

STUDIES EXPLORING NON-ADHERENCE IN ADULT RENAL  
TRANSPLANT RECIPIENTS

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A thesis submitted in partial fulfilment of the requirements of the  
University of Hertfordshire for the degree of Doctor of Philosophy

Department of Psychology and Sport Sciences

February 2020



## ACKNOWLEDGEMENTS

The completion of this thesis would not have been possible without the guidance and support received from my supervisors, Dr Shivani Sharma and Professor Ken Farrington. To Shivani, I could not be more grateful for the support, advice and opportunities you have afforded me since joining the University of Hertfordshire. You continually challenge me to reach my full potential, and I have learnt so much as a result. Thank you for being a wonderful mentor, role-model and friend. I feel privileged to have received advice, guidance and clinical expertise from Ken throughout my PhD. Thank you for being a brilliant mentor and always providing support when needed. It has been a pleasure working with my supervisory team and I feel extremely lucky that I was given the opportunity to complete this PhD. I hope this thesis facilitates further collaboration between us all.

Thank you to Dr Christopher Lawrence for your guidance, supervision and clinical expertise with the research conducted at Lister Hospital. I am very grateful for all of the support you provided me.

Thank you to all my research colleagues at the University of Hertfordshire and Lister Hospital for your support.

I am extremely thankful to my family and friends for supporting me throughout this journey, particularly to my parents, Martin and Karen. Thank you for always providing me with encouragement, love and guidance in all aspects of life. Special thanks to Roisin Mooney for providing me with advice and reassurance throughout my PhD. To my PhD buddies, Becki, Sonia and Diamantis, thank you all for your support and friendship.

Finally, thank you to all of the patients and clinicians who participated in the studies presented within this thesis. Your contributions, interest, time and kindness were very much appreciated.



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## PhD RELATED PUBLICATIONS

**Hucker, A.,** Bunn, F., Carpenter, L., Lawrence, C., Farrington, K., & Sharma, S. (2017). Non-adherence to immunosuppressants following renal transplantation: a protocol for a systematic review. *BMJ open*, 7(9), e015411.

**Hucker, A.,** Lawrence, C., Sharma, S., & Farrington, K. (2019). Adherence Behaviour in Subjects on Hemodialysis Is Not a Clear Predictor of Posttransplantation Adherence. *Kidney International Reports*, 4(8), 1122-1130.

## Abstract

Non-adherence to immunosuppressive medication is a major risk factor for poor clinical outcomes post-transplantation, including graft rejection and graft loss. However, it remains a common issue. Patients can experience side effects that are problematic and there may be a range of other life and psychosocial factors that interfere with treatment regimens. Withstanding such issues, adherence is vital to provide the kidney with the best chance of survival and function. In addition to patient outcomes, ill health resulting from non-adherence is costly to the NHS, since dialysis services are more expensive than those required to support transplantation. The programme of work within this thesis aims to further explore what is known about adherence in adult transplant recipients in order to drive advances in patient support. A series of studies were designed to assess different elements of adherence. This was achieved through: 1) a systematic review of existing research on adherence; 2) retrospectively considering the relationship between pre and post-transplant adherence in haemodialysis (HD) patients who later go onto receive a solid organ; 3) qualitative enquiry of the views and beliefs of clinical staff in relation to the importance of adherence for kidney transplant wait listing; 4) cross-sectional data collection with transplant recipients about treatment beliefs that may help understand behavioural patterns.

The systematic review provided a comprehensive evidence synthesis of literature exploring non-adherence to immunosuppressants among renal transplant recipients. A total of 60 studies were identified as relevant for inclusion. Studies varied in how they measured adherence, including self-report, electronic monitoring, pharmacy refill, blood levels and collateral report, with some studies combining more than one measure in an attempt to increase reliability. The overall non-adherence prevalence ranged across studies from 0.06% to 89.2%, dependent on how adherence was measured and operationalised. Self-report was the most commonly utilised measurement method to assess adherence behaviour. Meta-analysis of 38 studies revealed the pooled prevalence of self-reported non-adherence was 37.6%. The findings highlight a clear lack of consistency in how adherence is measured and defined, with greater guidelines needed across all measurement types.

A retrospective study examined the relationship between clinical measures of pre and post-transplant adherence in a group of patients who moved from HD to receive a transplant. Little previous research has explored if adherence behaviour transfers across modalities. Data was collected for 88 patients about adherence to HD regimens in the six months prior to transplantation, and for one-year post-transplantation following return transfer to the post-transplant clinic from the transplanting centre. Pre-transplant definitions of non-adherence included if patients: on average shortened their dialysis prescription by >10 minutes; shortened by >15 minutes; missed two or more HD sessions; and had mean serum phosphate levels >1.8mmol/l. Post-transplant definitions of non-adherence included: mean tacrolimus levels outside 5-10ng/mL; missed one or more post-transplant clinic appointments. Non-adherence ranged from 25%-42% pre-transplant and 15.9%-22.7% post-transplant dependent on how it was operationalised. There was little relationship between pre-transplant data and post-transplant adherence, with the exception of a significant relationship between pre-transplant phosphate and post-transplant clinic attendance. Patients who had missed one or more transplant clinic appointments had higher mean pre-transplant phosphate levels. Non-adherent patients with high phosphate levels pre-transplant and missed clinic appointments post-transplant were significantly younger.

Qualitative inquiry was used to gain in-depth understanding of how clinicians recognise non-adherence and whether or not pre-transplant adherence features in their decision making when determining if a patient is eligible for transplant listing. Thirty-six staff members who work closely with renal transplant recipients were recruited across two NHS trusts, and interviewed using a semi-structured interview. Staff members included nephrologists, transplant surgeons, registrars, transplant nurse specialists and pharmacists. Interviews were transcribed verbatim and analysed using thematic analysis. Five main themes were extracted on understanding of non-adherence: “Barriers to adherence” (including risk factors and control in ensuring adherence messages are conveyed), “Striving for normality” (in terms of how patients view transplantation as an opportunity for normality and to avoid dialysis), “Mutuality in maximising patient adherence” (through ensuring patients receive multi-disciplinary care, addressing barriers to adherence, and promoting patient

autonomy through education and peer support), “Complexity in shining light on adherence in wait listing” (highlighting subjectivity in the importance of adherence) and “Post-transplant normalization” (with patients less adherent due to perceptions of wellness and a lack of immediate consequences following missed medication doses). Findings demonstrate that clinicians recognise and understand the barriers that patients face with adherence, and work to try and make treatment management easier. Patient understanding and engagement was considered an effective way to promote adherence. Agreement on how adherence is viewed as part of eligibility for wait listing was lacking, with clinicians managing pre-transplant non-adherence in different ways.

A cross-sectional study further elucidated the relationship between self-reported adherence and markers of adherence obtained from clinical data. Additionally, the association between psychological factors, including illness perceptions and beliefs about medicines, with adherence was explored. Self-report measures used included the Medication Adherence Report Scale (MARS-5), Brief Illness Perceptions Questionnaire (Brief IPQ) and the Beliefs about Medicines Questionnaire (BMQ). Open-ended questions were also utilised to investigate how patients conceptualise their post-transplant treatment. Patients were recruited from one renal unit during the post-transplant weekly clinic, with 128 patients completing questionnaires. Findings showed no correlations between clinical data and MARS-5 adherence score. Certain illness perceptions were highlighted as independently predicting adherence behaviour. Perceptions of personal and treatment control were found to increase adherence. Conversely, perceptions of consequences and emotional representation were found to predict lower adherence. Patients reported higher scores on the necessity sub-scale than the concerns sub-scale of the BMQ, indicating they perceive the “benefits” of immunosuppressant medication to outweigh the “costs”, however, the BMQ sub-scales did not significantly predict MARS-5 adherence. The qualitative comments via open-ended questions provided a mixed view towards experience of transplantation. Those reporting positive experiences had feelings of regained life, however, for some, life after transplant did not meet their expectations due to e.g. symptom burden or side effects. The findings point to areas for potential intervention by considering whether illness perceptions in particular should be assessed to signal patients who may struggle to engage with treatment regimens.

In conclusion, it is clear that non-adherence is a prevalent issue among the renal transplant population. This thesis has advanced clear areas of inconsistency in adherence research, alongside chartering new courses for further research and the development of clinical practice. Clearer definitions and measures of adherence are needed to provide greater reliability in reported non-adherence prevalence rates, and to allow for comparisons to be made across studies. A longitudinal follow-up is necessary to explore how and at which point adherence behaviour changes post-transplant. Agreement is needed across clinicians on how to consider the importance of adherence in transplant eligibility for listing. Finally, promoting patient autonomy to self-manage treatment regimens through education and communication is essential to addressing barriers to adherence.

# Chapter 1: An introduction to Chronic Kidney Disease (CKD)

## 1.1 Introduction

This thesis presents a series of studies aimed at furthering understanding of adherence behaviour in kidney transplant recipients. As a starting point, an introductory chapter provides an overview of the kidneys and their function. The development of kidney disease and its treatment is also considered, with a specific focus on transplantation, as relevant to this thesis.

### 1.1.1 The role of the healthy kidney

To understand the significance of CKD, end stage renal disease and the need for transplantation, it is important to specify the structure and role of the healthy kidney(s). There are two kidneys situated on either side of the spinal column, around 10-12cm in length. They are bean shaped and about the size of a fist. The role of the kidney(s) is to remove waste and excess fluid from the body, including filtering food waste, toxins, medications and blood minerals (Fraser & Blakeman, 2016). This waste and excess fluid is removed via urine, a highly complex process involving excretion and re-absorption to maintain homeostasis of bodily levels and chemicals. In addition to removal of waste and fluid, the kidneys are responsible for regulating salt, potassium and acid levels in the body. Furthermore, the kidneys produce hormones that impact the functioning of other organs including, but not limited to, metabolism of calcium for bone health, production of red blood cells and blood pressure regulation (Ferguson & Waikar, 2012). They filter around 180 litres of blood daily. Glomerular Filtration Rate (GFR) is the volume of blood filtered by the kidney per unit of time ( $\text{mL}/\text{min}/1.73\text{m}^2$ ). Normal eGFR in young adults is considered to be around  $125\text{mL}/\text{min}$  per  $1.73\text{m}^2$  (Levey & Coresh, 2012). Across the adult population, healthy kidneys are considered to be able to filter more than  $90\text{mL}/\text{min}/1.73\text{m}^2$ .

The “nephron” is a functional unit of the kidney, with each kidney containing up to a million. Each nephron contains a filter, called a glomerulus and a tubule, within which a two-step process occurs. Once the blood enters the nephron, it is filtered by the glomerulus and the remaining fluid is passed along the renal tubule. In the tubule, chemicals and water are added or removed from the filtered fluid

according to the body's requirements. Needed substances including minerals and nutrients and almost all of the filtered water is reabsorbed into the blood. Waste products and extra water are removed for excretion via urine. This process ensures regulation of fluid volume, electrolyte balance and pH of bodily fluids.

## 1.2 The failing kidney

CKD is a long-term condition characterised by progressive decline in kidney function over time. The definition of CKD is based on the presence of decreased kidney function or damaged kidneys for more than three months (Levey & Coresh, 2012). The diagnosis implies persistently abnormal kidney function or structure. Complications and adverse outcomes can be delayed or prevented if CKD is detected early and treated (Levey et al., 2003). It frequently goes unrecognised, as it is often asymptomatic until later stages. The three-month duration is necessary to distinguish CKD from acute kidney injury (AKI). Whereas AKI is potentially reversible, CKD is progressive and irreversible.

AKI usually occurs following a specific, abrupt acute event, and is characterised by a decline in kidney function within hours (NICE, 2018), encompassing both injury (structural damage) and impairment (loss of function) (Makris & Spanou, 2016). Classification of AKI includes pre-renal, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases (Makris & Spanou, 2016). Of these only intrinsic represents direct damage to the kidney, whereas pre-renal and post-renal AKI are a result of extra-renal diseases leading to decreased GFR. The most common cause of AKI is pre-renal due to reduced perfusion of the kidneys leading to decreased GFR often due to hypovolaemia, sepsis, reduced cardiac output or drugs reducing blood pressure or renal blood flow. If treated early, it is often reversible. Intrinsic renal is a consequence of structural damage to the kidney itself caused by toxins, immunological causes and drugs. Any of the main components of the kidney, vascular, glomerular or tubulointerstitial, may be involved. Post-renal, the least common cause of AKI accounting for 10% of cases, occurs as a result of acute obstruction, such as due to prostatic hypertrophy, impacting urine flow leading to intratubular pressure and decreased GFR (NICE, 2018). The incidence of AKI has been increasing over time. Previous views on AKI suggested it could be

completely reversible, however, more recent literature using animal and human studies has indicated that AKI can cause long-term damage and may also damage other organs (Coca, Singanamala & Parikh, 2012). In a systematic review of 13 studies, patients with AKI were at greater risk of developing CKD, end stage renal disease and early mortality, compared to patients without AKI (Coca, Singanamala & Parikh, 2012).

### 1.2.1 Diagnosis and stages of chronic kidney disease

CKD can be diagnosed using blood and urine tests, which are designed to look for high levels of substances that indicate the kidneys are not working correctly. Beginning treatment at the correct time in relation to CKD progression is crucial to prevent adverse outcomes (Levey et al., 2003). In clinical practice the primary test for kidney function is a blood test that measures the levels of creatinine, a waste product, in the blood. This result is used in a calculation along with age, gender and ethnic group to estimate how many millilitres of blood the kidneys are able to filter a minute. This is known as estimated glomerular filtration rate (eGFR). eGFR is considered to be the most efficient overall index of kidney function in health and disease (Levey & Coresh, 2012). Urine tests check for blood and protein, and levels of albumin and creatinine (known as albumin:creatinine ratio). Alongside eGFR, this provides a more accurate understanding of how well the kidneys are functioning.

Additional tests that can be used to diagnose CKD and assess kidney damage include a kidney biopsy, where a small sample of tissue is extracted to examine for signs of damage, or scans including ultrasound, magnetic resonance imaging (MRI) or computerised tomography (CT). These scans are used to look for structural damage and obstruction (NHS, 2016). CKD is classified into five stages (see Table 1.1).

*Table 1.1: Chronic Kidney Disease stage classification (Levey & Coresh, 2012)*

Stage	eGFR	Disease status
1	>90mL/min per 1.73m <sup>2</sup>	No CKD (unless signs of kidney damage)
2	60-89mL/min per 1.73m <sup>2</sup>	No CKD (unless signs of kidney damage)
3a	45-59mL/min per 1.73m <sup>2</sup>	CKD (mild-moderate loss of function)
3b	30-44mL/min per 1.73m <sup>2</sup>	CKD (moderate-severe loss of function)
4	15-29mL/min per 1.73m <sup>2</sup>	CKD (severe loss of function)
5	<15mL/min per 1.73m <sup>2</sup>	ESKD (kidney failure)

In stages one and two kidney function is considered normal, however, there are other abnormalities which indicate kidney damage, including the presence of blood and protein in the urine and structural damage indicated by imaging (Levey et al., 2003). Patients are treated for any underlying conditions with the aim of slowing progression of CKD. Stage three is considered moderate decrease in kidney function, and clinicians aim to evaluate and treat complications. Stage four represents severely reduced kidney function, and at this stage preparations are made for renal replacement therapy (RRT). The final stage of CKD, stage five, is commonly referred to as “end stage renal disease”. Kidney failure is defined as either an eGFR less than 15mL/min per 1.73m<sup>2</sup> usually accompanied by symptoms of uremia or the need to begin RRT.

### 1.2.2 Risk factors and causes of chronic kidney disease

Risk factors for CKD can be categorised into two groups: initiating factors that increase patient risk of developing CKD, and perpetuating factors increasing the risk of CKD progression to end stage renal disease (Taal & Brenner, 2006; Evans & Taal, 2011) The different factors associated with each group are listed in Table 1.2.

*Table 1.2: CKD initiating and perpetuating factors (Taal & Brenner, 2006; Evans & Taal, 2011)*

<b>Initiating factors</b>	<b>Perpetuating factors</b>
Increasing age	African-American race
Gender	Proteinuria
Ethnicity	Hypertension
Family history of CKD	High dietary protein intake
Socio-economic status	Obesity
Metabolic syndrome	Anaemia
High normal urinary albumin excretion	Dyslipidaemia
Dyslipidaemia	Nephrotoxins
Nephrotoxins	Smoking
Primary renal disease	Cardiovascular disease
Urological disorders	
Cardiovascular disease	
Diabetes mellitus	

CKD may occur as a consequence of primary renal disease e.g. glomerulonephritis (inflammation of the glomeruli), polycystic kidney disease, and reflux nephropathy, or as a consequence of other chronic conditions such as high blood pressure (hypertension); diabetes; atheromatous vascular disease, chronic urinary obstruction, and long-term use of particular medications/drugs (NHS, 2016). Despite advances in diagnostic techniques and increasing knowledge of the disease, unknown aetiology of disease remains high in many countries. The most reliable and consistent data reporting prevalence rates of causes for CKD comes from incident renal replacement therapy patients and from countries where there are good renal registries.

