIRE

Please indicate how often you experience the following symptoms as part of your condition. If you experience any of these symptoms at this point in time, please tick the last grey column on your right

1) Pain	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
2) Nausea	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
3) Breathlessness	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
4) Weight loss	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
5) Fatigue	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
6) Stiff joints	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
7) Sore eyes	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
8) Headaches	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
9) Upset stomach	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
10) Sleep difficulties	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
11) Dizziness	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
12) Loss of strength	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
13) Hair loss	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
14) Itching	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
15) Loss of appetite	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
16) Poor concentration or mental alertness	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
17) Impotence or lack of sex drive	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
18) Muscle spasm or stiffness (including leg cramp)	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
19) Restless legs	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*

Symptom questionnaire continued (Transplantation supplement)

20) Weight gain	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
21) Increased appetite	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
22) Fever/Chills	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
23) Flu-like symptoms	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
24) Infections	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
25) Diarrhoea	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
26) llusions/Hallucinations	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
27) Disorientation	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
28) Excessive hair growth	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
29) Tremor	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
30) Extreme excitement	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
31) Restlessness	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
32) Clumsiness of movements	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
33) Swollen face	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
34) Acne	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
35) Impaired visual acuity (eg: cataracts; glaucoma)	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
36) Striation or bruises	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
37) Problems with the back	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
38) Problems with the gums	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
39) Numbness in the limbs	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
40) Weak muscles	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
41) Muscle wasting	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*
42) Other (please specify) _____	All of the time	Frequently	Occasionally	Never	*RIGHT NOW*

The Short Form 36 Health Survey Questionnaire (SF-36 V2)

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering as your immediate response is likely to be the most accurate.

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

(Circle One Number)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

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

(Circle One Number)

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

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

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying shopping bags	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **half a mile**	1	2	3
i. Walking **100 yards**	1	2	3
j. Bathing or dressing yourself	1	2	3

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

(Circle One Number on Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the **amount of time** you spent at work and other activities ?	1	2	3	4	5
b. **Accomplished less** than you would like ?	1	2	3	4	5
c. Were limited in the **kind** of work and other activities ?	1	2	3	4	5
d. Had **difficulty** performing the work and other activities?	1	2	3	4	5

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)?

(Circle One Number on Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the **amount of time** you spent at work and other activities ?	1	2	3	4	5
b. **Accomplished less** than you would like ?	1	2	3	4	5
d. Didn't do work or other activities **as carefully as usual** ?	1	2	3	4	5

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

(Circle One Number)

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

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

(Circle One Number)

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

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

(Circle One Number)

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

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**

(Circle One Number on Each Line)

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

11. Please choose the answer that best describes how **TRUE** or **FALSE** each of the following statements is for you.

(Circle One Number on Each Line)

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

IEQ

Your responses to this questionnaire help us understand how your illness (your transplant and any kidney related symptoms) disrupts your life. Answer each statement by circling one number under the description that matches your recent experience. The higher number you circle, the more you believe the illness disrupts your life.

	I Disagree				I Agree			
	Strongly	Moderately	Somewhat	A little	A little	Somewhat	Moderately	Strongly
1. My illness makes sleeping difficult	0	1	2	3	4	5	6	7
2. My illness creates problems between myself and my family (or friends)	0	1	2	3	4	5	6	7
3. My sex life is suffering	0	1	2	3	4	5	6	7
4. I am in pain or feel discomfort	0	1	2	3	4	5	6	7
5. I worry about my illness	0	1	2	3	4	5	6	7
6. Some people do not take my illness seriously enough	0	1	2	3	4	5	6	7
7. I experience many different symptoms	0	1	2	3	4	5	6	7
8. My appetite is poor	0	1	2	3	4	5	6	7
9. My illness is the main difficulty in my life	0	1	2	3	4	5	6	7
10. I don't work as well at my job, in school or at my hobbies	0	1	2	3	4	5	6	7
	I Disagree				I Agree			
	Strongly	Moderately	Somewhat	A little	A little	Somewhat	Moderately	Strongly
11. My illness threatens my life	0	1	2	3	4	5	6	7
12. My illness requires me to go for frequent treatment	0	1	2	3	4	5	6	7
13. My memory or mind is not as good now	0	1	2	3	4	5	6	7
14. I don't enjoy life as much	0	1	2	3	4	5	6	7
15. My illness is difficult to control	0	1	2	3	4	5	6	7
16. I depend on others to do things I used to do myself	0	1	2	3	4	5	6	7
17. I am less active now	0	1	2	3	4	5	6	7
18. I can be a burden on others to care for	0	1	2	3	4	5	6	7
19. At times, I wonder if I will ever be the person I was before I became ill.	0	1	2	3	4	5	6	7
20. All things considered, my illness disrupts my life	0	1	2	3	4	5	6	7

TEQ

Your responses to this questionnaire help us understand how your treatment disrupts your life. Answer each statement by circling one number under the description that matches your recent experience. The higher number you circle, the more you believe treatment disrupts your life.

	I Disagree				I Agree			
	Strongly	Moderately	Somewhat	A little	A little	Somewhat	Moderately	Strongly
1. Treatment side-effects make sleeping difficult	0	1	2	3	4	5	6	7
2. This treatment is worse than my illness	0	1	2	3	4	5	6	7
3. Treatment side-effects disrupt my sex life	0	1	2	3	4	5	6	7
4. There is pain / discomfort from treatment	0	1	2	3	4	5	6	7
5. I worry about treatment side-effects	0	1	2	3	4	5	6	7
6. My life revolves around this treatment	0	1	2	3	4	5	6	7
7. There are many bad side effects	0	1	2	3	4	5	6	7
8. Treatment side-effects ruin my appetite	0	1	2	3	4	5	6	7
9. As a result of treatment my appearance has worsened	0	1	2	3	4	5	6	7
10. As a result of treatment I don't work as well at my job, in school or at my hobbies	0	1	2	3	4	5	6	7
	I Disagree				I Agree			
	Strongly	Moderately	Somewhat	A little	A little	Somewhat	Moderately	Strongly
11. Treatment is ineffective	0	1	2	3	4	5	6	7
12. I frequently have to visit the doctor or clinic for treatment	0	1	2	3	4	5	6	7
13. Treatment side-effects disrupt my memory or mind	0	1	2	3	4	5	6	7
14. Treatment prevents me enjoying myself	0	1	2	3	4	5	6	7
15. Treatment side-effects are difficult to control	0	1	2	3	4	5	6	7
16. As a result of treatment, I depend on others for help with everyday activities	0	1	2	3	4	5	6	7
17. As a result of treatment I am less active	0	1	2	3	4	5	6	7
18. Going for treatment can burden on my family or friends	0	1	2	3	4	5	6	7
19. My illness is getting worse	0	1	2	3	4	5	6	7
20. All things considered, treatment disrupts my life	0	1	2	3	4	5	6	7

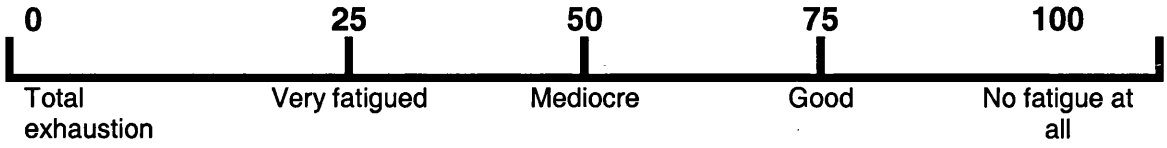
PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate <u>to what extent you feel this way right now, at this very moment</u>						
1	**cheerful**	very slightly or not at all	a little	moderately	quite a bit	extremely
2	**disgusted**	very slightly or not at all	a little	moderately	quite a bit	extremely
3	**attentive**	very slightly or not at all	a little	moderately	quite a bit	extremely
4	**bashful**	very slightly or not at all	a little	moderately	quite a bit	extremely
5	**sluggish**	very slightly or not at all	a little	moderately	quite a bit	extremely
6	**daring**	very slightly or not at all	a little	moderately	quite a bit	extremely
7	**surprised**	very slightly or not at all	a little	moderately	quite a bit	extremely
8	**strong**	very slightly or not at all	a little	moderately	quite a bit	extremely
9	**scornful**	very slightly or not at all	a little	moderately	quite a bit	extremely
10	**relaxed**	very slightly or not at all	a little	moderately	quite a bit	extremely
11	**irritable**	very slightly or not at all	a little	moderately	quite a bit	extremely
12	**delighted**	very slightly or not at all	a little	moderately	quite a bit	extremely
13	**inspired**	very slightly or not at all	a little	moderately	quite a bit	extremely
14	**fearless**	very slightly or not at all	a little	moderately	quite a bit	extremely
15	**disgusted with self**	very slightly or not at all	a little	moderately	quite a bit	extremely
16	**sad**	very slightly or not at all	a little	moderately	quite a bit	extremely
17	**calm**	very slightly or not at all	a little	moderately	quite a bit	extremely
18	**afraid**	very slightly or not at all	a little	moderately	quite a bit	extremely
19	**tired**	very slightly or not at all	a little	moderately	quite a bit	extremely
20	**amazed**	very slightly or not at all	a little	moderately	quite a bit	extremely
21	**shaky**	very slightly or not at all	a little	moderately	quite a bit	extremely
22	**happy**	very slightly or not at all	a little	moderately	quite a bit	extremely
23	**timid**	very slightly or not at all	a little	moderately	quite a bit	extremely
24	**alone**	very slightly or not at all	a little	moderately	quite a bit	extremely
25	**alert**	very slightly or not at all	a little	moderately	quite a bit	extremely
26	**upset**	very slightly or not at all	a little	moderately	quite a bit	extremely
27	**angry**	very slightly or not at all	a little	moderately	quite a bit	extremely
28	**bold**	very slightly or not at all	a little	moderately	quite a bit	extremely
29	**blue**	very slightly or not at all	a little	moderately	quite a bit	extremely

30	**shy**	very slightly or not at all	a little	moderately	quite a bit	extremely
31	**active**	very slightly or not at all	a little	moderately	quite a bit	extremely
32	**guilty**	very slightly or not at all	a little	moderately	quite a bit	extremely
33	**joyful**	very slightly or not at all	a little	moderately	quite a bit	extremely
34	**nervous**	very slightly or not at all	a little	moderately	quite a bit	extremely
35	**lonely**	very slightly or not at all	a little	moderately	quite a bit	extremely
36	**sleepy**	very slightly or not at all	a little	moderately	quite a bit	extremely
37	**excited**	very slightly or not at all	a little	moderately	quite a bit	extremely
38	**hostile**	very slightly or not at all	a little	moderately	quite a bit	extremely
39	**proud**	very slightly or not at all	a little	moderately	quite a bit	extremely
40	**jittery**	very slightly or not at all	a little	moderately	quite a bit	extremely
41	**lively**	very slightly or not at all	a little	moderately	quite a bit	extremely
42	**ashamed**	very slightly or not at all	a little	moderately	quite a bit	extremely
43	**at ease**	very slightly or not at all	a little	moderately	quite a bit	extremely
44	**scared**	very slightly or not at all	a little	moderately	quite a bit	extremely
45	**drowsy**	very slightly or not at all	a little	moderately	quite a bit	extremely
46	**angry at self**	very slightly or not at all	a little	moderately	quite a bit	extremely
47	**enthusiastic**	very slightly or not at all	a little	moderately	quite a bit	extremely
48	**downhearted**	very slightly or not at all	a little	moderately	quite a bit	extremely
49	**sheepish**	very slightly or not at all	a little	moderately	quite a bit	extremely
50	**distressed**	very slightly or not at all	a little	moderately	quite a bit	extremely
51	**blameworthy**	very slightly or not at all	a little	moderately	quite a bit	extremely
52	**determined**	very slightly or not at all	a little	moderately	quite a bit	extremely
53	**frightened**	very slightly or not at all	a little	moderately	quite a bit	extremely
54	**astonished**	very slightly or not at all	a little	moderately	quite a bit	extremely
55	**interested**	very slightly or not at all	a little	moderately	quite a bit	extremely
56	**loathing**	very slightly or not at all	a little	moderately	quite a bit	extremely
57	**confident**	very slightly or not at all	a little	moderately	quite a bit	extremely
58	**energetic**	very slightly or not at all	a little	moderately	quite a bit	extremely
59	**concentrating**	very slightly or not at all	a little	moderately	quite a bit	extremely
60	**dissatisfied with self**	very slightly or not at all	a little	moderately	quite a bit	extremely

Fatigue rating scale

Using a scale ranging from 0 to 100 where 0 means total exhaustion and 100 means no fatigue at all, please indicate how fatigued <u>you are feeling right now</u> by circling the appropriate number:



STAI QUESTIONNAIRE

Please read each statement and then tick the appropriate box for each question to indicate how you feel right <u>now, at this very moment</u>.