Diabetes and hypertension are the leading causes of CKD in high and many low and middle income countries (Evans & Taal, 2011; Jha et al., 2013). Around 40% of patients with diabetes will develop CKD. Glomerulonephritis, a wide term used to define primary and secondary conditions that cause inflammation and damage to the glomerulus, accounts for the cause of CKD in around 12% of incident renal replacement patients in the UK (Evans & Taal, 2011). Of genetic diseases, adult polycystic kidney disease is the most common monogenetic disorder causing CKD, usually presenting in the third or fourth decade of life. It is often experienced alongside other symptoms such as liver

cysts, cerebral aneurysms and cardiac abnormalities. Patients and family members of those diagnosed are screened via ultrasound to identify renal cysts. Long-term use of certain medications can cause AKI and CKD, often by provoking interstitial nephritis. These can include penicillin's, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, diuretics and anti-retrovirals (Evans & Taal, 2011). Patients who are most at risk for CKD should be screened regularly. These include older patients and those with diabetes and hypertension.

### 1.2.3 Progression of chronic kidney disease and comorbidities

The progression of CKD is associated with a number of potential adverse outcomes with complications leading to increased risk or mortality and poorer quality of life. Treatment to slow progression of kidney function decline and of co-morbid conditions, including to reduce risk for cardiovascular disease should begin during CKD stages 1 and 2 (Levey et al., 2003). As hypertension is considered both a cause and complication of CKD, this should be monitored and controlled across all patients. Additional complications of declining kidney function should be monitored and treated as appropriate during stage 3 CKD, as the prevalence of these complications increases when kidney function declines to less than 60mL/min per 1.73m<sup>2</sup>. These can include for example, cardiovascular disease (CVD), hypertension, bone mineral disorder, anaemia, kidney failure resulting in a need for renal replacement therapy (Bello et al., 2017).

### 1.2.4 Complications of chronic kidney disease

Patients with CKD have a high risk of developing complications, and therefore is essential to monitor risk factors in this patient population. Hypertension is a major complication which causes significant progression of CKD and decline in kidney function. Detection and control of high blood pressure is less than optimal, risking continued damage to kidney function (Muntner et al, 2010). Hypertension is associated with cardiovascular risk, and contributes to the increased cardiovascular risk associated with CKD. Cardiovascular disease (CVD) is the leading cause of mortality in CKD patients. As kidney function declines, the prevalence of CVD increases (Go et al., 2004). Cardiovascular mortality

rates are significantly higher in dialysis patients compared to age and sex matched individuals without CKD in the general population (Thomas, Kanso & Sedor, 2008).

Anaemia is a common complication experienced alongside progressive CKD, with a strong correlation between the prevalence of anaemia and the severity of CKD (Thomas, Kanso & Sedor, 2008). The overall prevalence of CKD anaemia is around 50% (McClellan et al., 2004). The most important cause of CKD associated anaemia is decreased erythropoietin synthesis, essential for stimulation and growth of red blood cells. This increases the risk of cardiovascular mortality and morbidity, and may lead to further deterioration of renal function (Thomas, Kanso & Sedor, 2008). CKD associated anaemia can be treated with erythropoiesis stimulating agents (ESAs) to reduce transfusion requirements and anaemia symptoms.

CKD associated bone and mineral disorders, including hyperphosphatemia, hyperparathyroidism, adynamic bone disease, and vascular calcification are common. Phosphate retention and impaired renal secretion of 1, 25 dihydroxy-vitamin D are major driving factors (Thomas, Kanso & Sedor, 2008). Bone disease can reflect high or a low bone turnover states. Osteitis fibrosa cystica is a high turnover condition and occurs as the result of hyperparathyroidism. Adynamic bone disorder is a low turnover state and associated with high calcium and low parathyroid hormone levels. Osteomalacia, in which there is a bone mineralisation disorder, can also occur. Mixed states (mixed osteodystrophy) are not uncommon. Vascular calcification is an associated condition, also contributed to by hyperphosphatemia, which is also a major risk factor for cardiovascular disease in CKD.

### 1.2.5 Prevalence of chronic kidney disease

CKD has been identified as a major public health problem worldwide. The 2010 Global Burden of Disease Study ranked CKD 18<sup>th</sup> in the list of causes of total number of global deaths (annual death rate 16.3 per 100,000) (Lozano et al., 2010; Jha et al., 2013). A systematic review exploring the global prevalence of CKD indicated a high global prevalence with a consistent estimated rate of between 11-13%, the majority of patients diagnosed with stage three CKD (Hill et al., 2016). The mean global

prevalence was 13.4% (11.7%-15.1%) in populations measuring prevalence by all five CKD stages (N=44) and 10.6% (9.2%-12.2%) in populations measuring stages 3-5 (N=68) (Hill et al., 2016).

These estimates indicate that global prevalence of CKD could be greater and therefore more common than diabetes (estimated prevalence 8.2%).

### 1.3 End stage renal disease

End stage renal disease (ESRD) occurs within stage five CKD when the kidneys are no longer able to support the needs of daily life in filtering waste and excess fluid from the body. At this stage, the kidneys are usually functioning at <10% of their healthy normal capacity (Timmers et al., 2008). At the end of 2016, approximately 63,162 adult patients were receiving renal replacement therapy in the UK (Renal Registry, 2017; 2018). Of these 40% were receiving haemodialysis, 6% peritoneal dialysis and 54% transplantation. The renal diagnoses in incident renal replacement therapy (RRT) patients were diabetes (29%), glomerulonephritis (14%), hypertension/renovascular disease (12%), pyelonephritis (6%), other (14%) and aetiology uncertain (14%).

#### 1.3.1 Pathways to treatment

Patients with ESRD require RRT in order to survive. RRT includes two dialysis modalities: haemodialysis and peritoneal dialysis, and kidney transplantation. At the end of 2016, transplantation remained the most common form of RRT in the UK (see above). This pattern is similar across other northern European countries (USRDS, 2018). Dialysis involves filtering the blood, extracorporeally using an artificial membrane (haemodialysis), or using a natural, *in-situ* membrane (the peritoneal membrane), in peritoneal dialysis, to remove the toxins and fluids that the kidneys can no longer remove due to loss of function (Timmers et al., 2008). Patients will usually be able to choose which type of dialysis is most appropriate for them. Kidney transplantation involves receiving a healthy kidney from a donor when the recipient has little or no kidney function. A summary of the different dialysis modalities and of transplantation is provided below.

### 1.3.2 Haemodialysis

Haemodialysis (HD) involves purifying the blood via an external artificial kidney. Prior to starting HD, patients often have an arteriovenous fistula (AV fistula) created in their arm, a blood vessel created by connecting an artery to a vein which is used in the HD treatment. The AV fistula makes the blood vessel stronger and larger, making the transfer of blood into the dialysis machine and then back into the patient easier. Ideally the AV fistula is created around 8 weeks before starting HD.

HD is the most common form of dialysis and involves three sessions per week lasting around four hours. Time spent on HD varies from patient to patient dependent on how much fluid needs to be removed (NHS, 2018). HD can take place in hospital or can be completed at home, however, hospital HD is most common. Two needles are inserted into the AV fistula: one needle removes blood and transfers it to the dialysis machine from which the machine filters the blood removing waste and excess fluid; the second needle is used to return the filtered blood back into the body.

Patients receiving HD must follow strict fluid and diet restrictions, as the dialysis machine is unable to remove a high volume of excess fluid consumed over dialysis free days. Excess fluid build-up can lead to serious complications in the tissue, blood and lungs. Fluid allowance is determined on patient size and weight, and the patient's residual urine volume. Most patients are restricted to 1000ml-1500ml fluid per day. Salt restriction is usually required. Other dietary restrictions must be followed as minerals normally filtered by the kidneys can build up and become problematic between dialysis treatments. These include potassium and phosphate. Medications are often also needed to manage such issues.

Advantages of HD include having four treatment free days. However, as HD is usually carried out in hospital at a dialysis clinic, patients must travel regularly for treatment and plan around the need for four-hour treatment sessions. Additionally, this can impact on patients' daily routines, including work and family life.

### 1.3.3 Peritoneal dialysis

Peritoneal dialysis (PD) uses the peritoneal membrane to act as an artificial kidney. There are two types of PD: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). Both treatments can be administered at home following patient training (NHS, 2018). Prior to starting CAPD or APD, an opening is made in the abdomen through which a catheter is inserted. This allows dialysis fluid to be infused into the peritoneal cavity. In CAPD, this is performed by the patient or helper. The fluid remains for a few hours and waste and excess fluid in the blood passing through the lining of the cavity are removed from the blood into the dialysis fluid. After the fluid has remained for a few hours, it is drained into a waste bag. New dialysis fluid then replaces the old fluid until the next draining session. Most patients on CAPD repeat this process around four times per day. The catheter is sealed, and bags disconnected between treatment sessions (draining old fluid and replacing new fluid).

APD is similar to CAPD, however, a machine is used to drain and replace fluid whilst the patient sleeps. A dialysis fluid bag is attached to the APD machine overnight during sleep and performs a number of draining and replacing fluid replacements over a period of 8-10 hours. Following treatment completion, some dialysis fluid will remain in the abdomen which is drained in the following treatment.

Fewer diet and fluid restrictions are required for patients receiving PD compared with HD, as treatment is being performed more continuously. Further advantages of PD include the ability to administer treatment from home requiring fewer hospital visits, and portable equipment (CAPD) allowing travel to be more accessible. Disadvantages of PD include risk of infection, such as peritonitis (an infection of the membrane lining the abdomen), the potential upsetting nature of having a catheter permanently inserted in the abdomen, and the need for everyday treatment.

### 1.3.4 Patient experience of dialysis

Due to the chronic nature of dialysis and the lifestyle it imposes, it has been related to poor health outcomes such as poorer health related quality of life and psychological well-being, with patients

often needing help and support to cope. Incident haemodialysis patients report feelings of emotional distress, treatment-related concerns and the need for social support (Lai et al., 2012).

Fatigue is common impacting between 42-89% of patients (Artom, Moss-Morris, Caskey & Chilcot, 2014). Symptoms of fatigue include tiredness, reduced physical activity and motivation and a lack of energy. This symptom may be related to the change in bodily function caused by renal failure and the side-effects of dialysis treatment. Higher levels of fatigue are reported by females and by older patients. However, it is possible that this is simply due to females being more likely to report symptom experiences compared to males (Van Wijk & Kolk, 1997). Patients are often affected by fatigue post-dialysis, with some patients taking many hours to recover.

Research has shown that 20-30% of patients with ESRD receiving dialysis experience depressive symptoms (Cukor, Coplan, Brown, Peterson & Kimmel, 2008). In terms of risk factors, younger patients are at greater risk of developing depression, as ESRD and the need for dialysis causes significant disruption to everyday life, notably to social aspects including changes to family and work roles, loss of time and a decline in mobility (Chilcot et al., 2008). These disruptions are in addition to other factors patients must manage, including medication, diet and fluid restrictions and potential side effects of treatment. Additionally, depression has been identified as a significant predictor of medication adherence, with patients who report greater symptoms of depression to report poorer medication adherence (Cukor, Rosenthal, Jindal, Brown & Kimmel, 2009). HD patients reported 37% “less than perfect adherence” to their prescribed treatment and medication regime. This included diet, fluid intake, medication and hospital or medical appointments.

Treatment methods to reduce depressive symptoms include anti-depressant medication and talking therapies, such as cognitive behavioural therapy (CBT). There have been mixed results in the effectiveness of pharmacotherapy studies in reducing depressive symptoms in ESRD patients. Findings must be interpreted with caution as some studies fail to use a placebo control group, have small sample sizes or fail to use the Diagnostic and Statistical Manual (DSM) criteria to diagnose major depressive disorder (Hedayati, Yalamanchili & Finkelstein, 2012). As anti-depressants can

have cardiac side-effects such as hypertension and arrhythmias, they must be carefully prescribed to ensure they are appropriate and safe to take for people with ESRD (Hedayati, Yalamanchili & Finkelstein, 2012). More recently, there has been consideration as to whether anti-depressants are doing more harm than good in terms of patient outcomes (Chilcot & Farrington, 2019), and that withdrawal strategies should be considered requiring careful risk assessment, patient education and counselling and an appropriate tapering regimen to mitigate any symptoms of withdrawal (Horowitz & Taylor, 2019).

CBT studies to treat depression in dialysis patients have shown some success. Cukor (2007) found patients showed significantly lower depressive symptoms following a 15-week CBT intervention, which were sustained at three-month follow-up. A randomised controlled trial (RCT) has investigated the effectiveness of group CBT for ESRD HD patients with a diagnosis of major depressive disorder (Duarte, Miyazaki, Blay & Sasso, 2009). They found a reduction in depressive symptoms and increase in quality of life at the end of the three-month treatment. This was sustained at six months follow-up. Currently, feasibility of routine CBT delivery remains unclear (Chilcot & Hudson, 2019). No studies or trials have explored the combined effects of CBT and anti-depressants. Further depression treatment trials are needed in dialysis patients with increased patient numbers to clearly establish effective and safe treatment methods for this patient population.

### 1.3.5 Transplantation

Transplantation involves receiving a healthy kidney from a donor when the recipient has little or no kidney function (i.e. is classified as having end stage renal disease). An operation is performed to transplant the donated kidney into the recipient. The donor kidney is placed in the lower abdomen. Typically, the patient's kidneys are left in their body unless there is need for removal, such as infection or pain. The blood vessels from the donor kidney are attached to nearby blood vessels in the body to ensure blood supply for the kidney to function suitably. The donor kidney vein is attached to the recipient's iliac vein and the donor artery is attached to the recipient's iliac artery. The ureter of the donated kidney is attached to the bladder, which carries urine from the kidney to the bladder. A stent

is sometimes placed to ensure good flow of urine and is removed 4-6 weeks post-transplantation (Kidney research UK, 2017; NHS, 2018). This is complex surgery which can take up to three hours to complete. Following the operation, patients begin taking immunosuppressant medication to prevent rejection of the transplanted organ. These can sometimes take time to become effective, and acute rejection is experienced typically within the first six weeks following transplantation. In most cases, the transplanted kidney will begin working immediately following surgery, however, in some cases it can take some time, a few days to a few weeks. This is known as delayed graft function. During this interim, patients may need to receive dialysis until the transplanted kidney begins to function. Patients are usually required to stay in hospital following the operation for around one week, and require regular appointments at the transplant clinic to check how the kidney is functioning and on immunosuppressant medication levels. During the first month post-transplantation, patients can be required to attend the transplant clinic more regularly, at least once per week, however, this reduces over time once kidney function is established and stable. Following one-year post-transplantation, patients can be seen every three to six months if there are no problems.

Kidney transplantation is suggested to be the most desired and cost-effective treatment option (Abecassis et al., 2008), above HD and PD. Patients who receive a transplant often have a longer life expectancy and improved quality of life (Jindal et al., 2003), including increased energy and a less restrictive diet in comparison to dialysis patients. Most patients with ESRD placed on the waiting list are healthier patients, therefore long-term survival is greater among patients on the waiting list following transplantation when compared to dialysis patients (Wolfe et al., 1999).

### 1.3.6 Patient experience of transplantation

In comparison to patients receiving treatment via dialysis, kidney transplantation is associated with improved clinical outcomes (Wolfe et al., 1999), better quality of life (Reimer et al., 2002) and fewer reports of psychiatric problems, such as depression. Despite this, kidney transplantation requires psychological adjustment and presents medication and treatment challenges (Chilcot, Spencer, Maple & Mamode, 2014), which can produce feelings of distress, fear and guilt. Recent studies have

reported depression prevalence rates 22% (Szeifert et al., 2010) and 26.6% (Palmer et al., 2013). Although percentages are lower in comparison to in dialysis patients, it still represents a significant number of transplant patients. Chilcot et al., (2014) suggest that although there is variation in prevalence estimates, approximately one in four patients screened positively for depression across the advanced kidney disease spectrum. This makes it one of the most common co-morbidities experienced by both patients on the transplant waiting list and transplant recipients. There are a number of factors associated with depression in kidney transplant recipients. Chilcot et al., (2014) summarise the common demographic, clinical and psychological correlates of depression identified in previous literature (see Table 1.3).

*Table 1.3: Factors associated with depression in kidney transplant recipients (Chilcot et al., 2014)*

Demographic	Clinical	Psychological
Age	Renal function	Previous history of depression
Marital status	Inflammation	Perceived stress
Lower income/employment	Comorbidity	Coping style
Gender	Serum haemoglobin	Illness beliefs
White race	Serum albumin	Social support
Education		

Poor psychological well-being has been related to poor clinical outcomes in kidney transplant recipients. Depression has been associated with a greater risk of mortality (Dobbels et al., 2008; Novak et al., 2010; Zelle et al., 2012). Additionally, it has been associated with a return to dialysis, twofold increase in graft failure and increased risk of mortality with a functioning graft (Dobbels et al., 2008). Explanations for these poorer health outcomes in patients with depression include non-adherence to treatment. Non-adherence is three times more likely among kidney transplant patients diagnosed with depression (DiMatteo et al., 2000).

Symptom occurrence, i.e. side effects, are regularly experienced by kidney transplant recipients, often due to medications being taken including immunosuppressants. These can range from physical symptoms such as muscle weakness, impotence, increase in hair growth, fatigue, tremors and increase in appetite to name a few (Kugler et al., 2009). Different symptom experiences effect patients in differing ways, with younger patients impacted by different symptoms than older patients, but all

leading to symptom distress. Patients can alter or stop taking medication taking in order to prevent symptom experiences and reduce symptom distress. This increases the risk of poorer health outcomes. Younger patients and females in particular have been identified as finding side-effects particularly distressing and are therefore the most at risk group for non-adherence and potentially poorer health outcomes (Kugler et al., 2009). Greater understanding of symptom experiences and appraisal of immunosuppressant medication side-effects is required in order to develop strategies to reduce the risk of non-adherence triggered by symptom experiences and distress, reduce the risk of non-adherence related graft rejection, and improved quality of life by individualised symptom management. Patients on immunosuppression are more vulnerable to infection and have an increased long-term risk of some types of cancer.

#### 1.4 Kidney organ donation

There are 24 centres providing kidney transplantation in the UK. Between 1 April 2017 and 31 March 2018 the median waiting time from patient dialysis start date to deceased donor transplant was 1148 days. This varied across transplanting centres ranging from 576 to 1661 days (NHS Blood and Transplant, 2018). Waiting time differs across ethnicities due to availability of donor organs, with BAME groups waiting the longest for a well-matched graft (Morgan et al., 2015). In the UK, the kidney is the most commonly transplanted organ, and additionally is the most common living donation transplant.

##### 1.4.1 Types of donation

Patients can receive a kidney via living or deceased organ donation. Deceased donations can be received from either a patient following brain death (known as DBD donors) or following circulatory death (known as DCD donors). Operations using deceased donor kidneys tend to be emergency procedures and patients can be notified at any time of day that an organ is available and given a short window of time to attend the transplanting centre. Living donation requires significant preparation and therefore operations can usually be scheduled and occur during the daytime.

DBD donation, previously known as heart beating donors, is a more traditional form of deceased donation and is therefore better known. Donors will have typically undergone a sudden catastrophic event which has led to loss of brain function, requiring them to be placed on a ventilator to maintain respiration. They will undergo testing to assess if brain function can be recovered and to establish if they will be able to breathe again unaided. If it is found that the donor has extensive brain damage which is deemed irreversible, they will be considered as a potential organ donor. If consent is gained, the organs are cooled for preservation prior to the ventilator being turned off and are then removed (Kidney Research UK, 2017).

DCD donation, previously known as non-heart beating donors, occurs again where donors have experienced irreversible brain damage and are on ventilator to aid breathing and heart and lung function, however, they do not meet the criteria following testing to be classified as brain-stem death. If the damage is deemed irreversible with no likelihood of recovery, the patient will be considered for organ donation. If consent is provided, the patient will be disconnected from the ventilator. The heart must stop beating within a suitable period of time for them to be considered eligible for donation, following which the organs are cooled for preservation and removed.

DCD consists of two types, controlled and uncontrolled. The clinical circumstances in which DCD can occur can be understood via the Maastricht classification (see Table 1.4). Uncontrolled DCD, consisting of categories one and two, refers to organ retrieval following unexpected cardiac arrest in a patient who cannot or should not be resuscitated. Controlled DCD, consisting of categories three and four, takes place after death following planned withdrawal of life sustaining treatments. These treatments are considered to be of no benefit to the patient and unlikely to lead to patient recovery.

*Table 1.4: The Maastricht classification of donation after circulatory death (Hoogland et al., 2011)*

Category	Type	Circumstances	Typical location
I	Uncontrolled	Dead on arrival	Emergency department
II	Uncontrolled	Unsuccessful resuscitation	Emergency department
III	Controlled	Awaiting cardiac arrest (following planned withdrawal of life sustaining treatments)	Intensive care
VI	Controlled	Cardiac arrest during or after brain death diagnostic procedure	Intensive care

The UK focuses primarily on controlled DCD. The higher number of controlled DCD in the UK is likely due to the number of deaths in intensive care where life sustaining treatment is limited or withdrawn. The number of DCD has continued to increase year on year, with the number of kidney donors increasing to 624 in 2018/2019 from 596 in 2017/2018 (NHS Blood and Transplant, 2019) allowing for more organs to be available for transplantation and thus reducing the number of patients on the transplant waiting list.

DCD kidney transplants are allocated via local allocation arrangements. These vary dependent on size of DCD centre programmes. DBD donors are allocated via the National Kidney Allocation Scheme, which determines allocation of all kidneys available for transplantation from donors following brain death. The National Allocation Scheme was introduced in April 2006 and aims to reduce waiting times for deceased donor kidney transplants across the UK. Patients are listed nationally through the scheme and prioritises patients with ideal tissue matches. Points are assigned to patients based on the level of tissue match between the donor and the recipient, the age of the recipient and location of the patients to the retrieval centre. A reduction of points is applied to patients over the age of 30 years, and to those that are located further away from the donor kidney retrieval centre. Patients with a higher total number of points based on the criteria listed above are offered the donated kidney (NHS Blood and Transplant, 2018).

There has been some hesitation around DCD grafts due to high incidence of delayed graft function and early graft loss (Mallon, Summers, Bradley & Pettigrew, 2013) and therefore are sometimes viewed as inferior to grafts received from DBD donors (Summers et al., 2015). Due to ischaemic

injury suffered by solid organs following circulatory death in the time interval between treatment withdrawal and cold perfusion, recipients of DCD kidney grafts experience a higher incidence of delayed graft function compared to recipients of DBD kidney grafts. This often requires a short period of post-transplantation dialysis, however, evidence indicates long term graft survival is similar to recipients of DBD kidney grafts. Schaapherder et al., (2018) found higher incidences of graft loss and delayed graft function in DCD grafts did not impact long-term survival and 10-year graft survival post-transplantation was similar between DCD and DBD grafts. The UK has developed a controlled DCD transplant programme to increase transplants and reduce the number of patients on the transplant waiting list. Data from UK transplant registry has also shown first-time recipients of kidney grafts from controlled circulatory-death donors have good outcomes in relation to graft function and survival that should be viewed as equivalent to recipients of DBD grafts (Summers et al., 2010). Additionally, data from UK transplant registry has shown kidney function at five years and graft survival at ten years post-transplantation is similar between DCD and DBD grafts (Summers et al., 2015).

Living donation can be received via directed or non-directed donation. Directed donation occurs where the donor specifies who they are donating the kidney to. This commonly occurs in living donations from close family members or friends. Non-directed donation, which is known as altruistic donation, occurs where the donor volunteers to donate their organ and does not specify who the organ is to be donated to, it can be given to anyone who is a match. Altruistic donors are therefore not usually acquainted with the recipient. This type of living donation is much less common than directed living donation. Patients preparing for RRT will be asked if they have any close relatives or friends who would be willing to be a living donor. Kidneys via living donation provide the transplanted kidney with the best chance of success and survival compared to kidneys from deceased donation (Kidney Research UK, 2017). Preparations for this begin early to allow ample time for testing to be completed with the potential donor to see if they would be eligible to donate and are a match for the recipient. Additionally, this time increases the likelihood that patients requiring transplantation can be transplanted prior to the need to start dialysis. Living donor grafts have very good kidney function

prior to removal, and the time period between removal from the donor and transplanting into the recipient is much shorter than between retrieval and transplantation from deceased donors. For these reasons, long-term graft function and likelihood of immediate function following transplantation is greater from living donor grafts.

Patients requiring kidney transplantation can be transplanted pre-emptively before the need for dialysis initiation or following receiving dialysis. Pre-emptive transplantation is established to be associated with more optimal outcomes in relation to patient and graft survival post-transplant (Abecassis et al., 2008). Pre-emptive transplants from living donors are more likely to be performed before the need for dialysis arises. This is often due to waiting time being longer for deceased donor transplantations, whereas living donor transplantations can often take place more quickly once a donor is established.

#### 1.4.2 Rates of donation

In 2017/18, 3,272 adult kidney transplants were performed in the UK. This was an increase of 7% in comparison to the previous year. Of these 2,320 were from deceased donors (940 DCD; 1,380 DBD), and 952 from living donors. The majority of transplanted patients were male (63%) and white (75%). The average rate of graft survival at five years from deceased donor transplantation is 86%, compared to 93% from living donor transplants. Additionally, the average graft survival rate at 10 years post-transplant is 75% via deceased donation.

Due to a shortage in deceased donor kidneys available for transplantation, this has resulted in patients receiving kidneys from less well-matched donors which potentially results in poorer transplant outcomes. A donor risk index has been developed which categorises kidneys based on anticipated outcome, allowing clinicians greater information to make decisions regarding organ allocation, and to better inform potential recipients of the organ(s) they are being offered. The donor index determines factors that influence transplant survival and time from transplant to either graft failure or patient death, depending on which comes first (Watson et al., 2012; NHS Blood and Transplant, 2018).

In an attempt to improve rates of organ donation and number of patients waiting for a transplant, the law in England is changing in Spring 2020 to an opt out system, meaning all adults will be considered an organ donor when they die unless they have recorded they do not wish to be one (opted-out) or if they fall into one of the categories meaning they are excluded from being a potential donor (Department of Health and Social Care, 2019). Families will be consulted and will provide consent for the retrieval. An opt-out system for organ donation is already in place in Wales, enacted in 2015. An initial increase in consent rates has been observed in Wales, however, success is dependent on patient families supporting the decision of their deceased relatives' decision regarding donation made when alive (Noyes et al., 2019). Whilst the law has been shown to be successful in encouraging potential donors to register a decision regarding organ donation, or to verbally express their wishes, barriers such as family members over-riding decisions or health issues have been shown to prevent successful donation (Noyes et al., 2019). This will need to be considered when the law is introduced in England.

### 1.5 Summary

CKD is a complex and progressive condition. Patients diagnosed with ESRD require RRT in the form of dialysis or transplantation. Both HD and PD are debilitating treatments and patients often experience lower health related quality of life and issues with psychological well-being alongside other restrictions and challenges as a result of their condition and treatment. Transplantation is considered the best and most cost-effective treatment option. Although challenges remain in managing long-term medication taking, coping with any side-effects associated with treatment and attending clinic for regular monitoring post-transplantation, quality of life, psychological well-being and patient experiences tend to be greater compared to those receiving dialysis. Rates of kidney donation are slowly improving year on year, however, the demand in terms of the number of patients on the waiting list still greatly outnumbers the supply of grafts available from donors. Due to this, donor grafts are considered a precious resource and it is important to ensure they have the best chance of survival. Therefore, it is essential that donor grafts are well matched to potential recipients, and that

they are given to recipients who will do their best to preserve kidney function long-term. However, clinical experience tells us that many grafts are lost due to potentially modifiable factors that are patient behaviour driven, such as adherence to immunosuppressant medication. This thesis aims to explore adherence behaviour in transplant recipients further. Specifically, through a series of studies, the programme of research will consider: how non-adherence is defined in this patient population, measured and estimated, how much clinicians consider adherence in wait listing decisions in light of retrospective data related to adherence pre- and post-transplant. A mix of quantitative and qualitative designs will yield knowledge that can help enhance service design in relation to optimising success of renal grafts.

## Chapter 2: Medication adherence in kidney transplant recipients

### 2.1 Introduction

Medication non-adherence is widely acknowledged as a common concern for all health care professionals, particularly those working with patients with long-term health conditions (Lehene & McCarthy, 2007). There are a number of empirical studies, comprehensive literature reviews and meta-analyses exploring adherence to treatment and the extent of non-adherence across a wide range of conditions. These studies aim to highlight the ‘problem’ and contributing factors so as to better inform health care providers about challenges to treatment engagement. In this chapter, attention is given to providing an overview of:

- How adherence has been operationalised and measured;
- Summarising what is known about the rate of non-adherence among the kidney transplant population;
- Considering implications of non-adherence for transplant recipients in terms of outcomes.

### 2.2 Definitions of adherence

Adherence to medication and treatment regimens is an important part of health care (Jimmy & Jose, 2011), particularly in long-term conditions (Lemay et al., 2018) such as kidney disease, including transplant recipients. The terms compliance and adherence are commonly used interchangeably by health care professionals; however, it is important to understand and differentiate the two (WHO, 2003). Compliance has been defined as “the extent to which the patient’s behaviour matches the prescriber’s recommendations” (p. 12, Horne et al., 2005), however, the use of this term is slowly declining as it suggests a lack of patient involvement in decision making processes. Adherence has been defined as “the extent to which the patient’s behaviour matches the agreed recommendations from the prescriber” (p. 12, Horne et al., 2005). This term is now regularly being used as an alternative to compliance as it aims to emphasise patient involvement and the need for agreement

between patient and doctor in treatment recommendations (WHO, 2003). Adherence implies that patients have the freedom to choose whether or not to see through recommendations. Additionally, failure to follow the treatment regimen prescribed should not provide cause to blame the patient (Horne et al., 2005). The WHO indicates that patients should be “active partners” with health care professionals in determining their own care and that good communication between these two parties is essential for successful clinical practice.

Non-adherence is complex and can emerge due to a multitude of reasons. The causes of non-adherence fall into two overlapping categories: intentional and unintentional (NICE, 2009). These two categories of non-adherence have been widely researched in the literature in relation to long term conditions. Unintentional non-adherence is often considered to occur when the patient intends or wants to follow the recommendations, but due to factors beyond their control are prevented from doing so. Such barriers can include forgetting, poor memory, difficulty understanding instructions, problems using medication/treatment, and inability to pay for treatment (NICE, 2009). Intentional non-adherence occurs when a patient consciously chooses not to follow the treatment regimen or treatment recommendations. It is suggested that this could be due to patient beliefs or preferences that then influence their perceptions of treatment or medication and motivation to either commence or continue treatment (Molloy et al., 2014).

Among the kidney transplant population, unintentional non-adherence is significantly more common than intentional non-adherence (Griva, Davenport, Harrison & Newman, 2012). Of 218 kidney transplant patients, 62.4% of patients self-reported unintentional non-adherence, compared with 13.8% who reported intentional non-adherence. Unintentional non-adherence most commonly occurred when patients found themselves outside of their normal daily routine, and mostly involved taking medication at the incorrect time. This finding has been confirmed in other studies, where forgetfulness was identified as the most common reason for non-adherence (Loghman-Adham, 2003; Lalic et al., 2014). Intentional non-adherence occurred when patients had concerns about their medication regimen (Griva et al., 2012). In addition, patients diagnosed with depression reported

higher intentional non-adherence. Low beliefs in necessity of medications were predictive of intentional non-adherence, and necessity beliefs were more important than concerns about medication in determining adherence behaviour (Griva et al., 2012).

### 2.3 Rates of non-adherence in kidney transplant population

Research suggests that between 30-50% of medications prescribed for patients with long term conditions are not taken as prescribed (WHO, 2003; NICE, 2009). Non-adherence to treatment, notably immunosuppressant medication, has been identified as a common issue within the kidney transplant population. Dew et al., (2007) reported that non-adherence to immunosuppressants is one of the most regular areas of study and is among the highest non-adherence rates in solid organ transplantation. Previous systematic reviews have been conducted to explore non-adherence prevalence rates among renal transplant recipients reported in existing literature. In a systematic review of 36 studies, Butler et al., (2004) reported a median non-adherence rate of 22.3% (IQR 17.7-25.9%) for cross-sectional studies, and median non-adherence rate of 15% (IQR 4.7-19.5%) for cohort studies. A review of adherence assessment methods, their significance and prevalence of studies published from January 2009 to December 2014 analysed 37 studies and found non-adherence rates ranging from 1.6% to 96% (Belaiche et al., 2017).

Non-adherence to immunosuppressive drugs was a common problem and identified as a risk factor for late acute rejection and graft loss in kidney transplant recipients within a review summarising data from across 38 studies (Denhaerynck et al., 2005). Non-adherence prevalence rates ranged widely from 2-67% dependent on measurement method used, how non-adherence was defined and operationalised, and case findings. Additionally, a mean prevalence calculated over ten studies measuring non-adherence by self-report was 28%. Rates of non-adherence are higher in renal transplant patients compared with other solid organ transplant recipients, with non-adherence rates to immunosuppressants estimated at 36 cases per 100 patients per year (Dew et al., 2007). This rate is twice than among heart transplant recipients and over five times greater than among liver transplant recipients. A key question then arises as to why kidney transplant recipients appear to be less adherent

than other organ recipients? This may be because the risk and consequences of rejection and graft loss is less catastrophic than rejection of, for example, a heart or lung, where options for sustaining life following rejection are more limited (Dew et al., 2007). However, it should be noted that a systematic review of qualitative studies revealed that prevailing fear of consequences was at the forefront for patients, but there may also be some negotiation of acceptable risks coupled with trivialization (Jamieson et al., 2016). Dew et al., (2007) also found that the estimated rate of non-adherence to appointments was 5.8 cases per 100 patients per year, however, this was determined by a small number of older studies including kidney (N=11), heart (N=7) and heart/lung (N=1) transplant recipients. When explored individually by transplant type, this was shown to be lower for kidney (4.7 cases) compared to heart transplant recipients (8.5 cases). Overall, Dew et al., (2007) indicate that post-transplantation, clinicians can expect on average 23 non-adherent patients for every 100 solid organ transplant recipients during a one-year follow up. This has significant implications for health services in terms of managing the added burden that comes with the consequence of intentional or unintentional deviation from suggested regimens.

Adherence to immunosuppressants are essential for kidney transplant recipients to prevent rejection of the transplanted organ. A meta-analysis of 21 studies suggested a strong relationship between adherent behaviour to medication and treatment for a number of different illnesses and lower mortality rates (Simpson et al., 2006). Additionally, hospitalisation rates shown across patients with varying chronic conditions are lower among adherent patients (Sokol et al., 2005; Ho et al., 2007). The WHO (2003) report on medication adherence indicated that “increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments”. The odds of graft loss among non-adherent kidney transplant recipients is five to seven times greater than in adherent patients (Butler et al., 2004; Chisolm et al., 2007).