	Not at all	Somewhat	Moderately	Very much
a. I feel calm	1	2	3	4
b. I am tense	1	2	3	4
c. I feel upset	1	2	3	4
d. I am relaxed	1	2	3	4
e. I feel content	1	2	3	4
f. I am worried	1	2	3	4

Thank you for completing this questionnaire

ST. PETER'S HOSPITAL
THE MIDDLESEX HOSPITAL

The Impact of Kidney Transplantation and Dialysis on People's Lives

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Questionnaires Part II

In this part of our survey we would like to obtain some information about how you now see your illness and your treatment. Finally we would like you to ask you for your views about your health and how you feel.

Filling in these questionnaires should take approximately 15-20 minutes and we would like to ask you to return the completed questionnaires within the next seven days.

Your responses are confidential and the completed questionnaires will not be seen by any of the staff involved in your care.

Please return the completed questionnaires in the stamped and addressed envelope provided.

Date:_____ **Code:** _____

If you have any questions or comments please feel free to contact Konstadina Griva on

Transplant Effects Questionnaire

We are interested in your own personal views of how you <u>now</u> see your experience with your kidney transplant. These are statements other people have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate

A1	Sometimes I think it would have been better for me not to go for a transplant	strongly agree	agree	Uncertain	disagree	strongly disagree
A2	Life after transplantation meets with my expectations	strongly agree	agree	Uncertain	disagree	strongly disagree
A3	My quality of life is now like it was before my illness	strongly agree	agree	Uncertain	disagree	strongly disagree
A4	It is difficult for me to adjust to my life after transplantation	strongly agree	agree	Uncertain	disagree	strongly disagree
A5	After transplantation I have difficulties in resuming an independent role	strongly agree	agree	Uncertain	disagree	strongly disagree
A6	Transplantation is an alternative treatment rather than a cure for my illness	strongly agree	agree	Uncertain	disagree	strongly disagree
A7	Now I have more freedom than I had before the transplantation	strongly agree	agree	Uncertain	disagree	strongly disagree
B1	With regard to my transplant I feel that I am carrying around something fragile	strongly agree	agree	Uncertain	disagree	strongly disagree
B2	I am worried about damaging my transplant	strongly agree	agree	Uncertain	disagree	strongly disagree
B3	I keep wondering how long my transplant will work	strongly agree	agree	Uncertain	disagree	strongly disagree
B4	I am worried about my routine transplant check-ups	strongly agree	agree	Uncertain	disagree	strongly disagree
B5	I am hesitant to engage in certain activities because I am afraid of doing harm to my transplant	strongly agree	agree	Uncertain	disagree	strongly disagree
C1	I monitor my body more closely than before I had the transplant	strongly agree	agree	Uncertain	disagree	strongly disagree
C2	Sometimes I forget to take my anti-rejection medicines	strongly agree	agree	Uncertain	disagree	strongly disagree
C3	I never miss my regular transplant clinic check-ups	strongly agree	agree	Uncertain	disagree	strongly disagree
C4	When I am too busy I may forget my anti-rejection medicines	strongly agree	agree	Uncertain	disagree	strongly disagree
C5	I report all my symptoms to my doctor/to the transplant clinic	strongly agree	agree	Uncertain	disagree	strongly disagree
C6	Sometimes I do not take my anti-rejection medicines	strongly agree	agree	Uncertain	disagree	strongly disagree
C7	It doesn't matter at what time of day I take my anti-rejection medicines	strongly agree	agree	Uncertain	disagree	strongly disagree
C8	I try to lead a healthier life than I did before the transplantation	strongly agree	agree	Uncertain	disagree	strongly disagree
C9	Sometimes I think I do not need my	strongly agree	agree	Uncertain	disagree	Strongly disagree

	anti-rejection medicines					
D 1	I find it difficult to adjust to taking my prescribed anti-rejection drug regime	strongly agree	agree	Uncertain	disagree	strongly disagree
D 2	I worry each time my anti-rejection drug regime is altered by my doctor	strongly agree	agree	Uncertain	disagree	strongly disagree
D 3	Dealing with the side-effects of my anti-rejection medicines is difficult for me	strongly agree	agree	Uncertain	disagree	strongly disagree
D 4	I have experienced unpleasant side-effects with my anti-rejection medicines	strongly agree	agree	Uncertain	disagree	strongly disagree
E 1	Sometimes I think that I have 'robbed' the donor of a vital part	strongly agree	agree	Uncertain	disagree	strongly disagree
E 2	I don't have any feelings of guilt toward the donor	strongly agree	agree	Uncertain	disagree	strongly disagree
E 3	The donor had to suffer to make me feel better	strongly agree	agree	Uncertain	disagree	strongly disagree
E 4	I feel guilty about having taken advantage of the donor	strongly agree	agree	Uncertain	disagree	strongly disagree
F 1	I think that I have a responsibility to the donor/the donors' family to do well	strongly agree	agree	Uncertain	disagree	strongly disagree
F 2	I have the feeling that the donor/the donors' family has some control over me.	strongly agree	agree	Uncertain	disagree	strongly disagree
F 3	I think that I have a responsibility to the transplant team to do well	strongly agree	agree	Uncertain	disagree	strongly disagree
F 4	Accepting an organ from another person has added stress to my life	strongly agree	agree	Uncertain	disagree	strongly disagree
F 5	I feel that I owe the donor/the donors' family something that I will never be able to repay	strongly agree	agree	Uncertain	disagree	strongly disagree
F 6	I think that I have a responsibility to my friends and my family to do well	strongly agree	agree	Uncertain	disagree	strongly disagree
G 1	Sometimes I wonder about the characteristics and the life style of the donor	strongly agree	Agree	Uncertain	disagree	strongly disagree
G 2	I am concerned that I could take on various qualities of the donor (e.g. personality/ habits/ behaviour change)	strongly agree	Agree	Uncertain	disagree	strongly disagree
G 3	My transplant is a threat to my personal identity	strongly agree	Agree	Uncertain	disagree	strongly disagree
G 4	My transplant is part of my body just like any other organ in my body	strongly agree	Agree	Uncertain	disagree	strongly disagree
G 5	I have got the feeling that the transplant still belongs to the donor	strongly agree	Agree	Uncertain	disagree	strongly disagree
G 6	Where the transplant comes from does not come into my mind at all	strongly agree	Agree	Uncertain	disagree	strongly disagree
H 1	My relationship with my family has deteriorated since transplantation	strongly agree	Agree	Uncertain	disagree	strongly disagree
H 2	I feel resentful towards people who will not consider organ donation	strongly agree	Agree	Uncertain	disagree	strongly disagree

H 3	The fact of needing a transplant added tension to my life	strongly agree	Agree	Uncertain	disagree	strongly disagree
H 4	There are bad feelings now in my family because of the search for a donor	strongly agree	Agree	Uncertain	disagree	strongly disagree
H 5	My relationship with my family has become closer since transplantation	Strongly agree	Agree	Uncertain	disagree	strongly disagree
H 6	The fact that I was looking for a transplant affected my relationship with friends and family	Strongly agree	Agree	Uncertain	disagree	strongly disagree
I 1	I am uncomfortable with other people knowing that I have a transplant	Strongly agree	Agree	Uncertain	disagree	strongly disagree
I 2	I avoid telling other people that I have a transplant	Strongly agree	Agree	Uncertain	disagree	strongly disagree
I 3	When I think about the donor I get emotional	Strongly agree	Agree	Uncertain	disagree	strongly disagree
I 4	I have difficulty in talking about my transplant	Strongly agree	Agree	Uncertain	disagree	strongly disagree

Living Related Donor Transplantation TxEQ supplement

These are statements other people who received a transplant from a living donor have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box.						
L 1	I am worried more about the donor than I am about myself	Strongly agree	Agree	uncertain	disagree	strongly disagree
L 2	I would feel guilty if anything happened to the donor	Strongly agree	Agree	uncertain	disagree	strongly disagree
L 3	My relationship with the donor has deteriorated since transplantation	Strongly agree	Agree	uncertain	disagree	strongly disagree
L 4	My relationship with the donor has become closer since transplantation	Strongly agree	Agree	uncertain	disagree	strongly disagree

Cadaver Transplantation TxEQ suppplement

These are statements other people who received a transplant from a non-living donor have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box.						
N 1	I feel guilty because the donor is dead while I am still alive	strongly agree	Agree	uncertain	disagree	strongly disagree
N 2	I don't feel responsible at all for the donors death	strongly agree	Agree	uncertain	disagree	strongly disagree
N 3	I want to have contact with the donor's family	strongly agree	Agree	uncertain	disagree	strongly disagree
N 4	I don't want to know too much about the donor	strongly agree	agree	uncertain	disagree	strongly disagree

Thank you for completing this questionnaire

Please turn the page

YOUR VIEWS ABOUT IMMUNOSUPPRESSIVE MEDICINES PRESCRIBED FOR YOU

We would like to ask you about your personal views about immunosuppressive medicines prescribed for you. These are statements other people have made about their 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.

Views about the immunosuppressive medicines prescribed for you						
BS1	My health, at present, depends on my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS2	Having to take medicines worries me	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
AS2	I sometimes alter the doses of my medicine to suit my own needs	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS3	My life would be impossible without my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS4	Without my medicines I would be very ill	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS5	I sometimes worry about long-term effects of my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS6	My medicines are a mystery for me	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
AS1	I sometimes forget to take my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS7	My health in the future will depend on my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS8	My medicines disrupt my life	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS9	I sometimes worry about becoming too dependent on my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BS10	My medicines protect me from becoming worse	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
CS11	I can cope without my medicines	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree

Questions about taking your medicines:						
AS3	Some people <u>forget</u> to take their medicines. Overall, how often does this happen to you?	Very often	Often	Sometimes	Rarely	Never
AS4	Some say that they <u>miss out a dose</u> of their medication, <u>or adjust it</u> to suit themselves. Overall, how often do you do this?	Very often	Often	Sometimes	Rarely	Never
AS5	Others say that they alter the dose of their medicines for one reason or another. How often do you do this with your medicines?	Very often	Often	Sometimes	Rarely	Never

IMMUNOSUPPRESSIVE MEDICINES PRESCRIBED FOR YOU

1) Azathioprine (*Azathioprine; Imuran*)
a) How often should you take this drug?
b) Do you think this drug causes side-effects? (If yes, please give details):
c) During the past four weeks how often have you not taken this drug?

2) Mycophenolate Mofetil (*CellCept*)
a) How often should you take this drug?
b) Do you think this drug causes side-effects? (If yes, please give details):
c) During the past four weeks how often have you not taken this drug?

3) Prednisolone (*Prednisolone, Precortisyl Forte, Prednesol*)
a) How often should you take this drug?
b) Do you think this drug causes side-effects? (If yes, please give details):
c) During the past four weeks how often have you not taken this drug?

4) Cyclosporine (*Neoral; Sandimmun*)
a) How often should you take this drug?
b) Do you think this drug causes side-effects? (If yes, please give details):
c) During the past four weeks how often have you not taken this drug?

5) Tacrolimus (*Prograf*)
a) How often should you take this drug?
b) Do you think this drug causes side-effects? (If yes, please give details):
c) During the past four weeks how often have you not taken this drug?

ILLNESS BELIEFS

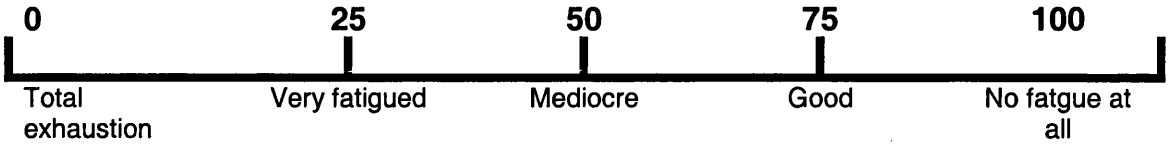
We are interested in your own personal views of how you <u>now</u> see you illness (condition). Please indicate how much you agree or disagree with the following statements about your illness by ticking the appropriate box.					
1) The symptoms of my illness change a great deal from day to day	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
2) The symptoms of my illness are distressing to me	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
3) The symptoms of my illness are puzzling to me	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
4) I am aware of my symptoms all the time	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
5) The symptoms of my illness are constant	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
6) A germ or virus caused my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
7) Diet played a major role in causing my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
8) Pollution of the environment caused my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
9) My illness is hereditary - it runs in my family	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
10) It was just by chance that I developed my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
11) My illness is largely due to my own behaviour	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
12) Other people played a large role in causing my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
13) My illness was caused by poor medical care in the past	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
14) My state of mind played a major part in causing my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
15) My illness will last a short time	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
16) My illness is likely to be temporary rather than permanent	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
17) My illness will last for a long time	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
18) My illness comes and goes in cycles	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
19) My illness is a serious condition	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
20) My illness has had major consequences for my life	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
21) My illness has become easier to live with	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
22) My illness has not had much effect	Strongly	Agree	Neither agree	Disagree	Strongly

on my life	agree		or disagree		disagree
23) My illness has strongly affected the way I see myself as a person	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
24) My illness has affected the way other people see me	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
25) My illness has serious economic and financial consequences	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
26) My illness will improve	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
27) There is a lot I can do to control my symptoms	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
28) There is very little that can be done to improve my symptoms	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
29) There is very little that can be done to improve my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
30) Recovery from my illness is largely dependent on chance or fate	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
31) What I do determines whether my illness gets better	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
32) What I do determines whether my illness gets worse	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
33) My treatment will be effective in curing/controlling my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
34) Stress was a major factor in causing my illness	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree

Thank you for completing this questionnaire

Fatigue rating scale

Using a scale ranging from 0 to 100 where 0 means total exhaustion and 100 means no fatigue at all, please indicate how fatigued <u>you are feeling right now</u> by circling the appropriate number:



STAI QUESTIONNAIRE

Please read each statement and then tick the appropriate box for each question to indicate how you feel right <u>now, at this very moment</u> .

	Not at all	Somewhat	Moderately	Very much
a. I feel calm	1	2	3	4
b. I am tense	1	2	3	4
c. I feel upset	1	2	3	4
d. I am relaxed	1	2	3	4
e. I feel content	1	2	3	4
f. I am worried	1	2	3	4

PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate <u>to what extent you have feel this way right now, at this very moment</u>.						
1	**cheerful**	very slightly or not at all	A little	moderately	quite a bit	extremely
2	**disgusted**	very slightly or not at all	A little	moderately	quite a bit	extremely
3	**attentive**	very slightly or not at all	A little	moderately	quite a bit	extremely
4	**bashful**	very slightly or not at all	A little	moderately	quite a bit	extremely
5	**sluggish**	very slightly or not at all	A little	moderately	quite a bit	extremely
6	**daring**	very slightly or not at all	A little	moderately	quite a bit	extremely
7	**surprised**	very slightly or not at all	A little	moderately	quite a bit	extremely
8	**strong**	very slightly or not at all	A little	moderately	quite a bit	extremely
9	**scornful**	very slightly or not at all	A little	moderately	quite a bit	extremely
10	**relaxed**	very slightly or not at all	A little	moderately	quite a bit	extremely
11	**irritable**	very slightly or not at all	A little	moderately	quite a bit	extremely
12	**delighted**	very slightly or not at all	A little	moderately	quite a bit	extremely
13	**inspired**	very slightly or not at all	A little	moderately	quite a bit	extremely
14	**fearless**	very slightly or not at all	A little	moderately	quite a bit	extremely
15	**disgusted with self**	very slightly or not at all	A little	moderately	quite a bit	extremely
16	**sad**	very slightly or not at all	A little	moderately	quite a bit	extremely
17	**calm**	very slightly or not at all	A little	moderately	quite a bit	extremely
18	**afraid**	very slightly or not at all	A little	moderately	quite a bit	extremely
19	**tired**	very slightly or not at all	A little	moderately	quite a bit	extremely
20	**amazed**	very slightly or not at all	A little	moderately	quite a bit	extremely
21	**shaky**	very slightly or not at all	A little	moderately	quite a bit	extremely
22	**happy**	very slightly or not at all	A little	moderately	quite a bit	extremely
23	**timid**	very slightly or not at all	A little	moderately	quite a bit	extremely
24	**alone**	very slightly or not at all	A little	moderately	quite a bit	extremely
25	**alert**	very slightly or not at all	A little	moderately	quite a bit	extremely
26	**upset**	very slightly or not at all	A little	moderately	quite a bit	extremely
27	**angry**	very slightly or not at all	A little	moderately	quite a bit	extremely
28	**bold**	very slightly or not at all	A little	moderately	quite a bit	extremely
29	**blue**	very slightly or not at all	A little	moderately	quite a bit	extremely

30	**shy**	very slightly or not at all	A little	moderately	quite a bit	extremely
31	**active**	very slightly or not at all	A little	moderately	quite a bit	extremely
32	**guilty**	very slightly or not at all	A little	moderately	quite a bit	extremely
33	**joyful**	very slightly or not at all	A little	moderately	quite a bit	extremely
34	**nervous**	very slightly or not at all	A little	moderately	quite a bit	extremely
35	**lonely**	very slightly or not at all	A little	moderately	quite a bit	extremely
36	**sleepy**	very slightly or not at all	A little	moderately	quite a bit	extremely
37	**excited**	very slightly or not at all	A little	moderately	quite a bit	extremely
38	**hostile**	very slightly or not at all	A little	moderately	quite a bit	extremely
39	**proud**	very slightly or not at all	A little	moderately	quite a bit	extremely
40	**jittery**	very slightly or not at all	A little	moderately	quite a bit	extremely
41	**lively**	very slightly or not at all	A little	moderately	quite a bit	extremely
42	**ashamed**	very slightly or not at all	A little	moderately	quite a bit	extremely
43	**at ease**	very slightly or not at all	A little	moderately	quite a bit	extremely
44	**scared**	very slightly or not at all	A little	moderately	quite a bit	extremely
45	**drowsy**	very slightly or not at all	A little	moderately	quite a bit	extremely
46	**angry at self**	very slightly or not at all	A little	moderately	quite a bit	extremely
47	**enthusiastic**	very slightly or not at all	A little	moderately	quite a bit	extremely
48	**downhearted**	very slightly or not at all	A little	moderately	quite a bit	extremely
49	**sheepish**	very slightly or not at all	A little	moderately	quite a bit	extremely
50	**distressed**	very slightly or not at all	A little	moderately	quite a bit	extremely
51	**blameworthy**	very slightly or not at all	A little	moderately	quite a bit	extremely
52	**determined**	very slightly or not at all	A little	moderately	quite a bit	extremely
53	**frightened**	very slightly or not at all	A little	moderately	quite a bit	extremely
54	**astonished**	very slightly or not at all	A little	moderately	quite a bit	extremely
55	**interested**	very slightly or not at all	A little	moderately	quite a bit	extremely
56	**loathing**	very slightly or not at all	A little	moderately	quite a bit	extremely
57	**confident**	very slightly or not at all	A little	moderately	quite a bit	extremely
58	**energetic**	very slightly or not at all	A little	moderately	quite a bit	extremely
59	**concentrating**	very slightly or not at all	A little	moderately	quite a bit	extremely
60	**dissatisfied with self**	very slightly or not at all	A little	moderately	quite a bit	extremely

BECK INVENTORY

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1.	**0**	I do not feel sad
	1	I feel sad
	2	I am sad all the time and cannot snap out of it
	3	I am so sad and unhappy that I cannot stand it
2.	**0**	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I fell I have nothing to look forward to
	3	I feel that the future is hopeless and that things cannot improve
3.	**0**	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on life, all I can see is a lot of failure
	3	I feel I am a complete failure as a person
4.	**0**	
	1	I get as much satisfaction form things as I used to
	2	I don't enjoy things the way I used to
	3	I don't get real satisfaction out f anything anymore
5.	**0**	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel guilty most of the time
	3	I feel guilty most of the time
6.	**0**	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
7.	**0**	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8.	**0**	I don't feel I am any worse than anybody else
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9	**0**	I don't have any thoughts of killing myself
	1	I have thought of killing myself but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10.	**0**	I don't cry anymore than usual
	1	I cry more than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I can't try even though I want to

11.
0 I am more irritated now than I ever am
1 I get annoyed or irritated more easily than I used to
2 I feel irritated all the time
3 I don't get irritated at all by the things that used to irritate me

12.
0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost most of my interest in other people
3 I have lost all my interest in other people

13.
0 I make decisions about as well as I used to
1 I put off making decisions more than I used to
2 I have greater difficulty making decisions than before
3 I can't make decisions at all anymore

14.
0 I don't fell I look any worse than I used to
1 I am worried that I look old and unattractive
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe I look ugly

15.
0 I can work as well as before
1 It takes an extra effort to get started in the morning
2 I have to push myself very had to do anything
3 I can't do any work at all

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake several hours earlier than I used to and cannot go back to sleep.