Non-adherence has consequences for both the individual in terms of personal costs, and additionally economic costs for society (NICE, 2009). Poor clinical benefit of medication is intimately related to a

lack of health improvement, and increased risk of morbidity and mortality for the patient. For society, medication wastage and increased costs on healthcare systems due to excess demands from patient ill health and deterioration are notable. In the UK context where health care is free at the point of need, there is an economic driver to improve adherence in transplant recipients. Kidney services consume 3% of the NHS budget. This is a sizeable proportion of budget as compared to the prevalence of kidney related conditions. The cost of treatment to the NHS between those receiving dialysis and those receiving immunosuppressant medication in subsequent years following transplantation are vastly different. Where dialysis costs on average £30,000 per patient per year, this can be compared to £17,000 for a kidney transplant and £5,000 per patient per year for immunosuppression required by a patient with a transplant. Therefore, kidney transplantation is suggested to lead to a cost-benefit in the second and subsequent years of ~£25,000 per annum (NHS England, 2013). As such, a non-adherent transplant patient risks graft failure, which adds excess burden to NHS resources as compared to doing the organ justice. Of course, there may be biological reasons impacting graft failure but research so far suggests that patient factors such as adherence behaviour also have a role to play. Morally, to do organs best service, patient adherence should also be ideal. Organ donation, both living and deceased, often has consequences e.g. emotional for donors and their families. For such reasons, donation is highly personal and indeed many governments try and keep a neutral stance on whether choosing not to donate is a 'bad thing' (Shaw, 2015). It could be argued that non-adherence, at least intentional, is a disservice to a donated organ and the donor. Curiously, research has shown that kidney transplant patients are more likely to be at risk of non-adherence when receiving organs from a live related donor (Denhaerynck et al., 2007). The personal, ethical and economic drivers make it paramount that effort is made to measure and support adherence behaviour.

#### 2.4 Measuring adherence

A number of different methods exist for measuring adherence, however, each method has strengths and limitations that require consideration when used and when interpreting results (Kreys, 2016). The measurement method used can impact non-adherence prevalence rates reported (DiMatteo, 2004). Existing methods can be categorised into two types: direct and indirect measurement, offering

differing levels of sensitivity (Osterberg & Blaschke, 2005). Direct measurements involve first-hand observation of, for example, medication intake and biological assay of medication levels or medication metabolites in biological fluids such as blood or urine (Osterberg & Blaschke, 2005). This method is considered to be more accurate, however, it is also more expensive, requires more time from health care providers and is a more complex measurement process. Based on this, it is a less suitable method to use when researching large populations.

Indirect measurements, such as self-report, collateral reports from family members or clinicians, electronic monitoring, prescription refills and pill counts to name a few examples, are more commonly used due to their less complicated nature in terms of implementation, and are generally less expensive (Osterberg & Blaschke, 2005; Schafer-Keller et al., 2008; Kreys, 2016). However, indirect measures, such as self-report, do not provide a clear and accurate representation of non-adherence rates and provide limited information on individual medication taking behaviour (Farmer, 1999; De Geest & Vanhaecke, 1999). A brief description and consideration of strengths and limitations of the different measurement methods are provided below.

*Self-report* measures can include, for example, questionnaires and diaries. These measurement methods are straightforward and easy to implement. Additionally, they are usually cheap to administer and feasible in most clinical settings (Schafer-Keller et al., 2008). However, limitations of this measurement method include susceptibility to recall and social desirability bias, notably via questionnaires. Furthermore, self-report measures tend to over-estimate adherence levels. DiMatteo (2004) found that self-report measures yield the highest non-adherence rates for immunosuppressant medication. Patients may also find expectations to regularly and continually answer questions or record their medication taking tiresome, providing potential barriers to recruitment processes (Kreys, 2016) and data accuracy. Diaries, although may be used to monitor medication taking, could be used as an intervention to improve adherence rates, and therefore may report higher levels of adherence compared to individuals not recording and monitoring medication taking via diaries or similar methods (Kreys, 2016).

**Pill counting** is a simple method to determine adherence to medication in tablet form. However, a limitation of this method is that it requires patients to bring their medication to every appointment with their health care professionals, and is reliant on patients not tampering with medication by storing or disposing of medication that has not been taken as prescribed (Schafer-Keller et al., 2008).

**Prescription refill** measurement methods do not require patient involvement and provides a naturalistic objective measure of adherence (Kreys, 2016). It can be used to assess adherence in large populations of patients and over multiple time points, such as longitudinal studies. However, limitations of this measurement method include lack of information on actual medication taking, as only information on collection of medication can be obtained. This method is suitable for observing adherence behaviour among patients with chronic conditions who require long-term medication, however, can be challenging to accurately track and record medications which require frequent changes to dosage, such as immunosuppressant medications – an essential medication for kidney transplant recipients. It also requires complete and accurate pharmacy records which can be difficult if patients are using a number of pharmacies for medication collection (Kreys, 2016).

**Electronic monitoring** including the medication event monitoring system (MEMs) are medication bottles which record every time the bottle is opened via a specialised microchip. Electronic monitoring is recommended as the reference standard for medication non-adherence (Cramer, 1995) that should be used to validate other adherence measures, as it can provide detailed information on individual(s) medication taking therefore providing a more accurate record of medication taking behaviour (Schafer-Keller et al., 2008). Additionally, reported adherence via MEMs are lower than self-reported adherence measures, and as self-reported adherence is often overestimated, medication adherence recorded via MEMs is considered to be a more accurate representation (Kreys, 2016). Furthermore, medication adherence rates recorded via MEMs have also been found to associate with clinical levels of medication in a number of treatment areas. However, this is provided that when patients open the bottle thus referencing a medication taking record, the medication is actually taken

and not discarded or transferred elsewhere. In addition, this method is expensive and often requires regular downloading of recorded information from the microchip. Furthermore, electronic monitoring could impact medication taking either negatively, by impacting established routines, or positively, by improving medication taking behaviour due to an intervention effect of being closely monitored (Deschamps et al., 2006), therefore effecting the validity of adherence rate reports. However, despite these potential limitations, due to its consideration as a superior method in measuring (non)adherence, it remains the reference standard (Schafer-Keller et al., 2008).

***Clinician reporting/Observations*** of patient's medication taking behaviour can be used as a marker of adherence. Recordings or reports of adherence can be monitored during routine visits with health care professionals. Regular monitoring e.g. of drug levels, may exist as part of routine treatment already by clinicians as a tool for monitoring treatment of illness or disease. This measurement method can verify adherence but, as with pill counts, requires patient-clinician interaction or meeting, requires familiarity with the patient and their treatment regimen (De Geest & Vanhaecke, 1999; Schafer-Keller et al., 2008), and is unable to explain the complexities of medication taking (Farmer, 1999). However, it may allow for severe non-adherence to be detected.

***Biological assay*** involves monitoring drug medication levels via e.g. blood levels. This measurement method portrays the patient's state of e.g. immunosuppression (Schafer-Keller et al., 2008). However, as every patient is individual and responds to medication in different ways including individual drug target levels, levels and assay, results can be impacted by a number of variables such as metabolic rate, drugs half-life, drug-drug interactions and "white-coat" adherence (i.e. patients demonstrating better adherence prior to clinical appointments or visits) (De Geest & Vanhaecke, 1999; Kreys, 2016). This can therefore make it challenging to determine non-adherence and accurate variance from medication prescription (Osterberg & Blaschke, 2005).

***Using a combination of adherence measures*** - The differing adherence measures mentioned above, although commonly used, often report variable rates of (non)adherence due to their individual

characteristics and definitions/cut-off points for non-adherence applied. Garber et al (2004) conducted a meta-analysis comparing a number of differing measures of adherence and found that less than half of the self-reported measures and non-self-reported measures were categorised as highly agreeable. Previous literature has indicated that utilising more than one method to measure adherence at the same time can improve accuracy of reported rates (Lam & Fresco, 2005) as using multiple methods can balance out measurement methods addressing limitations of individual measures (Kreys, 2016).

Across the previous literature within the kidney transplant population, there is a wide range of reported non-adherence prevalence rates. This is in part due to differences in measurement methods used and definitions of (non)adherence used (Schafer-Keller et al., 2008). Existing literature with transplant recipients has mostly used patient self-reporting as a method to measure adherence. Fewer studies have utilised direct measures, such as immunosuppressant blood levels, to measure non-adherence in existing transplant literature (Butler et al., 2004; Shemesh et al., 2004; O'Carroll et al., 2006).

Due to the importance of non-adherence to immunosuppressants in the kidney transplant population and the associated consequences, such as graft rejection and graft loss, Schafer-Keller et al., (2008) conducted a study to assess the diagnostic accuracy of adherence measures, including blood assay, self-report, collateral reporting and composite adherence scores (composite scores for combining various methods of non-adherence assessment) and compared these to electronic monitoring among adult kidney transplant recipients. All patients included were more than one-year post-transplant and taking immunosuppressants, with electronic monitoring data recorded. Findings showed a large variation in non-adherence prevalence rates across the differing measurement methods and cut-off points used. Additionally, the study assessed patient's adherence to one immunosuppressant drug only, which although providing a valuable indicator of medication taking behaviour, may not fully reflect adherence to the full immunosuppressive regimen (as patients often take a combination of two or three immunosuppressant drugs).

In addition, the approach highlighted as detecting the highest rate of non-adherence was the use of composite adherence scores, combining non-adherence information from patient self-reports, clinician or nurse's collateral reports and non-therapeutic blood assay results. Low sensitivity to non-adherence was reported when one measure only was used to record non-adherence, meaning it is likely truly non-adherent patients were not identified. High specificity was found to be best achieved by combining several methods, by combining a number of clinicians' reports of "fair" adherence, or by evaluating patients' self-reports. Schafer-Keller et al., (2008) concluded that for maximum validity, electronic monitoring should be combined with other measurement methods, as opposed to using it as a reference standard to evaluate them. These findings provide guidance on the efficacy of methods to measure adherence and some of the limitations and challenges with various measures that need to be considered in order to enhance understanding and detection of non-adherence, when researching in the kidney transplant population.

### 2.5 Models of non-adherence

As well as noting the occurrence of non-adherence, it is helpful to be able to conceptualise why such behaviour is frequent. There are a number of health psychology theoretical frameworks that have been used in previous literature to understand, predict and explain medication adherence (Munro et al., 2007) and are potentially useful in renal transplantation settings. The most commonly used models are social cognition, including the health belief model (Rosenstock, 1966; Becker & Maiman, 1975), theory of reasoned action (Ajzen & Fishbein, 1980) and theory of planned behaviour (Ajzen, 1991). Additionally, the self-regulation model (Leventhal, Nerenz & Steele, 1984) and the transactional model of stress and coping (Lazarus & Folkman, 1987) may be useful. Holmes, Hughes & Morrison (2014) suggest there are benefits to theory-led research findings that can then inform the development of interventions to improve adherence. This could be achieved through consolidating existing theories and behavioural models. In a meta-analysis of theory use in medication adherence intervention research, Conn et al., (2016) found that the models and theories most commonly linked to medication adherence were social cognitive theory, health belief model, transactional model, self-regulation model and motivational interviewing. However, a review of two of the most widely applied

theoretical frameworks in renal settings are reviewed as they may usefully inform the decisions taken in this programme of research when selecting methods to explore adherence in more detail.

### 2.5.1 Health Belief Model

The health belief model (HBM) is one of the most influential social cognition models to explain health behaviours (Rosenstock, 1966). The model was developed to predict preventive health behaviours and the behavioural response to treatment in patients both with acute and chronic illnesses. The model was developed further by Becker (1974) and applied to other health behaviours, such as medication/treatment adherence. The HBM suggests a set of core beliefs predicts behaviour. The original core beliefs are summarised in Table 2.1. According to the HBM, the core beliefs should be used as indicators of the likelihood that health behaviour changes will occur (Ogden, 2012).

Table 2.1: Components of the HBM.

<b>Components of the HBM</b>	<b>Definition</b>
<i>Susceptibility</i>	How susceptible the individual perceives they are to illness.
<i>Severity</i>	The perceived beliefs about the severity of the illness.
<i>Costs</i>	The perceived costs or negative aspects involved in carrying out the change in health behaviour.
<i>Benefits</i>	The perceived benefits involved in carrying out the change in health behaviour and the effectiveness of this.
<i>Cues to action</i>	The cues that cause or lead the individual to take action. These can be internal or external. This contributes to the individual's perception of threat.

The original model has been revised in response to criticism. The constructs “health motivation” and “perceived control” were added to the model as a result as part of further developments by Becker and colleagues. Health motivation refers to the individual's readiness to be concerned with health-related

issues, and perceived control refers to the individual's perceived control of the health issue and control over their ability to change their behaviour (Ogden, 2012).

The HBM effectiveness in predicting and explaining behaviour has been explored in previous literature via meta-analyses. In a meta-analysis of 18 studies, Carpenter (2010) found perceived barriers and benefits were the strongest predictors of behaviour. Perceived severity was found to be weakly predictive, and perceived susceptibility was found to be unrelated to behaviour. This is an interesting finding as perceived susceptibility is one of the most common constructs targeted via interventions (Jones, Smith & Llewellyn, 2013). The HBM has been used to inform the development and implementation of health behaviour change interventions, however, it is argued there is only weak evidence to support the HBM as being effective in predicting behaviour and behaviour change. This is due to the weakness of two constructs in predicting behaviour (Carpenter, 2010).

A systematic review of 18 intervention studies using the HBM as a theoretical basis to inform design explored the efficacy of these interventions to improve health care adherence (Jones, Smith & Llewellyn, 2013). Fifteen (83%) of the studies reported adherence to have significantly improved, with large effects reported in studies using health-care professional led interventions. Perceived benefits and perceived susceptibility were the constructs most commonly addressed via interventions, followed by perceived barriers. However, the review reported that success of the intervention was unrelated to the HBM constructs addressed and implemented. This finding is in contrast to some of the previous meta-analyses such as by Carpenter (2010), however, this review explored interventions to improve adherence behaviour only, whereas Carpenter (2010) reviewed studies exploring any health-behaviour. Most studies target certain constructs of the HBM, with very few studies using the HBM in its entirety when designing and implementing interventions. Jones, Smith & Llewellyn (2013) concluded in their review that evidence to support the use of the HBM in adherence enhancing interventions was weak, and this should be considered when developing interventions using the model.

The HBM has been used in previous literature to investigate treatment/medication adherence across a number of different chronic illness groups, including hypertension (e.g. Kamran et al., 2014), diabetes (e.g. Chao, Nau, Aikens, & Taylor, 2005) and renal disease (e.g. Kiley, Lam & Pollak, 1993; Welch, 2001). Kiley, Lam & Pollak (1993) found lower perceived benefits from the treatment regime to be associated with graft failure among renal transplant recipients. Elliott et al., (2015) found health beliefs associated with diet adherence among haemodialysis patients included perceived benefits and self-efficacy. Self-efficacy was the only health belief associated with phosphate control. Studies using the HBM have often found differing constructs or differing combinations of the HBM are predictive of adherence behaviour, rather than an effective interaction of the entire model (Holmes, Hughes & Morrison, 2014). Limitations of the model could explain some of the conflicting findings in studies using the HBM (Ogden, 2012). The model focuses on cognitive processing and fails to consider the role of emotional factors. Additionally, the model focuses on the individual and fails to include a component relating to the role of the environment. Health behaviours may be predicted by other factors, such as self-efficacy or potential prospective outcomes. Furthermore, the model suggests health behaviour change is due to individual factors, whereas there is evidence to suggest it is due to the perception of symptoms. Despite the limitations of the HBM, previous research has used the model to predict behaviour across a number of different healthcare contexts, including, for example, interventions to address screening of hypertension, exercise behaviours and smoking cessation.

### 2.5.2 Beliefs about Medicines

The beliefs about medicines questionnaire (BMQ) (Horne, Weinman & Hankins, 1999) was developed as an extension of the HBM. The measure was developed due to the need for a psychometric tool for operationalising and scoring beliefs that are commonly held about medication, assessing both specific and general beliefs about medication. The BMQ addresses the cost-benefit analysis of individual's perceived benefits and barriers of taking medication. The core themes that were identified in the development of the BMQ relating to medication prescribed for patients were: beliefs about the necessity of taking medication prescribed to maintain health (specific-necessity) and concerns about prescribed medication (specific-concerns). The BMQ-general scales indicated

negative views of medicines as overused (in terms of prescription by doctors) and harmful in the development of the measure.

Horne and Weinman (1999) used the BMQ to explore patients' beliefs about medicines and their role in adherence to treatment. This was explored using a chronic illness sample (N=324) of asthmatic, renal (haemodialysis), cardiac and oncology patients, chosen as adherence is known to be low in all four groups and to provide a representation of different conditions and treatment characteristics.

Findings showed specific beliefs about medicines were more predictive of reported adherence than clinical and sociodemographic variables, accounting for 19% of the variance explained in adherence.

A meta-analysis of studies (N=94) using the BMQ explored perceptions of necessity for medication and concerns about possible side-effects (known as necessity-concerns framework) in relation to a measure of adherence to medication in patients with long-term conditions (Horne et al., 2013).

Findings showed greater adherence levels were associated with stronger perceptions of the necessity of the treatment, and fewer concerns about treatment medication. This framework could therefore be useful to further understand patients' views on prescribed medications, providing clinicians with information to increase patient involvement in treatment decision making to support adherence.