17
0 I don't get more tired than usual
1 I get tired more easily than I used to
2 I get tired form doing almost nothing
3 I am too tired to do anything

18.
0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19.
0 I have not lost much weight, if any lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds

I am purposely trying to lose weight by eating less. YES____ NO____

20.
0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation
2 I am very worried about physical problems that is hard to think of much else
3 I am so worries about physical problems that I cannot think about anything else

21.
0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

Neuropsychological Assessment – Transplantation T1

Date: _____ **Code:** _____

SUBJECTIVE COGNITION SCALE

*I would like to ask you some questions about how your abilities may have changed for you **since your transplantation**. It is very important for our understanding of the effects of transplantation that you answer as honestly as possible.*			
Since the onset of Transplantation are you...			
1) more or less alert and thinking more or less clearly	More	No change	Less
2) forgetting things (eg. things that have happened recently; where you put things; keeping appointments)	More	No change	Less
3) having more or less minor accidents (eg. Dropping things; tripping)	More	No change	Less
4) reacting more or less quickly to things that are said or done	More	No change	Less
5) having more or less difficulty in solving problems and learning new things	More	No change	Less
6) having more or less difficulty in making decisions	More	No change	Less
7) able to keep your attention to a task for more or less time	More	No change	Less
8) making more or less mistakes	More	No change	Less
9) having more or less difficulty in doing things which include thought and concentration	More	No change	Less

1) Trailmaking A & B

Trail A: time to finish: |___|___| : |___|___| : |___|___|
Trail B: time to finish: |___|___| : |___|___| : |___|___|

2) Symbol Digit Modalities Test

Written assessment: |___|___|___|
Oral assessment:: |___|___|___|

3) Rey Auditory Verbal Learning Test

Trial1|___| *Trial2*|___| *Trial3*|___| *Trial4*|___| *Trial5*|___| *Trial6*|___|
Trial7|___|

4) Grooved Pegboard

dominant hand? _____ *(dominant hand trail is administered first)*

Dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|
Non-dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|

6) Fistula

right arm |__| left arm |__|

Neuropsychological Assessment – DIALYSIS T1

Date:_____ **Code:** _____

SUBJECTIVE COGNITION SCALE

*I would like to ask you some questions about how your abilities may have changed for you **since you started on dialysis**. It is very important for our understanding of the effects of dialysis that you answer as honestly as possible.*			
Since the onset of dialysis are you...			
1) more or less alert and thinking more or less clearly	More	No change	Less
2) forgetting things (eg. things that have happened recently; where you put things; keeping appointments)	More	No change	Less
3) having more or less minor accidents (eg. Dropping things; tripping)	More	No change	Less
4) reacting more or less quickly to things that are said or done	More	No change	Less
5) having more or less difficulty in solving problems and learning new things	More	No change	Less
6) having more or less difficulty in making decisions	More	No change	Less
7) able to keep your attention to a task for more or less time	More	No change	Less
8) making more or less mistakes	More	No change	Less
9) having more or less difficulty in doing things which include thought and concentration	More	No change	Less

1) Trailmaking A & B

Trail A: time to finish: |___|___| : |___|___| : |___|___|
Trail B: time to finish: |___|___| : |___|___| : |___|___|

2) Symbol Digit Modalities Test

Written assessment: |___|___|___|
Oral assessment:: |___|___|___|

3) Rey Auditory Verbal Learning Test

Trial1|___| *Trial2*|___| *Trial3*|___| *Trial4*|___| *Trial5*|___| *Trial6*|___|
Trial7|___|

4) Benton Visual Retention test

No correct: _____ *No of errors:* _____ *Type of errors:*_____

5) Grooved Pegboard

dominant hand? _____ *(dominant hand trail is administered first)*
Dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|
Non-dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|

6) Fistula right arm |__| left arm |__|

Neuropsychological Assessment – DIALYSIS T2

Date:_____ **Code:** _____

SUBJECTIVE COGNITION SCALE

*I would like to ask you some questions about how your abilities may have changed for you **since your last dialysis session**. It is very important for our understanding of the effects of dialysis that you answer as honestly as possible.*			
Since your last dialysis session are you...			
1) more or less alert and thinking more or less clearly	More	No change	Less
2) forgetting things (eg. things that have happened recently; where you put things; keeping appointments)	More	No change	Less
3) having more or less minor accidents (eg. Dropping things; tripping)	More	No change	Less
4) reacting more or less quickly to things that are said or done	More	No change	Less
5) having more or less difficulty in solving problems and learning new things	More	No change	Less
6) having more or less difficulty in making decisions	More	No change	Less
7) able to keep your attention to a task for more or less time	More	No change	Less
8) making more or less mistakes	More	No change	Less
9) having more or less difficulty in doing things which include thought and concentration	More	No change	Less

1) Trailmaking A & B

Trail A: time to finish: |___|___| : |___|___| : |___|___|
Trail B: time to finish: |___|___| : |___|___| : |___|___|

2) Symbol Digit Modalities Test

Written assessment: |___|___|___|
Oral assessment:: |___|___|___|

3) Rey Auditory Verbal Learning Test

Trial1|___| *Trial2*|___| *Trial3*|___| *Trial4*|___| *Trial5*|___| *Trial6*|___|
Trial7|___|

4) Benton Visual retention test

No correct: _____ *No of errors:* _____
Type of errors: _____

5) Grooved Pegboard

dominant hand? _____ *(dominant hand trail is administered first)*
Dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|
Non-dominant hand: |___|___| : |___|___| : |___|___| *drops:* |___|

Appendix D:

Medical measures recorded for the study

RENAL STUDY MEDICAL DOCUMENTATION

Date of assessment: **Code:**

please refer to clinical notes/values that are closest to the date of assessment

Primary kidney disease diagnosis (please circle all that apply)
date: _____ (day) _____ (month)_____ (year)

- hypertension 1
- diabetes 2
- polycystic kidney disease 3
- chronic glumeronephritis 4
- chronic pyelonephritis 5
- reflux nephropathy 6
- other (please specify) 7 _____

Renal Replacement treatment onset
date : _____ (day) _____ (month)_____ (year)

Comorbidity:

- diabetes (y / n).....(IDDM / NIDDM)
- hypertension (y / n)
- Ischemic Heart disease (y / n) ..... (please specify if necessary)
- OTHER COMORBID CONDITIONS (PLEASE LIST IF ANY)

Medication (dosages): EPO _____ **units per week**

_____ **mgs** _____ **mgs** _____ **mgs** _____ **mgs**
_____ **mgs** _____ **mgs** _____ **mgs** _____ **mgs**
_____ **mgs** _____ **mgs** _____ **mgs** _____ **mgs**

Hospitalisation episodes in the preceding 6-8 months: (y / n)

_____

_____

- **Access site problems** (HD patients only) (y / n)
- hospitalisation due to access problems (y / n)

_____

_____

- procedures performed due to access problems (y / n) ..... (please specify)

_____

_____

- **catheter site problems** (PD pts only) (y / n)
- hospitalisation due to access problems (y / n)

_____

_____

- procedures performed due to access problems (y / n) .....(please specify)

_____

_____

Current dialysis of TX treatment

CAPD	**1**	exchanges per day	_____
		litres per exchange	_____
		types of bags	_____
APD	**2**	hours per day	_____
		total volume	_____
		fill volume	_____
		no of cycles	_____
Hemodialysis	**3**	times a week	_____
		hours per run	_____
		dialysate used	_____
		blood flow rate	_____
		ACCESS	_____

Dialysis History (if details available):

dialysis period	type of dialysis treatment	date of onset of dialysis period	Date of discontinuation of dialysis period
number 1			
number 2			
number 3			

ACTIVE TRANSPLANTATION LIST **(y / n)**
If no why (please write in_____
Residual Urine Function **(y / n)** _____
IDWG_____

RENAL STUDY

RENAL STUDY MEDICAL DOCUMENTATION

Date of assessment: **Code:**

please refer to clinical notes/values that are closest to the date of assessment

OUTPATIENTS APPOINTMENT: _____

URINE:

please tick out of range values

Creatinine	_____	**nmol/L**	|___|
Total Protein	_____	**g/L (0-0.1)**	|___|
Total Protein	_____	**mg/mmol creat(0-13)**	|___|

SERUM:

Urea	_____	**mmol/L**	**(2.8-7.6)**	|___|
Bicarbonate	_____	**mmol/L**	**(20-30)**	|___|
Sodium	_____	**mmol/L**	**(136-145)**	|___|
Potassium	_____	**mmol/L**	**(3.3-4.8)**	|___|
Bilirubin Total	_____	**umol/L**	**(3-17)**	|___|
Creatinine	_____	**umol/L**	**(62-133)**	|___|
Calcium	_____	**mmol/l**	**(2.20-2.60)**	|___|
Inorganic Phosphate	_____	**mmol/L**	**(0.7-1.5)**	|___|
Alkaline Phosphatase	_____	**U/L**	**(45-122)**	|___|
Alanine Transaminase	_____	**U/L**	**(7-63)**	|___|
Gamma Glutamyl Transferase	_____	**U/L**	**(11-50M 7-32F)**	|___|
Albumin	_____	**g/L**	**(35-50)**	|___|

DRUG BLOOD LEVELS:

Cyclosporin:	_____	**ug/L**	|___|
Tacrolimus	_____	**ug/L**	|___|

HAEMATOLOGY:

WBC	_____	|___|
RBC	_____	|___|
HB	_____	|___|
HCT	_____	|___|
MCV	_____	|___|
MCH	_____	|___|
MCHC	_____	|___|
PLT	_____	|___|
NEU x10^9	_____	|___|
LYM x10^9	_____	|___|
MON x10^9	_____	|___|
EOS x10^9	_____	|___|
BAS x10^9	_____	|___|
NEUTS %	_____	|___|
LYMPHS %	_____	|___|
MONOS %	_____	|___|
EOSINOS %	_____	|___|
BASOS %	_____	|___|

Appendix E:

Open ended questions used in focus groups discussion for the development of Transplant Effects Questionnaire (TxEQ)

IMPACT OF TRANSPLANTATION

- What are the most important effects on you of having a transplant
- Are you happy about your decision to have a transplant
- Did/Does life after transplantation meet with your expectations
  Would you decide to do it again
  Would you recommend it to others
- Do you have any major concerns regarding you transplant
- What aspect of you transplant were you most afraid of before the transplnat
- After the operation, what were most anxious about
- Were there other problems that you have experienced in relation to your treatment/ in relation to your recovery
- Do you worry about the effect of immunosuppressants
- Do you think of kidney transplantation as an alternative treatment or a cure ESRD
  Dependence on dialysis treatment dependency on immunosuppressive drugs
- To what degree does the fear of losing the kidney remain significant
- Did/have you experienced any adjustment challenges following discharge form hospital
- Has your transplant affected you view of your body (your body image)
- Did you take up lots of activities after your transplant

TYPE OF RENAL REPLACEMENT TREATMENT

- Do you think that transplantation is a more satisfactory treatment for ESRD than dialysis
- Do you see the transplant as a release from the constraints of dialysis and as a return to a life of freedom
- Is there anything you lost when you left dialysis/anything you miss about dialysis

INTERPERSONAL ATTITUDES-DEPENDENCY INDEBTNESS GUILT AND BODY IMAGE

- Do you feel indebted to the donor in any way
- Is there a dependency between recipient and donor (e.g. issues of unrepayable obligation and proprietorial investment)
- Do you think you have responsibility for doing well (e.g. not rejecting the kidney, going back to work)
- Do you think the transplanted kidney is your kidney, or does it belong to the donor, or both
- Are you concerned that you could take on various qualities of the donor (personality/habits/behaviour change)
- Have you ever referred to the kidney as the donor's (if so when)

TYPE OF TRANSPLANT

- Was the type of transplant important (LRD;LURD;CAD). In what and would you have preferred another type of transplant

- Were there characteristics about the donor (e.g. age gender) which were important to you

INTERPERSONAL ATTITUDES: CADAVER TX

- What do you know about the donor
- Does it worry you that you do not know more about the donor
- Do you feel uncomfortable about being alive while the donor families'loved one is dead
- How much contact did you have with the donor family
- Did/do you feel obligated/ do you have the desire to meet the donor's family
- How much contact did you have with the donor's family
- Do you fear that the donor family might want some involvement in your life
- Do you feel indebted towards the donor and his/or her family
- Did waiting for the death of an unknown person caused strong feelings
- Do you ever think about the origin of the cadeveric kidney/ the donor and his or her family
- Did you ever wonder about the characteristics of the donor, and if so, which characteristics do you think about

INTEPERSONAL ATTITUDES: LRD TX: RELATIONSHIP RECIPIENT-DONOR

- How would you describe your relationship with the donor of your kidney
- Have there been any changes in your relationship with the donor since transplant
- How has the act of donation affected your relationship with the donor and your family
- Has the donor's interest in your life changed
- Do you sometimes wish you had received a cadaveric kidney instead of a kidney form a living related donor
- Do you think that the donor has given up something which is part of him/her for nothing in return
- Are there any conflicts within you family because of donation (or because of refusal to donate)
- Was it painful for you to discover which family members were willing to donate and which were not willing to donate
- Have the family relationships changes after donation
- Was it difficult for you to ask your family to donate a kidney
- Do you think your family has been brought together by the transplant experience or not
- How would you describe your feelings towards the donor

INTEPERSONAL ATTITUDES: LRD TX: PERCEIVED HEALTH OF DONOR

- Do you have guilt feelings toward the donor for the pain and suffering inflicted
- Do you have worries about the long-term impact of donation on the donor's QoL and acute (or long term) changes as a result of surgery
- Do you have a feat that donating a kidney will make the donor more vulnerable to possible development of kidney disease

INTEPERSONAL ATTITUDES: LRD TX: RELATIONSHIP RECIPIENT-DONOR

- How would you describe your feelings towards the nondonors
- Do you feel anger towards the non donors
- Do you think that the decision not to donate is understandable and excusable

Appendix F:

NP scores at Time 1 and Time 2 assessment in the four dialysis groups: hospital HD – Home HD – CAPD - APD

		Hospital HD		Home HD		CAPD		APD	
		T1	T2	T1	T2	T1	T2	T1	T2
TMT A	*M*	58.76	48.56	43.27	38	52.03	48.06	47.48	44
	Sd	42.28	36.21	21.01	34.07	22.61	45.52	31.92	30.43
TMT B	*M*	102.76	94.13	87.84	81.463	102.83	107.1	92.43	87.23
	Sd	60.46	58.19	33.49	4.07	42.25	45.52	49.51	47.15
SDMT-W	*M*	41.02	47.67	40.72	45.92	39.33	42.39	45.17	48.91
	Sd	13.05	16.01	10.72	13.58	12	14.68	13.29	13.66
SDMT O	*M*	46.08	52.81	50.64	40.72	42.91	45.98	48.83	53.3
	Sd	14.65	17.24	15.35	10.72	12.86	16.43	13.37	13.93
RAVLT-T	*M*	39.86	43.71	43.16	45.28	37.84	38.31	40.22	40.65
	Sd	12.51	12.51	10.3	13.55	9.19	8.13	9.19	9.82
RAVLT 1	*M*	5.17	6.02	5.08	5.32	4.73	4.8	5.09	5.65
	Sd	1.84	2.07	1.49	1.6	1.34	1.31	1.44	1.49
RAVLT 2	*M*	7.27	7.88	5.32	6.84	6.93	6.83	7.09	7.52
	Sd	2.43	2.59	1.6	2.3	1.76	1.73	2.06	1.81
RAVLT 3	*M*	8.23	8.96	7.96	9.04	8	8.27	8.22	8.48
	Sd	2.91	3.01	2.33	2.35	2.35	1.66	2.09	2.37
RAVLT 4	*M*	9.29	10.21	9	9.96	8.84	8.9	9.57	8.87
	Sd	3.19	3.02	3	2.47	2.52	2.29	2.59	2.56
RAVLT 5	*M*	9.88	10.63	9.48	10.84	9.33	9.51	10.26	10.13
	Sd	3.27	3.17	3.17	2.88	2.63	2.5	2.38	2.51
RAVLT-D	*M*	2.22	2.46	2.64	3	2.67	3.07	2.91	2.95
	Sd	1.71	2.2	1.68	1.82	2.20	1.51	2.23	1.82
GP DOM	*M*	93.5	89.18	78.78	76.82	95.66	96.73	89.73	83.04
	Sd	34.5	33.41	11.82	12.68	31.97	33.36	38.88	28.38
GP NDOM	*M*	104.68	98.56	91.03	88.93	105.65	109.67	102.56	91.29
	Sd	39.44	39.35	19.18	19.72	40.68	42.82	49.82	30.53
BVRT-C	*M*	5	5.79	5.24	6.36	4.15	4.73	5.91	5.39
	Sd	2.51	2.47	1.83	1.91	1.62	1.45	2.13	2.14
BVRT-E	*M*	9.17	6.71	7.52	6.4	9.46	8.28	6.52	6.95
	Sd	5.96	5.50	4.11	4.96	3.94	3.29	4.99	4.67
NP-TO	*M*	-.334	.712	1.36	1.79	-1.35	-2.52	1.65	1.02
	Sd	8.97	8.98	5.38	5.34	5.97	6.07	7.37	6.23

Note. T1 = time 1 assessment; T2 = time 2 assessment; TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; BVRT-C = Benton Visual Retention Test number of correct reproductions; BVRT-E = Benton Visual Retention Test number of reproduction errors; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; NP-TO = total NP performance score

[a] = Time to completion in seconds. [b] = number correct. [c] = number of errors. [d] = total of the 10 NP indices (z-scores)

Appendix G:

Norms and definition of neuropsychological impairments used in comparing group and individual neuropsychological scores to test norms/normative data

	Group mean based classification			Individual mean based classification		
	Age	Norm	NP deficit	Age	Norm	NP deficit
TMT-A Norms by: Davies 1968	50s		>49 secs	20s+30s 40s 50s 60s 70s		>42 >45 >49 >67 >105
TMT-B Norms by Davies 1968	50s		>135 secs	20s+30s 40s 50s 60s 70s		>94 >100 >135 >173 >292
SDMT-W Norms by: Centofant & Smith 1979	45 - 54 yr	46.8±8.4	< 38.4	18-24 yr 25-34 yr 35-44 yr 45-54 yr 55-64 yr 65-74 yr	55.2 ±7.5 53.6 ±6.6 51.1 ±8.1 46.8 ±8.4 41.5 ±8.6 37.4 ±11.4	<47.7 <47 <43 <38.4 <32.9 <26
SDMT – O Norms by Centofant & Smith 1979	45 - 54 yr	54.5±9.1	<45.4	18-24 yr 25-34 yr 35-44 yr 45-54 yr 55-64 yr 65-74 yr	62.7 ±9.1 61.2 ±7.8 59.7 ±9.7 54.5 ±9.1 48.4 ±9.1 46.2 ±12.8	<53.6 <53.4 <50 <45.4 <39.3 <33.4
GP–DOM Norms by Bornstein 1985	40 - 59 yr	68.1±10.6	>83.6	20-39 yr 40-59 yr 60-69 yr	60.9 ±16.2 68.6 ±15.0 75.5 ±14.6	>77.1 >83.6 >90.1
GP-NDOM No rms by Bornstein 1985	40 - 59 yr	74.2±15.6	>89.9	20-39 yr 40-59 yr 60-69 yr	66.2 ±17.1 74.2 ±15.7 83.1 ±15.5	>83.3 >89.9 >98.6
RAVLT-T male Norms by Gefen et al. 1990	50 - 59 yr	47.6 ±8.5	<.39.1	16-19 yr 20-29 yr 30-39 yr 40-49 yr 50-59 yr 60-69 yr ≧ 70 yr	53.4 ±5.4 54.9 ±7 46 ±10.9 47.5 ±8.3 47.6 ±8.5 36.7 ±8.4 32.6 ±8.3	<48 <47.9 <35.1 <39.2 <39.1 <28.3 <24.3

RAVLT-T Female Norms by Gefen et al. 1990	50 - 59 yr	47.6 ±7.7	<39.8	16-19 yr 20-29 yr 30-39 yr 40-49 yr 50-59 yr 60-69 yr ≥ 70 yr	56.5 ±6 55.3 ±6.6 55.9 ±6.3 52.1 ±7.1 47.6 ±7.7 49 ±7.1 41.6 ±6.6	<50.5 <48.7 <49.6 <45 <39.8 <41.9 <35
BVRT-C Norms by Benton 1974	45 – 54 yr	7	<7	15-44 yr 45-54 yr 55-64 yr	8 7 6	<8 <7 <6
BVRT-E Norms by Benton 1974	40 – 54 yr	4	>4	15-39 yr 40-54 yr 55-59 yr 60-64 yr	3 4 5 6	>3 >4 >5 >6

Note. TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; BVRT-C = Benton Visual Retention Test number of correct reproductions; BVRT-E = Benton Visual Retention Test number of reproduction errors; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; yr = years

Appendix H:

ANCOVA comparisons: diabetes, employment and absolute neurospychological scores at Time 1 and Time 2 assessments (combined dialysis sample)

Variable	Direction	NP test		Df	F	*p value*
Diabetes	Poorer	GP-DOM	T1	3, 140	15.408	.0001
			T2	3, 135	13.543	.0001
	Poorer	GP-NDOM	T1	3, 140	14.295	.0001
			T2	3, 135	12.091	.001
	Poorer	SDMT-W	T1	3, 141	7.789	.006
			T2	3, 137	6.897	.010
	Poorer	SDMT-O	T1	3, 141	8.236	.005
			T2	3, 137	7.649	.006
	Poorer	RAVLT-T	T1	3, 141	13,319	.0001
			T2	3, 137	4.099	.045
	Poorer	TMT A	T1	3, 141	9.095	.003
			T2	3, 137	9.102	.003
	Poorer	TMT B	T1	3, 141	4.732	.031
			T2	3, 137	7.467	.007
Employment	Better	GP-DOM	T1	4, 140	4.937	.028
			T2	4, 134	4.724	.031
	Better	GP-NDOM	T1	4, 140	11.005	.001
			T2	4, 134	10.574	.001
	Better	BVRT-CO	T1	4, 140	10.180	.002
			T2	4, 137	5.571	.02
	Better	BVRT-ER	T1	4, 140	10.566	.001
			T2	4, 137	5.573	.02
	Better	SDMT W	T1	4, 140	18.792	.0001
			T2	4, 136	16.730	.0001
	Better	SDMT O	T1	4, 140	16.558	.0001
			T2	4, 136	13.734	.0001
	Better	TMT A	T1	4, 140	14.165	.0001
			T2	4, 136	10.882	.001
	Better	TMT B	T1	4, 140	7.730	.006
			T2	4, 136	10.810	.001

Note. T1 = time 1 assessment; T2 = time 2 assessment;; TMT-A = trail making test part A; TMT-B = trail making test part B; SDMT-W = symbol digit modality test written administration; SDMT-O = symbol digit modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall at trial 1 to 5; RAVLT-D = Rey Auditory Verbal Learning Test drop in retention from trial 5 to 7; BVRT-C = Benton Visual Retention Test number of correct reproductions; BVRT-E = Benton Visual Retention Test number of reproduction errors; GP–DOM = Grooved Pegboard dominant hand; GP–NDOM = Grooved Pegboard non dominant hand; NP-TO = total NP performance score

[a] = Time to completion in seconds. [b] = number correct. [c] = number of errors. [d] = total of the 10 NP indices (z-scores)

* $p < .05$. ** $p < .01$. *** $p < .001$.