### 2.5.3 Self-regulation model

The self-regulation model (SRM) of illness cognition and behaviour was proposed by Leventhal, Nerenz and Steele (1984). It is often referred to as the common-sense model (CSM) due to its emphasis on personal, common-sense beliefs about illnesses. The model focuses on how individuals perceive and monitor behaviour over time to cope and make progress towards their goals. Research has identified the cognitive representations and behaviour that form illness representations (Moss-Morris et al., 2002; Broadbent, Petrie, Main & Weinman, 2006). Illness representations refer to organised beliefs surrounding an illness, following an illness threat. These beliefs guide coping procedures in an attempt to control the illness threat. Illness representations stored in memory are activated by stimuli (e.g. symptoms of disease). A summary and representation of the persons condition is created through considering current symptoms and context-based information, and then

matching this to pre-existing beliefs. This then informs coping and therefore which coping behaviours are selected to manage the current condition. The outcomes of these strategies are then reviewed in relation to how well they control the illness and e.g. symptoms. The outcomes of these evaluations result in changes and refinements of the illness representations and the adoption of new coping behaviours. The model consists of five key components of illness representations (Cameron & Moss-Morris, 2013). Table 2.2 summarises the definitions of the five key components.

Table 2.2: Illness representations of the self-regulatory model.

<b>Illness Representation</b>	<b>Definition</b>
<i>Illness identity</i>	The illness label or diagnosis used by the patient and associated symptoms attributed to the illness.
<i>Consequences</i>	The perceived or expected effects of the illness and outcomes such as physical, social and psychological well-being.
<i>Timeline</i>	The perceived expected duration of the illness, whether the illness is perceived to be acute, cyclical or chronic (long-term).
<i>Control or cure</i>	The perceived controllability and curability of the illness through treatment measures and behaviours.
<i>Cause</i>	The perceived causal factors or conditions of the illness.

Later versions of the model (Illness perceptions questionnaire-Revised: IPQ-R) have included further components representing perceptions in relation to illness coherence (understanding of the illness), the cyclical timeline of illness (symptoms can be acute, cyclical or chronic) and emotional representation (Moss-Morris et al., 2002). Illness concern (perceived concerns about the illness) has also been included in refined versions of the scale (Brief IPQ) (Broadbent, Petrie, Main & Weinman, 2006). The original illness perceptions questionnaire only investigated cognitive components, and therefore it was felt that this did not fully encompass patients' responses to illness. The IPQ-R was therefore developed to address this issue and the Brief IPQ later developed to provide a more concise version to measure illness representations.

The SRM suggests that how patients perceive their illness may influence how they manage it, including adaptation, coping and health behaviour. Previous literature has highlighted that patient behaviour is influenced by illness representations and could therefore be used to inform interventions in chronic illness groups (Petrie, Broadbent & Meechan, 2003). A meta-analysis of 45 empirical studies explored the intercorrelations between components of the SRM and categories of coping strategies finding significant relationships between certain illness representations and certain categories of coping strategies, and additionally between certain illness representations and illness outcomes (Hagger & Orbell, 2003). Specifically, they found perceptions of controllability/curability positively associated with cognitive reappraisal, problem-focused coping and emotion expression.

Existing literature has explored illness perceptions across a number of different chronic illness groups. Much research has been conducted in renal settings, notably dialysis patients. Illness perceptions has been associated with survival in haemodialysis patients, with treatment control predicting survival and reducing the risk of death by 11% (RR=0.91) (Chilcot, Wellstead & Farrington, 2011). Additionally, illness perceptions have been linked to psychosocial outcomes, including quality of life and depression in this patient population. Depression has been associated with lower perceived control and illness coherence and greater perceived consequences (Chilcot, Wellstead, Davenport & Farrington, 2011). Furthermore, quality of life is shown to be significantly lower in dialysis patients in comparison to the general population (Fowler & Baas, 2006), with quality of life associated with greater consequences, lower personal control and strong illness identity (Timmers et al., 2008).

Existing evidence has also explored illness perceptions in relation to adherence to treatment across a large number of different chronic illness patient populations. For example, in diabetes, medication adherence was associated with lower perceived consequences, higher personal control, fewer illness symptoms and lower distress levels (Broadbent, Donkin & Stroh, 2011). Hypertension studies have shown lower personal control, a strong sense of concern over illness and emotional reaction to illness to be associated with lower adherence levels (Ross, Walker & McLeod, 2004). In renal settings,

negative illness perceptions of disease have been associated with non-adherence to dietary restrictions in haemodialysis patients (Kim & Evangelista, 2010). Much of the literature within renal settings exploring illness perceptions and adherence has been among dialysis patients, less has been conducted in the kidney transplant population. Griva et al., (2012) found receiving a kidney transplant lead to greater positive perceptions of illness identity, consequences, intrusiveness and controllability, compared to receiving dialysis. Higher adherence has also been associated with higher perceived personal control and emotional response, and greater perceived consequences associated with non-adherence (Massey et al., 2013). Additionally, poorer illness perceptions have also been associated with lower quality of life and psychological distress (Knowles et al., 2016). As non-adherence to immunosuppressants is recognised as such a problematic issue within the kidney transplant population with potentially serious consequences, it would be beneficial to further investigate whether illness perceptions could play a role in non-adherent behaviour. Perhaps even more useful would be to track illness perceptions pre-transplant and over a longitudinal course post so that we are better informed about some of the reasons that patients may start to negotiate risks over-time (Jamieson et al., 2016).

Much of the existing literature in this area is cross-sectional in design, therefore longitudinal studies are needed in order to follow patient's treatment journeys and experiences from long term condition diagnosis to treatment management and self-management. It is also important to note that most long-term conditions have differing aetiology, trajectories and treatments. Experiences may therefore be varied across different long-term condition populations. As a result, illness representations associated with coping with long term conditions may vary across diseases. Evaluation of findings in relation to illness representations should therefore potentially be considered in respect to individual long-term conditions.

## 2.6 Summary

Adherence post kidney transplantation is essential for the patient, economy and society. It is essential to understand adherence behaviour more in this patient group to drive better outcomes and value for health services and organ donors alike. There are a number of different ways to measure adherence,

each associated with strengths and limitations. Although electronic monitoring is considered the most valid measurement method for adherence and should be used as a reference standard, previous literature has indicated a combination of measurement methods may be more reliable. Within this programme of research, different measurement methods will be used to assess (non)adherence to treatment across studies. These include clinical markers via blood assay, treatment and clinic attendance and self-reported adherence.

Previous literature has used health psychology models to understand and explain non-adherent behaviour. Questionnaire measures have been created associated with these models which have been validated and commonly used in previous research across a number of different chronic illness populations, including in renal settings. Within this programme of research, measurement methods informed by some of the health psychology models, such as the HBM and SRM, will be used to explore (non)adherence to treatment regimens in kidney transplant recipients. The following chapter provides an overview of the general methodology employed within the programme of research for this thesis.

## Chapter 3: General Methods

### 3.1 Introduction

The methodological features that relate to the studies within this programme of research are summarised within this chapter. The thesis overall aims to report a series of studies that are designed to assess different elements of adherence in renal transplant recipients. This will be achieved through:

- A systematic review of existing research on adherence in this patient population.
- Retrospectively considering the relationship between pre and post-transplant adherence in haemodialysis patients who later go onto receive a kidney transplant.
- Qualitative enquiry of the views and beliefs of clinical staff in relation to the importance of adherence for kidney transplant wait listing.
- Cross-sectional data collection with transplant recipients to unearth more about their belief structures that may help understand adherence behaviour.

A mixed-methods approach is being advanced. In summarising the thoughts of the main leaders in the field, Johnson et al., (2007, p118) state that “mixed methods research is the type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purpose of breadth and depth of understanding and corroboration”. It is recognised that adherence behaviour is likely complex, with intentional and unintentional factors from the patient side. It is also important to acknowledge that patients are placed within a health care system with providers also holding their own beliefs, structures and processes which may directly or indirectly also impact patient behaviour. In order to drive attempts at strengthening self-management in patients for medicine taking, it is useful therefore to gain data that is rich in different perspectives and that which allows for scoping patterns in behaviour as well as depth of experience. As such, mixed-methods is the approach used within the thesis. It draws on a range of methodological paradigms- systematic review methods, questionnaires, descriptive data audit, and qualitative

interviews. The focus of this chapter is on clearly defining the patient population of interest, alongside an overview of each of the research designs being used within individual elements of the thesis.

### 3.2 Patient population

The kidney transplant patient population was chosen for the focus of this programme in recognition that much of the research surrounding patients treated for end stage renal disease tends to feature those receiving dialysis. Since transplantation is considered the ‘gold standard’, this perhaps reflects a bias in research driven by the known challenges that are associated with dialysis. However, as discussed previously, there are a number of patient, societal and economic factors that should drive focus on adherence in transplant recipients. Literature to date in the kidney transplant population has highlighted that there are many complexities surrounding the treatment and follow-up process, notably non-adherence to immunosuppressants (Denhaerynck et al., 2005). The evidence clearly indicates that non-adherence to immunosuppressants is a major risk factor for poor clinical outcomes, including graft rejection and graft loss (Loghman-Adham, 2003; Butler et al., 2004) and that patients are informed of these consequences. However, despite this awareness, non-adherence remains a prevalent issue. This research programme was therefore designed to gain a deeper understanding of this issue from both patient and medical professionals’ perspectives. In terms of justice to donated organs, the thesis was specifically interested in mapping patterns of pre and post-transplant treatment adherence to unearth whether any issues can be anticipated in advance of solid organ transplantation and how much clinicians prioritize adherence behaviour before listing for transplantation. Factors that impact transplant recipients in intentional or unintentional non-adherence were also of interest, all following on from a comprehensive mapping of studies that have considered adherence in the kidney transplant setting. It is hoped that the body of research reported in this thesis would pave the way for targeted interventions that support clinical staff and patients to partner in enhancing adherence and ultimately health related quality of life and organ longevity.

All patient data included in this programme of research were collected from Lister Hospital, East and North Hertfordshire NHS Trust. The post-transplant service cares for nearly 400 patients. On average,

60-70 patients are transplanted each year, with up to 30% of these from living related/unrelated donors. Patients are cared for pre and post-transplantation, however, receive their kidney transplant elsewhere as Lister Hospital is not a transplanting centre. The kidney transplant team prepare patients and prospective live donors for transplantation via assessment and work-up, including providing information, observations and testing, before handing over to the transplant centre. Patients can be transplanted at one of three hospitals, Addenbrookes Hospital (Cambridge University Hospitals NHS Foundation Trust), Royal Free London NHS Foundation Trust or West London Renal and Transplant centre, Hammersmith Hospital (Imperial College Healthcare NHS Trust), with most patients transplanted at Addenbrookes Hospital compared to the other centres. Additionally, the majority of patients are transplanted following receiving HD. Between April 2013 and March 2016, of these three transplant centres, Addenbrookes Hospital was shown to have the shortest median waiting time to adult kidney transplant (95% CI 266-362 days), followed by Royal Free London (95% CI 611-843 days) and West London Renal and Transplant centre (95% CI 873-1061 days) (NHS Blood & Transplant, 2019). Patients return to Lister Hospital for post-transplant follow-up care once discharged from their transplanting centre. This is often between three and six months post-transplant.

### 3.3 Study Methodology

#### 3.3.1 Systematic review (Study 1)

Existing literature clearly indicates that non-adherence to immunosuppressant medication is a major risk factor for poor outcomes post transplantation and is a common issue among renal transplant recipients. Three core reviews have previously been published in 2003 (Jindal et al., 2003), 2004 (Butler et al., 2004) and 2017 (Belaiche et al., 2017), which aim to highlight the prevalence and extent of non-adherence in the kidney transplant patient population. Recognition of non-adherence as a problematic issue with potential serious consequences in renal care settings has resulted in increased research interest in recent years and subsequently a larger evidence base. Prior to planning and commencing any empirical studies for this programme of research, it was essential to highlight what existing literature had identified as key issues leading to non-adherence in this patient population. An

updated synthesis of the current existing body of literature in this area was therefore deemed necessary to gain a better understanding of non-adherence to immunosuppressants in the kidney transplant patient population.

It was considered that in addition to informing the programme of research for this thesis, the results from a review would be useful for clinical practice as a guide to inform the nature of interventions to address this issue. The results of an updated review in this area could provide a greater understanding of prevalence rates of non-adherence, methods employed for measuring adherence and factors impacting on non-adherence behaviour. Importantly, an updated review would take account of the proliferation of research into psychosocial factors that impact on patients- particularly as health psychology as a discipline has seen a rapid rise in the last decades (Thielke, Thompson & Stuart, 2011). Since the previous three reviews, it is also interesting to note any changes in the way that adherence has been reported across studies e.g. single versus multiple methods and cost effective versus accuracy trade-off.

A systematic review of quantitative studies was considered the best method for synthesising the existing literature on this topic area. The specific aims of the review were as follows:

1. Summarise the methods used to assess non-adherence and discuss how non-adherence is operationalized across studies.
2. Identify the prevalence of non-adherence by pooling data from across studies and consider whether reported non-adherence varies as a function of measurement source.
3. Provide a narrative summary of the main factors associated with non-adherence.

Systematic reviews involve comprehensive and detailed planning and a search strategy devised a priori (Uman, 2011). The aim is to reduce bias by identifying, evaluating and synthesising all existing literature on a topic area. Systematic reviews often follow a set of stages (Uman, 2011) and these were applied in this thesis as outlined below:

1. ***Formulating the research question*** – Defining a research/review question, devising a hypothesis and defining the systematic review title.
2. ***Defining inclusion and exclusion criteria*** – Defining inclusion and exclusion criteria so it is clear what types of studies should be included and excluded. PICO (population, intervention, comparison, outcomes) can be useful when determining this, and is often used to determine the key concepts prior to starting a review.
3. ***Developing a search strategy and locating studies*** – Developing a list of key search terms relating to each concept relating to your review question. These can be free text terms or specific key terms, such as MeSH terms (medical subject headings). Searches are often conducted in electronic databases, searching reference lists, considering grey literature, hand searching key journals or personal communication with experts in the field.
4. ***Selecting studies relevant for inclusion*** – Titles and abstracts of citations identified through the searches are reviewed to determine studies that appear to meet inclusion criteria and therefore need to be retrieved for full-text review. Full texts are then screened to determine studies that meet inclusion criteria for the review. This stage is usually completed by two reviewers to ensure inter-rater reliability.
5. ***Extracting data*** – Data is extracted from each of the studies relevant for inclusion in the review. This is usually extracted into a data table. Again, this stage is usually completed by two reviewers to check for data entry accuracy and to avoid errors, and to ensure inter-rater reliability.
6. ***Assessing study quality*** – Studies included in reviews are assessed for study quality via a quality assessment tool. Various quality assessment tools exist, and reviewers will choose an appropriate tool dependent on the type of review undertaken. Again, this stage is usually completed by two reviewers to ensure inter-rater reliability.
7. ***Analysing and interpret findings*** – Narrative summaries of the findings including key features of studies included relating to the review question are synthesised and interpreted. Data from independent studies can be combined, known as meta-analysis. Meta-analysis uses statistical techniques to synthesise data from a number of studies into one quantitative

summary effect size or estimate. Included studies of the same topic reporting similar data can be examined to determine overall trends. Meta-analysis is often included in systematic reviews when appropriate data is available to analyse.

- 8. *Disseminating findings*** – Summarising the findings and providing recommendations for future research or informing practice.

Knowledge and training on conducting systematic reviews appropriately was supported in two main ways. The researcher already had some prior experience from an MSc which included learning the principles of running a systematic review and conducting a mini systematic review as part of the required assessments. Additionally, support was provided from colleagues with expertise in designing and running systematic reviews and meta-analyses. These methods also underwent external review during publication of the protocol (Hucker et al., 2017) for the review.

Following identification of the aims and research questions for the systematic review, the inclusion criteria was determined. Studies eligible for inclusion were quantitative studies (excluding interventions) that measured non-adherence to immunosuppressants among adult kidney transplant recipients aged 18 years and over. A search strategy was developed by consulting existing relevant review search terms, previous literature and experts in the patient population and topic of adherence. A combination of free text and medical subject heading (MeSH) search terms were used in all databases. Appropriate MeSH terms used were identified via the PubMed index. Electronic databases in which the search strategy was run, such as PubMed and Scopus, were selected based on University or free access availability. Lateral search techniques, including checking reference lists and searching for grey literature, were also used to ensure all potentially relevant articles were captured.

The search strategy was run in each of the selected databases and citations imported into Endnote reference management software. Following removal of duplicates, the titles and abstracts were screened to identify suitability for inclusion. These were organised into three folders for full text screening: “yes” title and abstract appear to meet inclusion criteria, “maybe” meets inclusion criteria,

“no” clearly does not meet inclusion criteria. The full texts of citations allocated to the “yes” and “maybe” folders were subsequently accessed for review. A screening proforma (inclusion/exclusion table) was used to assist with the full text screening process. Questions based on the inclusion criteria were included in the table to assist the screening process and to easily determine which citations were relevant for inclusion. This provided a clear record of which citations were relevant for inclusion, as well as which were excluded and why. A data extraction form was used to extract the relevant information from each study to be included in the review. Studies were rated for quality assurance using the Downs & Black (Downs & Black, 1998) checklist. A detailed summary of the systematic review methodology is provided in Chapter 4 of this thesis.

In addition to providing a narrative summary of the findings from the eligible studies included within this updated review, meta-analysis was also used to pool together study outcomes to assess prevalence of non-adherence rates across studies. Endnote V7 was used to import and screen citations.