Appendix I:

Sociodemographic and medical characteristics in cyclosporin and tacrolimus-treated transplant patients

	Cyclosporin TX (N = 70)		Tacrolimus TX (N = 40)	
	M(SD)	*% (N)*	*M(SD)*	*% (N)*
Age	52.52 (12.67)		47.20 (11.84)	
Gender (% female)		32.9% (23)		50% (20)
Ethnicity (% white)		82.9% (58)		82.5% (33)
% Married		71.4% (50)		57.5% (57.5%)
% Employed (f/t, p/t post-TX)		49.3% (33)		47.5% (19)
% Employed (f/t, p/t prior-TX)		77.6% (52)		47.5% (19)
% Able to work (f/t, p/t)		72.1% (49)		66.7% (26)
Income				
% 0 - £10,000		17.1% (12)		33.3% (12)
% £ 10,001 - £ 20,000		15.7% (11)		30.6% (11)
% £ 20,001 - £ 30,000		18.6% (13)		16.7% (6)
% £ 30,001 and above		30% (21)		19.4% (7)
% not wish to answer		18.6% (13)		
Education (years)	10.88 (3.66)		11.58 (3.80)	
Time with TX (months)	83.03 (44.79)		24.07 (39.74)	
Time RRT (months)	117.27 (71.53)		77.47 (60.09)	
Time DL (months)	25.23 (27.70)		42.61 (36.89)	
ESRD severity	7.93 (7.56)		2.95 (1.88)	
Number of comorbidities	3.28 (1.65)		8.58 (8.88)	
Glomerular Filtration Rate	37.98 (11.58)		40.62 (16.36)	
% diabetes		1.4% (1)		12.5% (5)
% Hypertension		91.4% (64)		85% (34)
% Heart Disease		30% (21)		22.5% (9)
% Past Rejection (% yes)		50% (35)		25% (10)
Primary kidney disease				
% GN		21.4% (15)		10% (4)
% AKPD		14.3% (10)		10% (4)
% Reflux nephropathy		8.6% (6)		15% (6)
% IgA nephropathy		5.7% (4)		7.5% (3)
% Obstructive uropathy		5.7% (4)		2.5% (1)
% Diabetes		1.4% (1)		10% (4)
% hypertension		7.1% (5)		12.5% (5)

Note: TX = transplantation; f/t = full time; p/t = part time; RRT = renal replacement therapies; DL = dialysis; ESRD = end stage renal disease; GN = glumeronephritis; APKD = adult polycystic kidney disease

Appendix J:

Multiple regressions to predict HQoL in dialysis with mood entering before beliefs: standardised regression coefficients (β), cumulative explained variance (R^2) and cumulative adjusted variance (Adj. R^2)

	PCS			MCS		
	β	R^2	Adj.R^2	β	R^2	Adj.R^2
Block 1						
Work Status	.140*	.212	.206			
Age	-.165*	.295	.285			
Education						
Gender				.105 ns	.035	.029
Income						
Block 2						
Dialysis group				.162*	.075	.062
ESRD severity	-.248***	.408	.395			
Kt/V	.125*	.438	.422			
Albumin	.076 ns	.458	.439			
Haemoglobin						
Block 3						
NP functioning						
NP impairments						
SCS TO	-.010 ns	.475	.452	-.141 ns	.194	.177
Block 4						
CDI	-.218**	.549	.526	-.356****	.348	.329
Block 5						
IEQ	-.245***	.587	.563			
TEQ				-.181*	.370	.347
IPQ consequences						
IPQ control						
IPQ identity						

Note: PCS = physical component score (SF-36); MCS = mental component score (SF-36); ESRD = end-stage renal disease; Kt/V = dialysis adequacy; NP = neuropsychological; SCS-TO = subjective cognition summary score (cognitive complaints); CDI = cognitive depression index; IEQ = illness intrusiveness; TEQ = treatment intrusiveness

* $p < .05$. ** $p < .01$. *** $p < .001$. ns = non significant

Appendix K:

HQoL in LRD and CAD TX recipients in the combined TX sample recruited from MIDDX and RFH hospital transplant units

SF-36 subscale	LRD *Mean (SD)*	CAD *Mean (SD)*	*F*	*p value*
General Health	43.42 (11.84)	42.41 (12.55)	.654	.420
Physical functioning	45.51 (12.83)	38.75 (15.80)	2.035	.155
Social functioning	44.71 (8.92)	43.03 (9.60)	1.149	.285
Role physical	45.56 (12.32)	40.99 (15.13)	1.304	.255
Role emotional	47.55 (11.4)	46.06 (13.31)	.699	.404
Bodily Pain	49.49 (11.53)	46.87 (15.75)	.721	.397
Vitality	51.20(8.16)	51.50 (12.53)	.957	.329
Mental Health	48.74 (9.41)	50.12 (10.06)	.227	.635
Physical Component Score	45.12 (12.83)	40.11 (15.30)	.351	.554
Mental Component Score	48.94 (7.56)	50.78 (9.37)	.233	.630

Note: LRD = living related donor transplant recipients; CAD = cadaver transplant recipients

Appendix L:

Multiple regressions to predict PCS and MCS in TX with mood entering before beliefs

	PCS			MCS		
	β	R^2	Adj.R^2	β	R^2	Adj.R^2
Block 1						
Work Status	.040 ns	.204	.197			
Education						
Age	-.200**	.270	.257	.299***	.073	.065
Income	.182**	.302	.283			
Block 2						
ESRD severity	-.342****	.462	.443			
GFR				.149 ns	.124	.109
Albumin						
Haemoglobin	.151*	.535	.514			
Block 3						
NP functioning						
NP deficits						
SCS-TO						
Block 4						
CDI				-.273**	.227	206
PNS PA						
Block 5						
IEQ	-.254****	.630	.610			
TEQ						
IPQ						
consequences						
IPQ control						
IPQ identity-x	-.199**	.658	.636			
BMQ-concerns				-.214*	.269	.243
TX worry						

Note: PCS = physical component score (SF-36); MCS = mental component score (SF-36); ESRD = end-stage renal disease; GFR = glomerular filtration rate; NP = neuropsychological; SCS-TO = subjective cognition summary score (cognitive complaints); CDI = cognitive depression index; PNS PA = PANAS positive affect; IEQ = illness intrusiveness; TEQ = treatment intrusiveness; TX worry = TxEQ worry about the transplant subscale

* $p < .05$. ** $p < .01$. *** $p < .001$. ns = non significant

Appendix M:

Published paper: The Transplant Effects Questionnaire (TxEQ): the development of a questionnaire for assessing the multidimensional outcome of organ transplantation

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The Transplant Effects Questionnaire (TxEQ): The development of a questionnaire for assessing the multidimensional outcome of organ transplantation – example of end stage renal disease (ESRD)

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Objectives. To develop a questionnaire to assess the responses of transplant recipients to the receipt of an organ, including their self-care behaviour.

Design. Following a literature review, open-ended interviews and a focus group, a transplant questionnaire was developed. Two studies (Study 1: $N = 231$, Study 2: $N = 105$) were conducted to evaluate its psychometric properties.

Methods. A pool of 51 items was derived from themes identified in published studies and from interviews and a focus group discussion with renal transplant recipients. These were constructed into a questionnaire and were then administered to two renal transplant out-patients populations. Item responses of study sample 1 were subjected to principal components analysis (PCA) using varimax rotation to examine the structure of responses. In order to investigate the stability of the factor structure found in Study 1, item responses of the second sample were subjected to confirmatory factor analysis (CFA) using structural equation modelling.

Results. PCA indicated six factors that accounted for 64.2% of the variance. With extraneous items omitted, the final questionnaire derived from Study 1 has 24 items clustered around five conceptual coherent factors: worry about transplant (22.1%),

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guilt regarding donor (11.9%), disclosure (9.58%), medication adherence (8.73%), and responsibility (6.63%). CFA on the final 24-item version of the TxEQ revealed that the resulting model was a good fit for the Study 2 data (RMSEA = 0.08, *p*close = .005).

Conclusions. The TxEQ has potential application as a measure in the area of transplantation research. CFA demonstrated that the factor structure of the TxEQ is consistent across different renal transplant out-patients populations. Further research is currently in progress to assess other groups of transplant recipients and to examine its relationship to other measures.

There is increasing demand for outcome analysis including health-related quality of life after medical and surgical interventions. Because of the high cost, interest in transplantation outcomes is particularly intense (Wright-Pinson *et al.*, 2000). Advances in medical and surgical technology and the advent of new immunosuppressive medication, immunological conditioning, sophisticated tissue typing and histocompatibility techniques have revolutionized organ transplantation and improved survival rates considerably (Hunt, 1998; Schweitzer & Hobbs, 1995). Organ transplantation has now become a viable treatment alternative for many medical disorders and is principally limited in the developed world by a shortage of organs (Cecka, 2000). Despite the improved efficacy, however, there remains a significant failure rate in the acceptance of the donated organ and the risk of mortality of a return to intensive treatment. For example, in heart transplants, 1-year survival in the USA in 1999 was 83.2% and the survival rate for lung transplantation was 70.6% (Keck *et al.*, 1999). In pancreas transplantation, reported 1-year patient and graft survival rates were 91% and 69% (Sutherland, Moudry-Munns, & Gillingham, 1998). In the case of kidney transplantation, the 5–7 year failure rate is 50% for cadaver transplants. So for many recipients of donated organs there are considerable risks of failure, which often results in death. In kidney transplantation, there is also a real prospect of a return to dialysis (US Renal Data System, 1992).

In general, the relative success of transplantation has led to a shift in research agendas beyond the success of the procedure and graft survival to include an examination of recipients' psychological response to organ transplantation and their functioning and quality of life (Hanaeur, 1994). Given that potential recipients of an organ have generally poor functioning, it is not surprising that transplantation has been found to lead to quality of life improvements (Bravata, Olkin, Barnato, Keefe, & Owens, 1999; Dew *et al.*, 1997; Wright-Pinson *et al.*, 2000). What is more important is that the levels of quality of life in studies of transplant patients have typically been reported as equivalent or to nearly equivalent to that of the general population (Dressler, 1991; Evans *et al.*, 1985; Insense, Vilardell, Aranzabal, & Lago, 1999; Painter *et al.*, 1997). However, health care providers and transplant recipients themselves have become increasingly aware that organ transplantation may give rise to a new set of stressors, psychosocial challenges and adaptive demands (Grady, Jalowiec, & White-Williams, 1996; Hanson, 1987; Hathaway & Strong, 1988; McQuellon *et al.*, 1998; Robertson, 1999; Wainwright, Fallon, & Gould, 1999). It may be expected that recipients of different transplanted organs will have many similar types of concerns but that these may vary in the degree of importance that is attached. Commonly reported stressors identified across a range of transplant populations include the cost and side-effects of immunosuppressive medication, worries about the viability of transplanted organ, fear of rejection, and the need to adhere to a rigorous post-transplant care regime (Fallon, Gould, & Wainwright, 1997; Frey, 1990; Gubby, 1998; Hathaway, Strong, & Ganza, 1990; Hauser, Williams, Strong, Ganza, & Hathaway, 1991; Hayward *et al.*, 1989;

Kong & Molassiotis, 1999; Sutton & Murphy, 1989; White, Ketefian, Starr, & Voepel-Lewis, 1990). It has been argued that a viable organ transplantation, albeit a life-saving procedure for several end-stage medical conditions, does not cure disease but rather extends life by trading one chronic disease for another, i.e. chronically compromised immune system leading to significant pressures to adhere to a complex regimen (Johnson, 1990). Immunosuppressive therapy continues indefinitely after organ transplantation and is often accompanied by some dietary restrictions. Transplant recipients are also required to regularly attend out-patient transplant clinic and laboratory appointments and check-ups, although their frequency decreases with time. They are also expected to engage in several preventative or health protective behaviours (e.g. using sun-block agents) or monitoring behaviours (e.g. monitoring themselves for early signs of rejection and taking appropriate action if symptoms are detected). Accumulating evidence suggests that a considerable number of transplant recipients fail to adhere completely to the above treatment recommendations (Bunzel & Laederach-Hofmann, 2000; Colon, Popkin, Matas, & Callies, 1991; Rovelli *et al.*, 1989; Schweizer *et al.*, 1990). This is of particular concern in the light of evidence indicating that poor adherence is a major determinant of graft failure (Dunn *et al.*, 1990; Hong *et al.*, 1992; Kalil, Heim-Duthoy, & Kasiske, 1992; Schweizer *et al.*, 1990) and mortality (Rondriguez, Diaz, Colon, & Santiago-Delphin, 1991). A recent review on studies in organ transplantation concluded that there are few studies addressing this important dimension (Rodrigue, Greene, & Boggs, 1994).

Besides the more direct issues related to post-transplantation treatment regime, studies have identified a number of other areas of concern and potential stress for organ recipient. These include impact on family relationships, physical and psychosocial post-transplant adjustment (e.g. resuming an independent role, changes in physical and social activity), integration of the transplant to body image, and emotional responses, most notably feelings of gratitude and guilt towards the donor or donor's family as well as feelings of personal inadequacy and/or responsibility for ultimate graft survival (Bosnak, 1996; Bunzel, Schmidl-Mohl, Grundbock, & Wollenek, 1992; Bunzel & Wollenek, 1992; Bunzel, Wollenek, & Grundbock, 1992; Hathaway *et al.*, 1990; Kuhn *et al.*, 1988; Lewino, Stocks, & Cole, 1996; Mai, 1986; Rauch & Kneen, 1989; Robertson, 1999; Schlebusch, 1986; Schlebusch, Pillay & Louw, 1989, 1992; Witzke *et al.*, 1997).

The issue confronting transplant recipients, although clearly of high relevance, remain largely unexplored by generic Health-related Quality of Life (H-QoL) instruments widely used in transplantation research. Although these have provided useful data and offer ready comparisons across studies and patient groups, because such instruments must address a wide range of issues, they fail to capture the specific and often subtle emotional and behavioural concerns of transplant recipients. Measurement specificity is the alternative approach, and the value of condition-specific instruments has been widely recognized (Bradley, 1994; Welch, 1994). Specific instruments are expected to provide a more sensitive measurement of processes and responses unique to transplantation, but existing transplantation-specific measures have been proven to be unproductive, as they present limitations both in terms of their content and coverage as well as their psychometric properties. Transplantation-specific quality of life instruments (Quality of Life Inventory, QOLI: Carrington, Tarter, Switala, & Van Thiel, 1996; Bone Marrow Transplantation Symptoms Checklist: Fife *et al.*, 2000; End Stage Renal Disease Symptom Checklist-Transplantation Module, ESRD-SCL: Franke *et al.*, 1999; Heart Transplant Symptom checklist: Grady & Jalowiec 1995; General Health/QoL

rating scale: Lanuza, Lefaiver, Cabe, Farcas, & Garrity, 2000; Kidney Transplant Questionnaire, KTQ: Laupacis *et al.*, 1993) assess mainly physical functioning, usually incorporating psychological and/or social functioning, thus having little consideration of transplant-specific emotional responses or treatment-related issues.

There appear to be no widely used psychometrically sound instruments to assess the specific responses to receiving an organ transplant. A few studies feature transplant-specific measures but those that do, tend to employ idiosyncratic instruments, the psychometric properties and development of which are not always described in sufficient detail for research or clinical use (Fife *et al.*, 2000; Kerr, Johnson, Pandian, Gillingham, & Matas, 1997; Lanuza *et al.*, 2000; Siegal, Hanson, Viswanathan, Margolis, & Butt, 1989; Teichman, Burker, Weiner, & Egan, 2000; Witzke *et al.*, 1997; Wolcott, Wellisch, Fawzy, & Landsverk, 1986). For example, Wolcott *et al.* (1986) developed a recipient questionnaire for bone marrow transplant patients but do not report on its psychometric properties nor item content. Other investigators (Bortman *et al.*, 1999; Greenstein, Siegal, & the Compliance Study Group, 1997; Ostrowski, Wesolowski, Makar, & Bohatyrewicz, 2000; Schlitt *et al.*, 1999) employed transplantation-specific questionnaires but analysed each item separately, reporting the percentages of patients endorsing or not a particular item rather than identifying subscales and establishing or examining the psychometric properties of their measure.

One central problem in the existing questionnaires is their limited scope. Typically the measures are tailored to study particular samples, such as kidney, bone marrow or heart transplant patients (Franke *et al.*, 1999; Grant *et al.*, 1992; Jacobs *et al.*, 1998; Ketefian & Starr, 1990; Laupacis *et al.*, 1993; McQuellon *et al.*, 1997; Molassiotis, 1999; Parfrey *et al.*, 1989; Park *et al.*, 1992; Sutton & Murphy, 1989; Wirth & Barton, 1985) or designed to assess newly transplanted patients (Hayward *et al.*, 1989). This restricts their use with other transplant populations. Furthermore, the existing transplant-specific questionnaires appear to cover some, but not all, of the important aspects of post-transplant experience identified in the literature.

Other transplantation-specific measures have been designed especially to measure a very specific single concept such as body image (Fife *et al.*, 2000; Body Image Questionnaire, BIQ: Schlebusch *et al.*, 1992), symptom experience (Heart Transplant Symptom Checklist: Grady & Jalowiec, 1995; Transplant Symptom Frequency and Distress Scale: Lough, Lindsey, Shinn, & Stotts, 1987), treatment (Heart Transplant Regimen: Grady & Jalowiec, 1995), knowledge about transplant regimen (De Geest *et al.*, 1995) or understanding of self-care principles (Wirth & Barton, 1985) and, thus, albeit of great value, their narrow focus implies limitations. Transplant stressor instruments, on the other hand, are somewhat more comprehensive in their content but have been designed to measure and document the stressors of organ transplantation rather than measuring the effects of these stressors (Heart Transplant Stressor Scale: Grady & Jalowiec, 1995; Recipient Stressor Scale: Gubby, 1998; Kidney Transplant Recipient Scale, KTRSS: Hayward *et al.*, 1989; Kidney Transplant Questionnaire, KTQ: Ketefian & Starr, 1987). Overall, none of the existing measures elucidates the emotional and behavioural issues associated with transplantation and this limits our understanding of the psychological processes of organ transplantation.

With these issues in mind, the aim of this study was to develop a transplant-specific instrument to provide a thorough coverage of an individual's emotional and behavioural response to receiving a transplanted organ and the pressures and stresses that this may cause. The Transplant Effects Questionnaire (TxEQ) reported in this paper is an instrument designed to allow a comprehensive, sensitive, and easy to administer

instrument of those aspects of transplantation that have been identified as being the most important. Although it was developed on individuals in receipt of a renal transplant, it has been designed to be applicable to all forms of organ transplantation.

Method

Development of the Transplant Effects Questionnaire (TxEQ)

To identify the issues facing transplant recipients, the published literature was examined by means of a computer-based search using the MedLine and PsychLit databases. Combinations of the following key words were used: transplantation, transplant, cadaver, living related, donor, quality of life, stressors, adherence, compliance, immunosuppressive medication, side effects. Additional papers were obtained by manually searching references lists of the obtained papers.

Based on the review, a list of relevant open-ended questions was then constructed for use in a focus group and individual interviews with kidney transplant recipients. The questions covered the following issues:

- impact of transplantation on patients and their families (e.g. What are the most important effects of having a transplant?)
- contrast between life prior to and post-transplant (e.g. Does life after transplantation meet your expectations?)
- concerns related to anti-rejection medication and side-effects of anti-rejection medication (e.g. Were there any problems you have experienced in relation to your treatment or to your recovery?)
- interpersonal attitudes towards donor or family (e.g. What do you know about the donor?; Do you ever wonder about the characteristics of the donor?)
- feelings of indebtedness, gratitude and guilt towards the donor or donor family (e.g. How would you describe your feelings toward the donor/donor family?; Do you feel obliged to pay back the donor for the gift of the donated organ?)

Issues identified in this two-stage procedure were combined into items and refined by two raters. The resulting 315 items were subsequently assessed for comprehensibility and redundancy by two raters. This process resulted in 51 items that represented nine key themes relating to receiving a transplanted organ: outcome of transplantation, fear of rejection, self-care principles, adherence, feelings of guilt, feelings of indebtedness, having a foreign body part, relationships with family and friends, and emotions. The relevance, clarity and conciseness of the reduced pool of 51 was then subjected to expert panel review (transplant professionals including consultants and nurses). Lastly, the resulting scale was successfully piloted with a small group ($N = 7$) of renal transplant recipients. Two studies were then conducted to examine and test the psychometric properties and structure of this final pool of 51 items.

STUDY 1

Exploratory factor analysis

Participants

Following ethics committee approval all ($N = 333$) patients registered at a London teaching hospital were sent a covering letter and a questionnaire pack consisting of

the 51-item Transplant Effects Questionnaire (TxEQ), questions about their medical history, and demographic questions. Other self-report questionnaires were completed but are not considered in this report. To ensure and encourage frank responses, the questionnaire had a code number but not the participant's name. A period of 4 weeks was allowed in which to return the questionnaire. After that time a reminder letter and another copy of the questionnaire were sent to non responders and another 2 weeks were allowed for completion, after which time data collection was terminated.

A total of 231 patients completed the questionnaire, giving a response rate of 69.4% Participants were almost equally divided between male and female, had a mean age of 45 years and had been living with a renal transplant for a mean of 9.93 (SD 6.76) years (see Table 1).

Table 1. Participants in Study 1 and Study 2

	Study 1	Study 2
N	231	105
Sex (% female)	48.9	39.0
Source of transplant (% living related)	22.1	22.9
Current employment status (% employed)	58.4	47.6
Relationship status (% living with partner)	57.6	69.5
Age (years)	45.15 (SD 14.51)	50.85 (SD 12.18)
Mean number of comorbid illnesses	0.67 (SD 1.11)	0.73 (SD 1.09)
Dialysis experience (% previous dialysis patients)	90.5	93.3
Mean total time spent on dialysis (in months)	34.52 (SD 42.47)	28.61 (SD 29.26)
Mean number of transplants	1.19 (SD 0.45)	1.13 (SD 0.39)
Mean time since transplantation (in years)	9.93 (SD 6.76)	6.49 (SD 5.16)

Measures

Transplant Effects Questionnaire (TxEQ)

The instructions of the TxEQ were as follows: 'We are interested in your own personal views of how you *now* see your experience with your kidney transplant. These are statements other people have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box'.

The measure contained 51 positively and negatively worded items. A positive and negative wording of most of the items was used to avoid acquiescence, affirmation or agreement bias. They were presented in a mixed order and rated by the participants using a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree' (scored from 1 to 5).

Analysis

Statistical analysis was performed using the Windows versions of SPSS(6.1) and AMOS. Item responses from the Study 1 sample were subjected to an exploratory principal components analysis (PCA) with varimax rotation (Kaiser normalization). As a means of eliminating items to achieve a simple coherent structure, extraneous items were omitted on the basis of the Kaiser-Meyer-Olkin (KMO) statistic for each item, factor scree plot, and final factor loading as described below (Norusis, 1992).

Results

Initial PCA resulted in a 15-factor structure. A factor scree plot suggested a six-factor solution (46.7%). Subsequent omission of 27 items with low loadings (< .45) spread across these factors and less than 30% overlapping variance replicated the six-factor solution, accounting for 64.2% of the variance in the responses to the Transplant Effects Questionnaire. The KMO statistic for the 24 items ranged from .69 to .86 (mean = .79) (Table 2). All six factors identified had acceptable internal reliabilities. Cronbach αs ranged from .72 to .86.

Items were grouped in conceptually coherent factors. Factor 1 comprised six items relating to worries regarding the transplant (22.3%). Items loading on factor 2 referred to feelings of guilt towards the donor (11.9%). Three items loaded respectively on the third factor, tapping disclosure issues regarding the transplant (9.6%), and on the fourth factor, reflecting medication adherence (8.7%), whereas factor 5 contained items relating to perceived responsibility towards others (6.6%). However, factor 6 (5.0%) appeared to be thematically incoherent, with two items (C9 and D1) relating to adherence and a third (G2) to taking on qualities of the donor. However, the two adherence items did load on the adherence factor (factor 4) (.22 and .29, respectively) despite varimax rotation. It was therefore decided to group items C9 and D1 into factor 4 and drop item G2 from further analysis. The resulting adherence factor showed high internal consistency (α = .79). In summary, the exploratory factor analysis (EFA) determined six factors which were reduced to five thematically coherent factors: worry about the transplant, guilt, adherence, disclosure, and responsibility.