Recognising the ‘Open Science’ movement that is gaining momentum in many disciplines, including Psychology, the review methods were pre-registered on Prospero - an open access online database for systematic review protocols that are in health-related areas. The systematic review protocol was also published in the BMJ Open (Hucker et al., 2017). Open science encompasses a range of practices aimed at making science more reliable, including wider availability of research data and materials, valuing replicability, consideration of power in relation to statistical analysis, the use of double-blind peer review and the use of open access publishing (Allen & Mehler, 2019).

### 3.3.2 Retrospective data analysis (Study 2)

A retrospective research design involves starting the study after data collection or follow-up has been completed. Eligible participants are identified retrospectively, and data measurements are retrieved to form a baseline. Following this, the data for the research is assessed and studied during the historical observation period, for example disease occurrence or death (Euser, Zoccali, Jager & Dekker, 2009). There are strengths and weaknesses to this type of methodology. A strength of retrospective studies is that data collection can be completed more quickly and can be used to answer new research questions

using existing data. Limitations include that data is not collected in real time and researchers can only use data that has previously been measured and recorded, often for a different purpose or different research study.

There is much previous literature exploring non-adherence in haemodialysis patients, and the impact this has on patient's physical well-being, quality of life and outcomes, including mortality.

Additionally, the same can be said for research exploring non-adherence to immunosuppressants among kidney transplant recipients including graft rejection and graft loss (Loghman-Adham, 2003; Butler et al., 2004). Limited research has explored if there is a relationship in patterns of adherent/non-adherent behaviour in patients when on haemodialysis and again following kidney transplantation i.e. within patient variability across different treatment modalities. It was considered important to assess if non-adherent haemodialysis patients become non-adherent transplant recipients since a high percentage of HD patients can be expected go on to receive a donor organ. Within a year of starting dialysis, 45% of patients under 65 years are listed for a transplant (Renal Registry, 2014). This increases to 57% by two years, and 66% by five years. Clinical data from electronic patients' records was used to assess such within patient adherence patterns across treatment types. Clinical data collected as part of routine care can provide accurate measurements and representations of patient's behaviour. As these measurements are taken regularly at treatments and appointments, it provides evidence of behaviour over time and therefore potential patterns of behaviour. However, as mentioned previously, every patient is individual and responds to medication in different ways including individual drug target levels, levels and assay, and so results can be impacted by a number of variables and should be interpreted with caution (De Geest & Vanhaecke, 1999; Schafer-Keller et al., 2008; Kreys, 2016). Notwithstanding this, such data is cost effective and the method represents a less intrusive approach to addressing an important question. As the treatment and medications required for haemodialysis patients and transplant recipients are different, markers and measurements of (non)adherent behaviour vary pre-transplant, when on haemodialysis, compared to post-transplant. Effort was made to address this difference when interpreting findings from retrospective data analysis.

In clinical data, there is no standardised methodology for defining and measuring (non)adherence. Previous literature was used as a guide to develop criteria (Leggat et al., 1998; Saran et al., 2003; Hecking et al., 2004; Schafer-Keller et al., 2008; Wileman et al., 2011). This included using data such as time actually spent on dialysis during a session, compared to prescribed time, dialysis attendance and medication taking of phosphate binders as measurements for pre-transplant adherence to haemodialysis, and immunosuppressant drug levels and attendance to clinic appointments as measurements for post-transplantation adherence. Explanations of the definitions, measurements and cut-off points used, including how these measurement values were determined and calculated using the clinical data from electronic records are described in chapter five of this thesis.

### ***Research questions***

To examine the relationship between clinical measures of pre-transplant adherence to haemodialysis and clinical measures of post-transplant adherence, the following research questions were addressed:

1. Do non-adherent haemodialysis patients become non-adherent transplant recipients?
2. Are there particular patterns of non-adherence to haemodialysis which are more likely to associate with poor adherence following transplantation?

### 3.3.3 Qualitative Interviews (Study 3)

Qualitative research is now recognised as important in understanding human behaviour and psychological experiences (Rohleder & Lyons, 2015). In health and medical settings, it is considered as a way of understanding the perspectives, experiences and contexts of illness and well-being from the patient's viewpoint. Where quantitative research aims to answer a pre-determined hypothesis using statistical and/or experimental research methods, qualitative research uses in depth and rich data to answer questions on experiences and meaning, to develop ideas or hypotheses, or in health and medical settings for example, to inform clinical practice. The most common forms of data collection in qualitative research is in-depth interviews, focus groups and observations, with the most widely used in psychology being individual interviews with participants (Lyons, 2015).

Interviewing can be used to understand the lived experiences of others, and the meanings that they make of that experience (Seidman, 2006, as cited in Lyons, 2015). There are different styles of interviewing, including structured, semi-structured and non-directive (unstructured) (Lyons, 2015). Structured interviews are quick to capture data and uses a pre-prepared interview schedule that is followed exactly as written. Interaction is often kept to a minimum. The interview is interviewer-led (Adhabi & Anozie, 2017) and is easy to analyse. Often, structured interviews are a precursor to more open-ended discussions, such as non-directive (unstructured) interviews. Semi-structured interviews can be slow and time-consuming to capture data and to analyse. A list of questions (interview schedule) is devised along with probes (Jamshed, 2014). Probing of views can be used to encourage participants to expand on their responses. The interview can be interviewer-led or interviewee led, allowing give and take within the discussion. Participants are able to respond to questions and probes as they see fit with minimal interference. Not all questions devised may be asked, and additional questions can be included by the interviewer. This type of interview style allows for exploration of subjective meaning. Non-directive (unstructured) interviews are used to explore topics in depth, however, questions are not usually pre-planned (Gray, 2018). There are objectives to the research and what will be addressed. Participants are allowed to talk freely, and interviewer input is kept to a minimum. The interviewer may check or rephrase answers to ensure understanding. This style of interview can be more challenging to analyse. Of these interview styles, semi-structured interviews are most commonly used in qualitative analysis especially in healthcare and medical settings (Dejonckheere & Vaughn, 2019) and were utilised in this thesis. This approach, in the context of CKD and transplant more specifically has already been successfully applied. For example, several studies have gleaned insights into patient experiences, such as positive and negative consequences of transplantation (Schipper et al., 2014) and with medical professionals research using semi-structured interviews has yielded studies exploring, for example, perceptions around self-management by kidney transplant recipients (Ndemera & Bhengu, 2018) and barriers to living donor kidney transplantation (Sandal et al., 2019).

The one-to-one interviews were integral to understanding clinicians' and healthcare professionals' views surrounding non-adherence in the kidney transplant population. The interviews provided rich and detailed data from staff perspectives on non-adherence, techniques that are or should be implemented to improve adherence, and the importance of non-adherence in patient eligibility for transplantation. One-to-one interviews were deemed appropriate over group interviews or focus groups to explore this topic area as the research was interested in the views of diverse staff from differing positions and it was felt that they may feel more comfortable on a 1-1 basis. This also avoided a power imbalance e.g. that may occur between transplant surgeon and nurses, senior medical staff versus junior.

The growth of technological platforms has led to a range of interview modes such as face-to-face, telephone, skype, written interviews over email, and can be synchronous (conducted with the researcher and the participant at the same time) or asynchronous (where the researcher and the participant are not completing the interview at the same time e.g. via email). Face-to-face interviews were chosen to ensure rapport development and flow, and to allow for non-verbal cuing and body language to be identified and responded to appropriately during the interview. With consent from participants, all interviews were audio recorded. Transcription of the interviews was conducted verbatim, that is, interviews were transcribed word for word.

Thematic analysis as described by Braun and Clarke (2006) was used to analyse the one-to-one interviews. Thematic analysis provides a systematic method for identifying patterns of meaning (themes) across a data set (Braun & Clarke, 2012), and can be used to understand mutual and shared experiences and meaning. Thematic analysis aims to look for similarities or commonalities in relation to a topic area across a whole data set. Themes identified from the data are related and help answer the research question. Thematic analysis offers flexibility to the researcher and can report on semantic meanings of data or latent meanings (the assumptions or meaning underpinning what is actually being stated by the participant). Additionally, it can be used within different theoretical networks (Braun & Clarke, 2006). Due to this flexibility, thematic analysis was considered as the appropriate form of

analysis for this programme of research compared to other alternative forms (such as Grounded Theory, Discourse Analysis, Interpretative Phenomenological Analysis or Narrative Analysis) which are related to pre-existing theoretical frameworks and/or assumptions. There are a number of different ways in which thematic analysis can be conducted which span across three continuums: inductive vs deductive; realist vs. constructionist and semantic vs. latent. A summary of each approach is provided below (Braun & Clarke, 2006; Braun & Clarke, 2012):

***Inductive vs. deductive thematic analysis:***

- ***Inductive*** – Bottom-up approach. Analysis is data-driven and does not fit a pre-existing coding framework. Coding and themes are derived from the data content.
- ***Deductive*** – Top-down approach. Analysis is driven from pre-existing concepts/ideas/topics. Coding and themes are derived from existing theoretical concepts and ideas.

***Semantic vs. latent themes:***

- ***Semantic*** – Codes and themes are derived from explicit or surface level meaning. Analysis is descriptive does not go beyond what has been said or written.
- ***Latent*** – Goes beyond semantic content and considers deeper meaning. Codes and themes are derived from underlying ideas, assumptions and conceptualisations. Analysis and theme development involves interpretation.

***Essentialist/realist vs. constructionist epistemology***

- ***Essentialist/realist*** – Analysis reports reality of participants data, including experiences and meanings.
- ***Constructionist*** – Analysis reports how experiences, meanings and realities are an effect of conversations and discussions within the wider society, therefore socially produced/reproduced.

Coding and analysis can use a combination of approaches. However, this programme of research adopted an inductive thematic analysis approach, due to the lack of previous literature in relation to clinician/health care professionals understanding and experience of non-adherence, as experienced by kidney transplant recipients. Additionally, there is little evidence of the importance of non-adherence in transplant eligibility for transplantation. Latent themes were developed considering the ideas and concepts underpinning the data.

In doing qualitative research, it is essential for a researcher to acknowledge their own position in relation to the topic area. Reflexivity is important for developing awareness of how the researcher may have informed the research, for example, considering personal circumstances, identity and experiences (Dodgson, 2019). Recognition that the researcher brings subjectivity to the research process should be viewed as a strength, rather than a weakness.

In order to ensure quality in qualitative research, tools and criteria's have been developed to assess quality. One example includes the COREQ (COnsolidated criteria for REporting Qualitative research) developed by Tong, Sainsbury & Craig (2007) as a formal reporting checklist for in depth interviews and focus groups (often the most common form of qualitative data collection in health research). The aim of the checklist is to improve rigor, credibility and comprehensiveness of interview and focus-group research, and to promote clear reporting among researchers.

There are six phases to conducting thematic analysis (Braun & Clarke, 2006):

1. ***Familiarisation with the data:*** Immersing with the data to ensure familiarisation with breadth and depth of content. This involves reading and re-reading the data in an active way, searching for meanings and patterns. Data should be read through at least once prior to coding (phase 2). Note taking or initial ideas about what is in the data can be marked down during this phase ready for coding.

2. **Generating initial codes (coding):** Production of initial codes from the data. This stage involves generating codes for interesting and important features of the data. The entire dataset is coded in a systematic fashion collating relevant codes and data extracts ready for further phases of analysis.
3. **Searching for themes:** Evaluating and collating the different codes into potential themes, and collating relevant coded data extracts with the relevant identified potential themes. Here the researcher is analysing codes and exploring how they could be combined to form an overarching theme. This phase also involves considering the relationship between codes, themes and between different levels of themes (e.g. themes and sub-themes). Initial codes may be used to form main themes, sub-themes or may be discarded. The phase ends with a group of candidate themes, sub-themes and data extracts coded in relation to these to be reviewed in the subsequent phase.
4. **Reviewing themes:** This phase involves refinement of the themes generated in phase 3. Candidate themes are reviewed against the data to ensure there is enough data to support them and answer the research question(s). Themes may be combined, refined and separated, or discarded during this phase. Data within themes should be related in a meaningful way, and there should be clear and distinct differences in data between themes. By the end of the phase there should be a clear understanding of the different themes, how they may fit together and the story they tell in relation to the research question(s).
5. **Defining and naming themes:** Define and further refine themes, and analysing data within them. This means capturing and identifying what the underlying essence of each theme is about and the focus. The “story” of each theme is identified both within the theme and in the broader context of the data in relation to the research question(s), ensuring no overlap between themes. This phase also involves clearly defining and naming the themes.
6. **Producing the report (writing up):** This final phase involves the final analysis and write-up of this in a report. The analytic narrative and data extracts should be used to provide a concise and interesting representation of the “story” the data tells both within and across themes. Use of data extracts (quotes) should be used to indicate the prevalence of each theme. The analytic

narrative should go beyond simply describing the data, and provide an argument in relation to the research question(s) relating to previous literature in order to contextualise the findings.

This process was followed during analysis of the one-to-one qualitative interviews. All analyses were conducted in NVivo version 12.

The researcher had prior experience of qualitative research through both undergraduate and MSc studies which included learning about qualitative research and analyses techniques, completing an advanced qualitative research methods module and undertaking a mixed-methods dissertation using thematic analysis. Training sessions on how to use NVivo to support qualitative analysis were also completed. Additionally, support was provided from members of the PhD supervisory team who have expertise in qualitative research and analyses.

### ***Research questions***

Semi-structured interviews with clinicians working closely with adult renal transplant recipients aimed to address the following research questions:

1. How do clinicians understand the term non-adherence in relation to renal transplant recipients?
2. What factors do clinicians believe influence adherence to treatment regimens following transplantation?
3. How important is patient adherence to clinicians when determining eligibility for transplantation?
4. Do clinicians believe non-adherent patients pre-transplant are likely to be non-adherent post-transplant?

#### 3.3.4 Cross sectional questionnaire (Study 4)

Self-reported questionnaires are easy to administer and feasible in most clinical settings (Schafer-Keller et al., 2008). Due to this, data can be collected from a large number of participants during a

short period of time. This makes cross-sectional questionnaires an important methodology to elucidate patterns in patient behaviour and predictors of the same. A core aim of the thesis was to pave the way for more attempts at intervening to help strengthen adherence behaviour. As such, a questionnaire study was designed in order to glean relationships between patient beliefs about their treatment and how this might relate to self-reported adherence. Notwithstanding the limitations of self-report measures, these are the most pragmatic way to assess adherence behaviour especially in clinical settings where time and resource pressures are real. Bringing together core themes from the thesis and existing literature, a study was designed to explore how beliefs about immunosuppressants and towards medication in general, illness representations and clinical factors related to self-reported adherence among kidney transplant recipients. Due to limited previous literature exploring psychological factors such as these on adherence among this patient population, this study aimed to identify predictors of adherence/non-adherence, potentially highlighting areas which could be targeted for intervention to improve adherence behaviour.

Validated measures were chosen for use in this programme of research that have previously been used and tested in the transplant population. Permission to use the questionnaires was sought from the original developer for those not in the public domain.

Due to the infrequency of hospital appointments, the optimum time to collect questionnaire data from kidney transplant recipients is when they are attending for a clinic appointment to check their transplant function etc. During this visit, patients often have to wait to be seen by a consultant nephrologist, and therefore have time between having their observations taken (e.g. blood pressure and weight) and being called for their appointment. This time was therefore seen as the optimum recruitment period. In order to ensure relevance of the study focus and acceptability of measures, the public involvement in research group (PIRg) hosted within the school of health and social work at the University were consulted for feedback on the appropriateness and feasibility of the final questionnaires chosen for administration. The PIRg group aims to provide feedback and a direct voice

from service user's experiences in contributing to the development of research projects. A summary of the questionnaires used within this programme of research are detailed below.

### ***Medication adherence report scale (MARS-5)***

The medication adherence report scale (Horne & Weinman, 2002) was used to assess adherence to immunosuppressant medication among renal transplant recipients. The wording of the questionnaire items was adapted to fit this context as is common practice. Adherence is commonly explored within chronic illness populations, as often non-adherence can have serious consequences in terms of treatment, quality of life and life expectancy. Various self-report questionnaires have been devised to measure adherence. The MARS elicits patient's reports of non-adherence and originated as a 9-item scale, however, a reduced five item version was created providing for a more concise version of the measure (Horne & Weinman, 2002). The scale assesses both intentional and unintentional non-adherence. Questions assessing unintentional non-adherent behaviour include: "I forgot to take them". Questions assessing intentional non-adherent behaviour include: "I alter the dose"; "I stop taking them for a while"; "I decide to miss out a dose"; "I take less than instructed". Each question is rated on a five-point scale ranging from 1 (very often) to 5 (never). Scores are then combined to give a total score ranging from 5-25. Lower total scores on the scale indicate high levels of non-adherence.

Questions are phrased in a non-threatening manner to avoid patients feeling pressure to report high adherence, and patients are reassured that responses are anonymous and confidential. The following statement precedes the scale items: "*Many people find a way of using their medicines that suits them. This may differ from the instructions on the label or from what their doctor has said. Here are some ways in which people have said they use their medicines. For each statement, please tick the box which best applies to you*" (Horne & Weinman, 2002).

The scale has been shown to have high internal reliability (Horne & Weinman, 2002). The MARS-5 has been used in previous literature to measure adherence behaviour across a number of different chronic illness settings, including renal settings within haemodialysis patients (e.g. Wileman et al.,

2015) and kidney transplant recipients (e.g. Butler et al., 2004; Griva et al., 2012; Vankova et al., 2018) showing good internal reliability. The MARS-5 was therefore deemed an appropriate and concise questionnaire to measure adherence within this programme of research.