STUDY 2

Confirmatory factor analysis

Participants

Study 2 protocol involved both extensive questionnaire evaluation and comprehensive neuropsychological assessment. For this study, 111 sequential patients were approached to participate and 105 consented to the full protocol (response rate = 94.6%). The resulting sample had a mean age of 50.85 years and consisted of 39.9% females. Mean time since transplantation was 6.5 years (see Table 1).

t-Test analyses of the two samples on sociodemographic and medical history variables revealed only two significant differences: Study 2 participants were significantly older ($t(232) = 3.71; p < .001$), and had been living with their current transplant for less time than Study 1 participants ($t(258) = 5.11, p < .001$).

Analysis

To test whether the internal structure reported in Study 1 held also in patients from a different sample, confirmatory factor analysis was performed on the data from Study 2. Item responses from the Study 2 sample were subjected to confirmatory factor analysis using structural equation modelling. Closeness of fit based on the root mean square error of approximation index (RMSEA) (Browne & Cudeck, 1993) was used to examine the extent of fit in the questionnaire factor structures from the two study samples. The RMSEA measure was used in preference to the CFI (or any other measure of fit) because

it provides a robust measure of closeness of fit for the model, which is considered by Browne and Cudeck (1993) to be "more reasonable than the requirement of exact fit". In addition, McCallum, Browne, and Sugawara (1996) recommend the use of RMSEA instead of point estimates of model fit in the population. Work by Rigdon (1996) has demonstrated the utility of the RMSEA as an index of the degree to which a confirmatory structure approximates the data being modelled. Browne and Cudeck (1993) have suggested that values of .05 and below indicate a close fit of the model and the values of the RMSEA between .05 and .08 approximate a reasonable error in approximating a given structure. They also provide a test of the hypothesis that the population RMSEA for the model is no greater than .05. Failure to reject this hypothesis at $p < .05$ signifies that the model is a close fit to the data.

Table 2. Factor loadings, communalities, percentage of variance explained for principal components analysis using varimax rotation with Kaiser normalization on the 24 identified items of the Transplant Effects Questionnaire (TxEQ)

Items		Loading
Factor 1: '*worry about transplant*' Eigenvalue= 3.14; Cronbach α = .81		
Percentage of total variance explained: 13.1%; percentage of cumulative variance explained: 13.1%		
B2	I am worried about damaging my transplant	.82
B1	With regard to my transplant I feel that I am carrying around something fragile	.76
B5	I am hesitant to engage in certain activities because I am afraid of doing harm to my transplant	.75
B3	I keep wondering how long my transplant will work	.71
C1	I monitor my body more closely than before I had the transplant	.64
D2	I worry each time my anti-rejection drug regime is altered by my doctor	.47
Factor 2: '*guilt regarding donor*' Eigenvalue= 2.94; Cronbach α = .76		
Percentage of total variance explained: 12.2%; percentage of cumulative variance explained: 25.3%		
E4	I feel guilty about having taken advantage of the donor	.83
E1	Sometimes I think that I have 'robbed' the donor of a vital part	.76
E3	The donor had to suffer to make me feel better	.73
F2	I have the feeling that the donor/the donor's family has some control over me	.66
E2	I do not have any feelings of guilt toward the donor	− .56
Factor 3: '*disclosure*' Eigenvalue= 2.47; Cronbach α = .86		
Percentage of total variance explained: 10.4%; percentage of cumulative variance explained: 35.7%		
I2	I avoid telling other people that I have a transplant	.90
I1	I am uncomfortable with other people knowing that I have a transplant	.86
I4	I have difficulty in talking about my transplant	.85

Table 2. contd.

Items		Loading
Factor 4: '*adherence*' Eigenvalue= 2.46; Cronbach α = .79		
Percentage of total variance explained: 10.3%; percentage of cumulative variance explained: 45.9%		
C6	Sometimes I do not take my anti-rejection medicines	.85
C2	Sometimes I forget to take my anti-rejection medicines	.83
C4	When I am too busy I may forget my anti-rejection medicines	.80
C9	*Sometimes I think I do not need my anti-rejection medicines*	.23
D1	*I find it difficult to adjust to taking my prescribed anti-rejection drug regime*	.29
Factor 5: '*responsibility*' Eigenvalue= 2.22; Cronbach α = .72		
Percentage of total variance explained: 9.3%; percentage of cumulative variance explained: 55.1%		
F3	I think that I have a responsibility to the transplant team to do well	.77
F6	I think that I have a responsibility to my friends and my family to do well	.75
F5	I feel that I owe the donor/the donor's family something that I will never be able to repay	.73
F1	I think that I have a responsibility to the donor/the donor's family to do well	.65

Results

Internal structure

Confirmatory factor analysis (CFA) was performed using the AMOS structural equation modelling application (Arbuckle, 1997). A measurement model was defined with five uncorrelated latent variables (as described in the exploratory factor analysis section above). The resulting model was found to be a good fit for the data (RMSEA = .08; *p*close = .005) as defined by Browne and Cudeck (1993).

Test-retest reliability

One-month test-retest reliability of the TxEQ was found to be acceptable for all subscales except for the responsibility subscale (see Table 3).

Table 3. One month test-retest reliability

	Worry	Guilt	Disclosure	Adherence	Responsibility
Test-retest reliability	r_{t1t2}= .797 *N* = 81	r_{t1t2}= .689 *N* = 73	r_{t1t2}= .600 *N* = 82	r_{t1t2}= .772 *N* = 82	r_{t1t2}= .70 *N* = 80

DISCUSSION

In this paper we have described the development and initial evaluation on renal transplant recipients of the psychometric properties and structure of the Transplant Effects Questionnaire (TxEQ) constructed to assess the multidimensional effects of organ transplantation. The evidence of the range of areas and concerns of transplantation coupled with the absence of a comprehensive transplantation instrument provided the rationale for the development of this measure. The items were elicited based on an extensive review of the transplantation literature, a transplant focus group and in-depth interviews with transplant recipients. The combined approach of such quantitative and qualitative methodologies was thought to be the best approach to capturing transplant recipients' perspectives on their post-transplant experience.

Data from 336 renal transplant recipients were used to examine the internal consistency and internal structure of the resulting TxEQ. Principal components analysis of the TxEQ items produced a conceptually coherent factor structure, which was further confirmed on another dataset using structural equation modelling. The resulting five TxEQ subscales were concerns and worries specific to the transplant, feelings of guilt regarding the donor, disclosure, perceived responsibility and medication adherence.

The first two subscales appear to tap emotional responses that are likely to be triggered by transplantation (i.e. worrying over graft function and feelings of guilt towards the donor). These two dimensions tie in with earlier research findings (Franke *et al.*, 1999; Freyberger, 1983; Gubby, 1998; Kong & Molassiotis, 1999; Schlebusch, 1986; Schlebusch *et al.*, 1989; Viederman, 1981). Patients' concerns regarding the viability of their transplanted organ are well rooted in reality despite the major advances made in recent years. Although the figures for different transplanted organs do vary (Keck *et al.*, 1999; Sutherland *et al.*, 1989; US Renal Data System, 1992), in the case of renal transplantation in the UK, the participants in this study, the rejection rate of kidneys is approximately 36% over 5 years (Renal Association, 1997). Patients' awareness of this possibility is likely to be further confirmed by the need to take anti-rejection medication, the experience of symptoms, or possibly the occurrence of episodes of infection.

Feelings of guilt towards the donor have been reported in a range of other, mainly qualitative, studies (Chambers, 1982; Chaturvedi & Pant, 1985; Mai, 1986). There is little research evidence on guilt, however, in what may be considered the most pertinent area, where the organ may have been sourced from a living donor, as is the case in renal transplantation, bone marrow transplantation and in some cases of lung and liver transplantation. Further research is required to establish the extent to which transplant recipients of other organs experience guilt and what underlies this dimension. The TxEQ specifically assesses guilt in relation to the donor and the donor's family.

Whether to disclose the fact that one has a chronic illness is an option where the treatment or illness is not easily observed (Greene, 2000). in the case of kidney transplantation, it appears that this is an important issue for some individuals. One may speculate that some are concerned about how they will be responded to, whilst others may be relatively unconcerned about others knowing that they have had a kidney transplant (Ndlovu & Louw, 1998). Issues of stigmatization associated with cancer survivorship in bone marrow transplantation, for instance, might be related to disclosure tendency in those patients (Baker, Zabora, Polland, & Wingard, 1999).

The fourth factor identified was that of adherence. Treatment adherence has been widely studied in transplant populations. Although existing research has been hampered because of various assessment methods, each having its own strengths

and weaknesses (Brickman & Yount, 1996), there is evidence to suggest that some transplant patients do not follow the advice and recommendations made regarding immunosuppressive medication (Wainwright & Gould, 1997) despite the associated health risks that this behaviour might precipitate.

The last TxEQ factor refers to responsibility towards family friends or the medical team to do well, an issue which has not received attention in transplantation research. The 'responsibility' dimension of the TxEQ appears to tap issues related to outcome responsibility likely to encompass both a cognitive (i.e. perceptions of responsibility) as well as an affective component (i.e. feelings of responsibility). Responsibility as measured by the TxEQ may hence be seen as qualitatively distinct from concepts such as locus of control or responsibility for graft survival studied in previous research (Bremer, 1995; Bremer, Haffly, Foxx, & Weaver, 1995; Frazier, Davis-Ali, & Dahl, 1994; Kiley, Lam, & Pollack, 1993; Kugler *et al.*, 1994). Responsibility towards others may well be dependent on a range of other factors such as perceived social support and/or patient's satisfaction with interpersonal relationships or with health care received. The modest test-retest reliability coefficients observed may thus reflect changes in those relationships over the inter-test interval. Further research is warranted in order to examine its reproducibility and stability.

The preliminary data reported here indicate that the psychometric properties of TxEQ are acceptable and support its use as a transplant specific research tool. TxEQ is self explanatory, simple to use and time and cost-effective, features that make it an ideal instrument for use in a clinical environment. The TxEQ has potential to monitor on a regular basis the responses, psychological adjustment and treatment adherence in transplant recipients alongside the routine post-transplant medical assessments. From a research perspective, TxEQ may be used separately or in conjunction with more generic HQoL measures. The questionnaire might also contribute to research on the effects of different transplantation modalities, such as cadaver to living-related grafts, and it can also be used to assess the impact of the more recent and rather 'controversial' animal-derived transplants. Further research is currently in progress to assess other groups of transplant recipients and examine the instrument's relationship to other measures and to the clinical status of transplant patients.

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APPENDIX

Scoring algorithms for the TxEQ

Step 1:
Strongly agree = 1; agree = 2; uncertain = 3; disagree = 4; strongly disagree = 5

Step 2:
Recode all items *except* c2, c4, c6, c9, d1, e2, i1, i2, i4: (1 = 5) (2 = 4) (3 = 3) (4 = 2) (5 = 1)

Step 3:

Compute factor 1 : Worry about transplant
With higher scores indicating more worry

worry = b1 + b2 + b3 + b5 + c1 + d2

Compute factor 2 : Guilt regarding donor
With higher scores indicating more feelings of guilt

guilt = e1 + e2 + e3 + e4 + f2

Compute factor 3 : Disclosure
With higher scores indicating more disclosure

disclosure = i1 + i2 + i4

Compute factor 4 : Adherence:
With higher scores indicating better adherence related behaviour

adherence = c2 + c4 + c6 + c9 + d1

Compute factor 5 : Responsibility
With higher scores indicating more responsibility

responsibility = f1 + f3 + f5 + f6