### ***Beliefs about Medicines Questionnaire (BMQ)***

The beliefs about medicines questionnaire (Horne, Weinman & Hankins, 1999) was developed using a sample of patients with long term health conditions comprised of six different groups, of which dialysis patients was one. The self-report questionnaire aimed to assess the commonly-held beliefs about medicines, exploring beliefs and views people hold about general and specific medication. The BMQ was used to assess perceived necessity of and concerns about immunosuppressant medication. The wordings of the items were adapted to fit this context. The BMQ is comprised of two sections: BMQ-general and BMQ-specific. The sections each represent two sub-scales. The specific section measures how necessary patients perceive their specific medication to be (specific-necessity) (5 items) and how concerned they are about potential negative effects of taking it (specific-concerns) (5 items). The general section measures the way in which doctors use medication and whether patients perceive medication is overused (general-overuse) (4 items) and degree to which people perceive medication is harmful (general-harm) (4 items). Each item is rated on a five-point scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Satisfactory validity and reliability of this questionnaire has been demonstrated previously. Cronbach's alpha for internal consistency and test-retest reliability of the scales was reported within accepted limits (Horne, Weinman & Hankins, 1999).

To score the BMQ, responses on the scales are summed to give a scale score. Higher scores indicate greater beliefs in the concepts of that scale. On the BMQ-specific section, items 1, 3, 4, 7 and 10 relate to the specific-necessity scale, and items 2, 5, 6, 8 and 9 relate to the specific-concerns scale. As each of these scales has 5 items, total scores range from 5 to 25. On the BMQ-General section, items 11, 14, 17 and 18 relate to the general-overuse scale, and items 12, 13, 15 and 16 relate to the general-harm subscale. As each of these scales has 4 items, total scores range from 4 to 20.

Much previous literature across a number of different chronic illness settings has shown associations between beliefs about medicines and adherence (Horne & Weinman, 1999), including stroke (Sjolander, Eriksson & Glader, 2013) diabetes and rheumatoid arthritis (Wei et al., 2017) and heart disease (Dias, Pereira, Monteiro & Santos, 2014). The relationship between beliefs about medicines and adherence has been somewhat explored within the kidney transplant population showing perceived necessity of medications to be high and concerns low (Lennerling & Forsberg, 2012; Massey et al., 2013). Perceptions of necessity have been shown to decrease over time (Massey et al., 2013). Additionally, one study has explored beliefs about medicines in both dialysis and kidney transplant recipients (Drangsholt et al., 2019). However, much of this previous research has been within European samples. Therefore, within this programme of research it was considered important to explore this relationship further within a UK sample of kidney transplant recipients, recognising that healthcare and cultural context may have some role to play on how patients shape their beliefs about medicines over assuming that patterns are similar across different settings.

### ***Brief Illness Perceptions Questionnaire (Brief IPQ)***

The brief illness perceptions questionnaire (Broadbent, Petrie, Main & Weinman, 2006) was used to assess patients' illness perceptions to renal transplantation. The wordings of the items were adapted to fit the context of renal transplantation. The brief IPQ is a nine-item questionnaire designed to measure patients cognitive and emotional representations of their illness. The psychometric properties of the scale were evaluated across six chronic illness groups, including renal disease. The items were created by forming one question that represented each sub-scale of the revised Illness perceptions questionnaire (IPQ-R) (Moss-Morris et al., 2002). The brief IPQ has eight items and one item that was part of the causal scale used in the IPQ-R. The eight items are rated using a 0 to 10 response scale. The first five items assess cognitive illness representations: consequences (item 1), timeline (item 2), personal control (item 3), treatment control (item 4) and identity (item 5). Two items assess emotional representations: concern (item 6) and emotions (item 8). One item assesses coherence (item 7). The causal representation (item 9) is an open-ended question, which asks the patient to list three causal factors in their illness (the ones they consider most important). The final open-ended question

was adapted to “perceived causes of kidney disease/ graft rejection”. Pearson correlations found the items to have good test-retest reliability, and the results also demonstrated good predictive and concurrent validity (Broadbent, Petrie, Main & Weinman, 2006). A subset of patients were asked to complete the Brief IPQ and the IPQ-R and found that both correlate highly showing that the brief version is equally tapping into the same constructs as the full.

It is possible in some circumstances to compute an overall score representing the degree to which the illness is perceived as threatening or benign. Internal consistency of this score should be checked and is dependent on the illness studied. Computing the score requires reverse scoring items 3, 4 and 7 and adding these to items 1, 2, 5, 6 and 8, with a higher score indicating that the illness is perceived as more threatening (Broadbent, Petrie, Main & Weinman, 2006). This allows exploration of illness perceptions as a whole when analysing as well as or as an alternative to exploring individual illness perception constructs.

Illness perceptions have been widely explored in the literature across a number of different long term conditions, including renal settings within dialysis and kidney transplantation. However, much of the literature has focused on the role and importance of illness perceptions in HD patients (Chilcot, 2012), with less exploring the role of illness perceptions in kidney transplantation. Additionally, there is limited existing literature exploring the relationship between adherence and illness perceptions within kidney transplant recipients. Therefore, as research indicates that a multitude of factors can contribute to (non)adherent behaviour, it was considered important to explore this within a UK sample for this programme of research.

### ***Open-ended questions***

Open-ended questions included within questionnaires allow participants to provide more detailed responses, including information, attitudes, feelings and understanding on a topic area. This can allow the researchers to gain a better understanding of the participant’s true feelings on a topic issue, and can be of notable use when most questionnaires use closed questions with, for example, Likert scale

responses. Five open-ended questions were included for patients to provide detailed written responses relating to adherence to treatment. A summary of the open-ended questions that were included is provided in chapter seven of this thesis. The questions themselves were analysed using thematic content analysis (as described by Braun & Clarke, 2006) to assess for common themes across the written responses. Further explanation of the questionnaire study and a summary of the study findings are provided in chapter seven of this thesis.

### ***Research questions***

The questionnaire was used to address the following research questions:

1. Is self-reported adherence associated with markers of adherence obtained from clinical data?
2. Are illness perceptions associated with self-reported adherence to immunosuppressants?
3. Are medication beliefs associated with self-reported adherence to immunosuppressants?
4. How do patients conceptualise their post-transplant treatment?

### **3.4 Statistical Analysis**

Statistical analysis for the retrospective and questionnaire studies were conducted in SPSS version 25 and in Open Meta-Analyst for the systematic review and meta-analysis. For all quantitative studies, descriptive data was first analysed alongside patterns of normality in the data. Each individual study details the precise analyses that were undertaken to address the research questions being considered. In the main, the thesis draws on descriptive statistics and multiple regression techniques as analyses for describing trends in behaviour, highlighting associations between variables, and predicting behaviour.

### **3.5 Statement of contribution**

All studies that form this thesis were conceptualised and designed collaboratively by the PhD student (AH) and supervisory team. The PhD student (AH) completed: all University and NHS ethics documentation and applications to gain study ethical approvals, data collection and analysis for all studies. Findings were discussed with members of the supervisory team.

### 3.6 Summary

This body of work aims to make a broad contribution to the understanding of adherence in kidney transplant recipients. The individual studies that comprise the thesis have specific questions that are best addressed using diverse methods ranging from a systematic review, qualitative analysis, to quantitative data gathered through both retrospective and live data collection techniques. In doing so, the value of mixed-methods research is highlighted as a useful approach at a time when healthcare delivery and complexity is ever increasing. The mixed-methods nature of the research alongside breadth of quantitative techniques used to map patterns in patient behaviour yields useful insights. These could make a novel and pragmatic contribution to driving clinical understanding of adherence and ultimately attempts to improve outcomes for patients.

# Chapter 4: Non-adherence to immunosuppressants following renal transplantation: A systematic review and meta-analysis

## 4.1 Introduction

Non-adherence to immunosuppressive medication is as a major risk factor for poor clinical outcomes post-transplantation. However, it remains a common issue in this patient population, identified as the second most common cause of late graft failure (Loghman-Adham, 2003). As with all medications, patients can experience side effects that are problematic (National Kidney Foundation, 2015). This can include an increased risk of infection, diabetes, and increased susceptibility to certain types of cancers, increased blood pressure and weight gain (National Kidney Foundation, 2016). It is also true that the process of immunosuppression itself may add to the burden of co-morbidity (Silkensen, 2000). Despite the nuances of medication, adherence to the immunosuppressive regimen is vital to provide the kidney with the best chance of survival and function following transplantation.

A previous review estimated the prevalence of non-adherence in renal transplant recipients at 2-67%, dependent on measurement method used (Denhaerynck et al., 2005). In a meta-analysis, the odds of graft failure were seven times greater in non-adherent patients compared to adherent patients (Butler et al., 2004). Factors identified as determinants of non-adherence post-transplant were consistent with more recent literature, such as younger age, being unmarried and perceiving low social support (Denraeynck et al., 2005; 2007), as well as high emotional distress and high transplant related stress (Jindal et al., 2003). In addition to this, having a donor graft from a living relative has also been identified as a risk factor for non-adherence (Denhaerynck et al., 2007). This perhaps seems counter-intuitive, as you might expect patients receiving transplants from living-related donors to feel greater motivation and responsibility to look after the transplant and likely receive more pressure from e.g. family members to be adherent to treatment. Furthermore, ill health resulting from non-adherence is costly for the NHS, since dialysis services are considerably more expensive than those required to support a functioning transplant (Jindal et al., 2003). Moreover, a prerequisite for optimal adherence is access to medication where in localities such as the United States, as patients do not benefit from

insurance coverage to support access to immunosuppressive medication, they are at greater risk of graft failure due to non-adherence driven by financial barriers (Gill & Tonelli, 2012).

There are a number of reasons as to why patients may not adhere to their immunosuppressant regimen, some of which have already been touched on above. It is important to mention that non-adherence can be unintentional or intentional. Unintentional non-adherence is significantly more common than intentional non-adherence (Griva et al., 2012), and most often occurs when patients find themselves outside of their normal daily routine. In contrast, intentional non-adherence occurs when patients have concerns about their medication regime. Psychological distress, notably anxiety, hostility and depression, have been identified as having an impact on medication adherence (Achille et al., 2006), with depression also being associated with higher intentional non-adherence (Griva et al., 2012). In addition, non-adherent patients have a greater symptom burden, higher distress levels (Lee et al., 2015), and report higher frequency of stress (Brito et al., 2015). Hence renal transplant recipients may require a range of support to help them maintain a lifestyle associated with their health status. A recent systematic review evaluated interventions to improve medication adherence in adult renal transplant patients (Low et al., 2014), suggesting that those targeting behavioural risk factors or multidimensional interventions (Chisholm et al., 2001; Chisholm-Burns et al., 2013) combining educational, behavioural and emotional factors are more likely to be effective in improving non-adherence to medication.

Clearly the consequences of non-adherence are far reaching for patients in terms of reduced health related quality of life and survival. Added to this is significant cost burden related to increased care needs (Gill & Tonelli, 2012). It is vital therefore that the clinical community has access to the most up-to-date evidence to help guide efforts at supporting patients. There are two core reviews available, published in 2003 (Jindal et al., 2003) and 2004 (Butler et al., 2004), which aim to highlight the extent of non-adherence in this patient group. Additionally, a more recent review published in 2017 (Belaiche et al., 2017) explored factors relevant to medication non-adherence, however, search dates were limited between January 2009 to December 2014 to account for the most recent literature at the

time of the search. It is fair to say that progressive recognition of non-adherence in the renal care setting has resulted in a larger evidence base. A synthesis of the full body of existing research in the area would therefore be welcome to further guide clinical practice and to inform the nature of intervention.

In light of this, the systematic review and meta-analysis provides the most comprehensive evidence synthesis of what is known about non-adherence in adult renal transplant recipients. The review:

- Summarises the methods used to assess non-adherence and discusses how non-adherence is operationalized across studies.
- Identifies the prevalence of non-adherence by pooling data from across studies and considers whether reported non-adherence varies as a function of measurement source.
- Provides a narrative summary of the main factors associated with non-adherence.

## 4.2 Methods and Design

The systematic review has been written using the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) (Liberati et al., 2009) and was registered on the PROSPERO database (registration number: CRD42016038751). Study eligibility criteria are highlighted below.

### 4.2.1 Types of Studies

The review included published peer reviewed studies and grey literature in the English language. A language based criterion was used due to the resources required to manage data published in different languages. All quantitative studies that examined non-adherence to immunosuppressant's in renal transplant patients were included (cross-sectional, cohort and case series studies were included). All studies included a measure of non-adherence as a primary outcome. Randomised controlled trials were not included, as the systematic review did not analyse interventions.

#### 4.2.2 Participants

The review included patients aged 18 years and over who had received a solid organ kidney transplant. Participants were included irrespective of graft function (functioning or failed) at the time of entry into the study. Children and adolescents were excluded from the review as evidence suggests that different challenges contribute to non-adherence in this group (Dobbels et al., 2010).

#### 4.2.3 Outcomes

##### *Primary Outcomes:*

Studies were included if one of the outcomes was the degree of non-adherence to immunosuppressants. It was anticipated that this would be measured in a number of ways across studies including self-report, electronic monitoring of pill bottles and observations to name some examples.

##### *Secondary Outcomes:*

For the studies that met the primary inclusion criteria, the following outcomes were also assessed if sufficient information was available: whether non-adherence was intentional or unintentional (forgetting), risk factors for non-adherence, for example, age, time since transplantation, comorbidities, psychological correlates of non-adherence (e.g. depression, illness perceptions), and clinical outcomes such as graft failure, graft survival and mortality.

#### 4.2.4 Information Sources

Searches included the following electronic databases: PubMed, Scopus, CINAHL, The Cochrane library, PsychARTICLES, and Google scholar. There were no date limits on the searches in all databases, and databases were searched until December 2017. In addition, lateral search techniques were utilized, such as checking reference lists for related articles and using Google scholar to conduct key word and citation searches.

#### 4.2.5 Search Strategy

A combination of free text terms and medical subject headings (MeSH) were used in all databases. The search strategy used in PubMed is included in table 4.1. This was adapted accordingly to the subject headings of the remaining databases. Only free text terms were used in Scopus, as MeSH terms were not an option. Search terms within concepts were combined using “OR”. The three search concepts were combined using “AND”.

Table 4.1: Search strategy for systematic review of quantitative studies assessing levels of adherence in adult renal transplant recipients

Concept 1 – Population	Concept 2 – Adherence (Outcome)	Concept 3 - Immunosuppression
kidney transplantation (MeSH)	adherence, medication (MeSH)	immunosuppression (MeSH)
“kidney transplant*” (free-text term)	adherence (free-text term)	immunosuppress* (free-text term)
“renal transplant*” (free-text term)	non-adherence (free-text term)	
	noncompliance (free-text term)	
	compliance (free-text term)	
	“treatment refusal” (free-text term)	
	“patient compliance” (free-text term)	
	“medical compliance” (free-text term)	
	“medical adherence” (free-text term)	
	“medical non-adherence” (free-text term)	
	concordan* (free-text term)	

(free-text term) = free-text term/text word

(MeSH) = medical expert subject heading

\* = Truncated terms

#### 4.2.6 Study screening and selection process

Citations from all database searches were imported into Endnote V7 reference management software.

A check was run to identify, note and remove any duplicate citations. Retrieved records were

screened by title and abstract by two reviewers independently in order to assess suitability for inclusion. The second reviewer was an UG researcher who was trained in how to assess studies for the review. Any disagreements were resolved by discussion or consultation with a third reviewer (a member of the supervisory team). Full texts of potentially relevant citations were independently assessed for inclusion in the review using a piloted screening proforma. The second reviewer independently screened 25% of the titles and abstracts and full texts for quality assurance. Figure 4.1 provides a flow diagram of the number of citations identified, screened and included in the review.

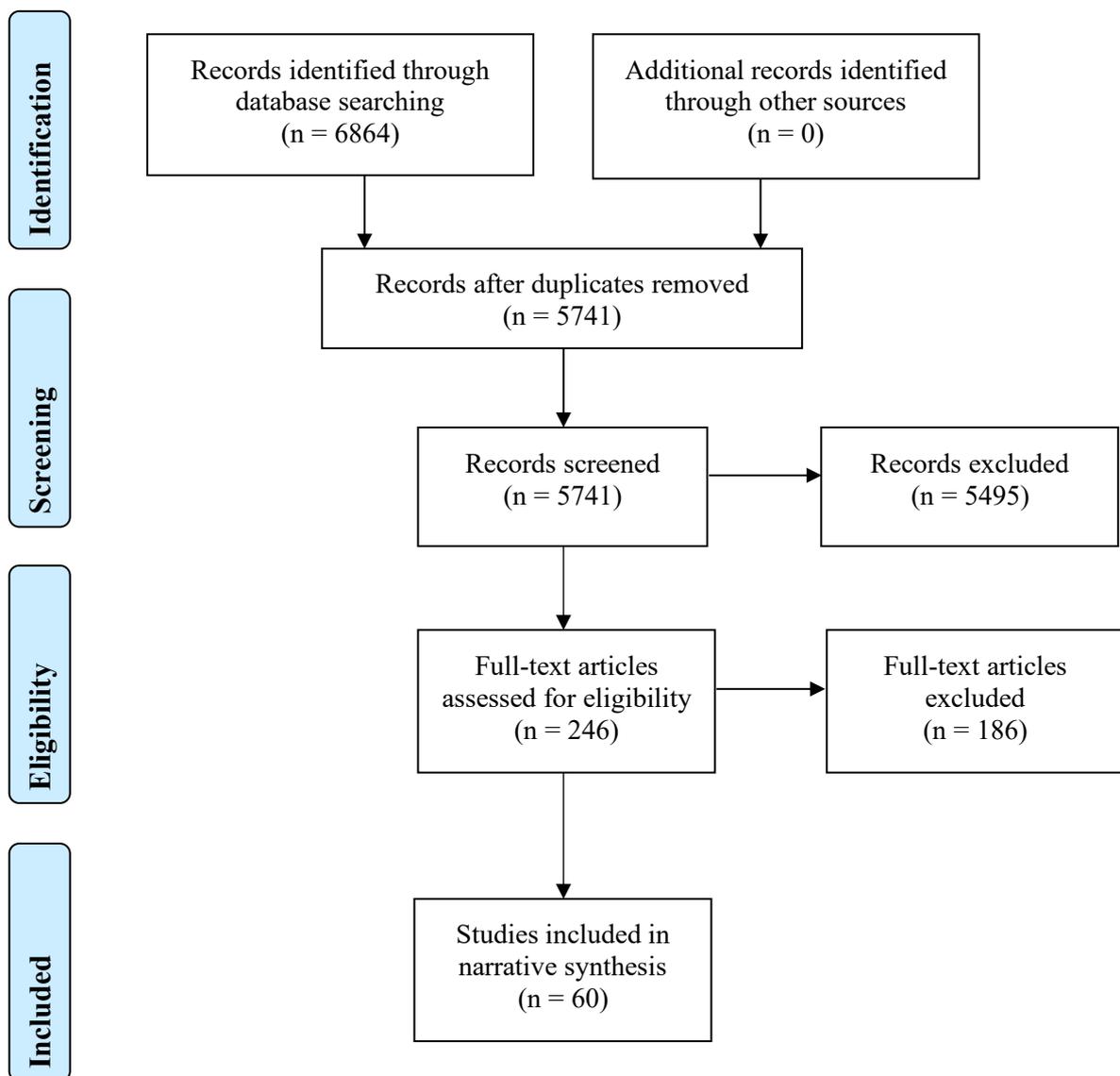


Figure 4.1: PRISMA flow chart displaying systematic review screening process.

#### 4.2.7 Data collection process

A pre-piloted form was used to extract the relevant information from each study to be included in the review. The form was created in Microsoft excel. One reviewer (AH) independently extracted the relevant information from the full text papers into the data extraction table. The second reviewer independently extracted relevant information from 25% of the full text papers. This was pilot tested on a few studies prior to the review to ensure consistency between the two reviewers, and to ensure the correct information was included. The use of two reviewers for data extraction was used to reduce the risk of error. Any disagreement was resolved by discussion with a third reviewer.

#### 4.2.8 Data items

Data was extracted using the following categories, if available:

- General information: study title, author and year of publication, country of origin,
- Study methods/ characteristics: study design (including how adherence was defined and measured), study aims and research questions, inclusion/ exclusion criteria, sampling methods,
- Demographics about the participants (age, sex, ethnicity, socio-economic characteristics),
- Number of non-adherent patients,
- Outcomes of the study, correlates and any other clinical measures (such as graft survival, number of graft failures (assessed as caused by non-adherence) and mortality/ survival).

#### 4.2.9 Outcomes and prioritisation

The primary outcome was the degree of non-adherence to immunosuppressants. For studies that met the primary inclusion criteria, the following outcomes were also assessed if available: whether non-adherence was intentional or unintentional (e.g. forgetting), which was most often reported via self-report; psychological correlates such as depression or anxiety (measured using any validated scale); illness perceptions; clinical outcomes (e.g. graft rejection, graft failure and mortality).

#### 4.2.10 Risk of bias in individual studies

Studies were rated for quality assurance using the Downs and Black (Downs & Black, 1998) checklist for non-randomised studies, case-control, cross-sectional and cohort studies. This consists of five domains: study quality, external validity, study bias, confounding and selection bias and study power. Since the studies included in this review did not examine the effectiveness of health care interventions, all items on the checklist that related to interventions or comparative groups (e.g. blinding, randomisation) were not used. One reviewer rated all the studies, and a second reviewer independently rated 25% of the studies chosen at random. Any discrepancies between reviewers was resolved by discussion with a third reviewer.

#### 4.2.11 Data synthesis

A narrative synthesis was used to summarise the studies relevant for inclusion and the different methods of measuring adherence. In addition, we investigated how studies define non-adherence, whether this was consistent across studies, and factors associated with non-adherence.

Meta-analysis was used to pool together study outcomes to assess prevalence of non-adherence rates across studies. Heterogeneity was assessed using the  $I^2$  test (Higgins & Thompson, 2002). An  $I^2$  value of 25% is categorised as low, 50% moderate and 75% high (Higgins et al., 2003). The analysis was conducted using Open Meta-Analyst. As the review included observational studies, random effects meta-analysis was used to account for studies varying due to differences in patient populations.

### 4.3 Results

A narrative review will be used to summarise the findings from the sixty studies included within the review. Only factors significantly associated with non-adherence have been reported. In addition, a one-group meta-analysis will be used to estimate the pooled prevalence of non-adherence across studies using self-report measures only. Further meta-analysis and meta-regression could not be performed due to heterogeneity in methods of non-adherence assessment and reported outcomes

across studies. Study outcomes and statistical analysis varied, from studies reporting no statistical analysis while others univariate or multivariate associations, or both.

#### 4.3.1 Narrative synthesis

##### *Summary of studies*

A total of 6,864 citations were identified through database searching. Following removal of duplicates, 5,741 were screened by title and abstract leading to 5,495 removed due to not meeting the inclusion criteria. The full texts of 246 articles were assessed for eligibility, with 186 excluded. Sixty studies published between 1997 and 2017 were included within the final review (see Table 4.2).

##### *Study characteristics*

The included studies were conducted in a range of countries, with the majority conducted in North America (N=26, 43.3%) and Europe (N=24, 40%). The most studies were conducted in the USA (N=24, 40%). Only three studies included in this review were conducted in the UK. Across the 60 studies, study sample sizes ranged from 18 to 31,913. The two studies with the largest sample sizes included 17,181 (Chisolm et al., 2016) and 31,913 (Spivey et al., 2014), however, both of these studies involved analysis of pharmacy refill data via medication possession ratio. The remaining 58 studies sample sizes ranged from 18 to 3676.

The majority of studies were cross-sectional in design (N=36, 60%). A smaller number of observational (N=14, 23.3%) and longitudinal (N=8, 13.3%) studies were included. The majority of studies had more males than females, with percentage of males ranging from 45% (Russell et al., 2006) to 83.3% (Chisolm et al., 2000). Only seven studies had more females than males (Greenstein & Siegal, 1998; Feldman et al., 1999; Siegel & Greenstein, 1999; Siegal et al., 2002; Russell et al., 2006; Chisolm-Burns et al., 2010; Weng et al., 2017). Between April 2018 and March 2019, across all transplant centres in the UK more males (53% to 73%) received a kidney transplant than females (27% to 47%) (NHS Blood & Transplant, 2019). The majority of studies included in this review therefore seem to represent the true difference in rate of transplants between males and females.

### *Measurement methods*

Adherence was assessed via a variety of methods including self-report, electronic monitoring, blood levels, physician rating and prescription refill. The most commonly used measure across studies was self-report, with 43 (71.7%) studies using a self-report measure. Electronic monitoring was used in 12 (20%) studies, pharmacy refill in eight (13.3%) studies and blood levels in nine (15%) studies. Physician rating/collateral report was the least commonly used measurement method used in seven (11.7%) studies. One study used an investigator rating (see Table 4.2). Twelve (20%) studies measured adherence through an association of methods (Butler et al., 2004; Chisolm et al., 2005; Rosenberger et al., 2005; Schafer-Keller et al., 2008; Gelb et al., 2010; Schmid-Mohler et al., 2010; Griva et al., 2012; Ortega et al., 2013; Marsciano et al., 2015; Pabst et al., 2015; Silva et al., 2016; Lehner et al., 2017). Authors often provided a prevalence rate for each of the individual measurement methods used as well as a composite score (combination of all measures utilised).

The most commonly used self-report measure was the Basel Assessment of Adherence with Immunosuppressive Medication Scales (BAASIS) used in 13 (21.7%) studies (Schmid-Mohler et al., 2010; Lennerling & Forsberg, 2012; Massey et al., 2013; Burkhalter et al., 2014; Tielen et al., 2014; Marsciano et al., 2015; Massey et al., 2015, Massey et al., 2015; Pabst et al., 2015; Reber et al., 2016; Silva et al., 2016; Lehner et al., 2017; Scheel et al., 2017). This was closely followed by the Immunosuppressant Therapy Adherence Scale (ITAS) used in ten (16.7%) studies (Chisolm et al., 2005; Chisolm-Burns et al., 2010; Chisolm-Burns et al., 2012; Cheng et al., 2012; Gorevski et al., 2013; Weng et al., 2013; Hamedan & Aliha, 2014; Tsapepas et al., 2014; de Fatima et al., 2016; Little et al., 2016). Less commonly used measures included the Morisky Medication Adherence Scale (MMAS) used in five (8.3%) studies (Butler et al., 2004; Goldfarb-Rumyantzev et al., 2011; Couzi et al., 2013; Liu et al., 2015; Adhiraki et al., 2016), the Transplant Effects Questionnaire (TxEQ) used in three (5%) studies (Gelb et al., 2010; Pabst et al., 2015; Demian et al., 2016), the Medication Adherence Report Scale (MARS) used in two (3.3%) studies (Butler et al., 2004; Griva et al., 2012), and the Simplified Medication Adherence Questionnaire (SMAQ) used in one (1.7%) study (Lalic et al., 2014). Other self-report measures were utilised in 11 (18.3%) studies (Siegal & Greenstein, 1997;

Greenstein & Siegal, 1998; Siegal et al., 2002; Rosenberger et al., 2005; Gremigni et al., 2007; Schafer-Keller et al., 2008; Tielen et al., 2011; Morales et al., 2012; Calia et al., 2015; Teng et al., 2015; Weng et al., 2017).

Studies using pharmacy refill and electronic monitoring were less clear in how they defined non-adherence, or only reported adherence. In some studies, using pharmacy refill data, patients with <80% refill were characterised as non-adherent (Chisolm et al., 2000; Chisolm et al., 2005; Chisolm et al., 2007; Chisolm et al., 2016). Similarly, with electronic monitoring, different reporting was used to report adherence or non-adherence. Some studies reported the percentage of openings e.g. >85-100%, 50-85%, <50% (Weng et al., 2005; Israni et al., 2011), whilst others similarly reported medication adherence scores above/below 0.90 or 0.80 (Russell et al., 2006; Russell et al., 2009; Russell et al., 2010; Russell et al., 2013). One study reported that those missing at least 20% of days medication were determined as non-adherent participants (Butler et al., 2004), whilst another reported using an algorithm to yield a non-adherence prevalence rate (Schafer-Keller et al., 2008).

#### *Prevalence of non-adherence*

The prevalence of non-adherence was dependent on the measurement method used. Non-adherence ranged from 0.06% to 89.2%. Non-adherence ranged from 7.4% to 89.2% in studies using self-report measures, and from 1.6% to 86% in studies using Electronic monitoring. Slightly narrower ranges were identified in studies using immunosuppressant blood levels (7% to 49%), pharmacy refill data (5% to 58%) and physician ratings (0.9% to 41%).

#### *Factors associated with non-adherence*

Studies that identified factors associated with non-adherence are summarised below. The remaining studies either did not explore or assess the factors or identified them as not significantly associated.

*Gender* - Eight (13.3%) studies associated male gender with non-adherence (Denhaerynck et al., 2007; Griva et al., 2012; Hamedan & Aliha, 2014; Burkhalter et al., 2014; Spivey et al., 2014; Liu et

al., 2015; Chisolm et al., 2016; Demian et al., 2016; Weng et al., 2017). These studies mostly used self-report measures to assess adherence rates. Only three (5%) studies associated female gender with non-adherence (Chisolm et al., 2005; Pabst et al., 2015; Lehner et al., 2017). All studies used a self-report measure alongside other measures of adherence, including blood levels, physician ratings and prescription refill records.

*Age* - Younger age was associated with non-adherence in seventeen (28.3%) of the included studies (Siegal & Greenstein, 1997; Greenstein & Siegal, 1998; Denhaerynck et al., 2007; Gremigni et al., 2007; Gelb et al., 2010; Goldfarb-Rumyantzev et al., 2011; Chisolm-Burns, 2012; Griva et al., 2012; Couzi et al., 2013; Massey et al., 2013; Russell et al., 2013; Burkhalter et al., 2014; Hamedan & Aliha, 2014; Spivey et al., 2014; Massey et al., 2015; Demian et al., 2016; Lehner et al., 2017). However, three (5%) studies identified older age as a predictor of non-adherence (Chisolm et al., 2005; Chisolm-Burns et al., 2008; Chisolm et al., 2016).

*Education and employment* - Lower education levels were associated with non-adherence in two (3.3%) studies (Griva et al., 2012; Weng et al., 2017). In comparison, one (1.7%) study identified higher education level as associated with non-adherence (Greenstein & Siegal, 1998). More studies commented on employment and income. Five (8.3%) studies associated full time/part-time employment with non-adherence (Greenstein & Siegal, 1998; Goldfarb-Rumyantzev et al., 2011; Griva et al., 2012; Massey et al., 2015; Demian et al., 2016) with one (1.7%) study further specifying white collar occupation (Greenstein & Siegal, 1998). In relation to income, low household income was associated with non-adherence in three (5%) studies (Weng et al., 2013; Marsciano et al., 2015; Weng et al., 2017) with one (1.7%) study also specifying lack of employment (Weng et al., 2013). Higher income was only associated in one (1.7%) study (Chisolm et al., 2005).

*Transplant vintage* – Eight (13.3%) studies associated greater transplant vintage with non-adherence (Siegal & Greenstein, 1997; Greenstein & Siegal, 1998; Chisolm et al., 2005; Chisolm-Burns et al., 2008; Griva et al., 2012; Burkhalter et al., 2014; Hamedan & Aliha, 2014; Weng et al., 2017)

suggesting patients who have been transplanted for longer are more likely to be/become non-adherent over time. However, the time it takes to become non-adherent post-transplant is not clearly specified. Conversely, two (3.3%) studies associated non-adherence with shorter transplant vintage (Tielen et al., 2014; Liu et al., 2015) with one (1.7%) study specifying a lower two-year graft survival (Tielen et al., 2014).

*Donor type* - Receiving a transplant from a living donor was associated with non-adherence in seven (11.7%) studies (Butler et al., 2004; Denhaerynck et al., 2007; Goldfarb-Rumyantzev et al., 2011; Griva et al., 2012; Spivey et al., 2014; de Fatima et al., 2016; Lehner et al., 2017). Two of the seven studies specify this as a living related donor graft (Denaherynck et al., 2007; Griva et al., 2012), however although this is not specified in the remaining five studies, living related donations are more common than unrelated donations (altruistic donors).

*Medication related factors* - Side effects were associated with non-adherence in three (5%) studies (Siegal & Greenstein, 1997; Rosenberger et al., 2005; Cheng et al., 2012) and with feeling worse in one study (Lalic et al., 2014). Type of immunosuppressant taken was associated with non-adherence in four (6.7%) studies. Taking the immunosuppressant tacrolimus was identified in one study (Chisolm et al., 2005) whereas taking the immunosuppressant cyclosporine was identified in two studies (Chisolm et al., 2005; Denaherynck et al., 2007). Additionally, not taking tacrolimus was associated with non-adherence in one study (Spivey et al., 2014). Furthermore, experience of rejection (Chisolm et al., 2005) and adverse events (Couzi et al., 2013) were also associated in two (3.3%) studies.

Issues with taking and timing of medication (Massey et al., 2013) and having to take immunosuppressants too many times per day and having too many tablets to take at one time (Morales et al., 2012) were associated with non-adherence. Additionally, two (3.3%) studies identified treatment regimen inconvenience (Ortega et al., 2014) and interruption to daily routine (Schmid-Mohler et al., 2010) as associated with non-adherence. Forgetfulness was associated with

non-adherence in eight (13.3%) studies (Siegal & Greenstein, 1997; Butler et al., 2004; Russell et al., 2009; Chisolm-Burns et al., 2010; Schmid-Mohler et al., 2010; Chisolm-Burns et al., 2012; Couzi et al., 2013; Lalic et al., 2014). Forgetting to take medication can often occur when patients find themselves outside of their normal routine.

*Psychological factors* - Experience of psychological distress was related to non-adherence.

Depression was associated with non-adherence in eight (13.3%) studies (Gelb et al., 2010; Griva et al., 2012; Gorevski et al., 2013; Weng et al., 2013; Burkhalter et al., 2014; Pabst et al., 2015; Reber et al., 2016; Little et al., 2017) and one (1.7%) study associated it with ongoing feelings of sadness (Siegal & Greenstein 1997). Anxiety was associated with non-adherence in two (3.3%) studies (Pabst et al., 2015; Reber et al., 2016), increased stress in one (1.7%) study (Weng et al., 2013) and symptom distress in three (5%) studies (Rosenberger et al., 2005; Denaherynck et al., 2007; Teng et al., 2015). Additionally, lower self-efficacy was associated with non-adherence in three (5%) studies (Denaherynck et al., 2007; Russell et al., 2013; Silva et al., 2016) and lower quality of life in one (1.7%) study (Hamedan & Aliha, 2014).

*Patient beliefs*

Beliefs, attitudes and concerns have been reported as factors associated with non-adherence. Low beliefs in the need for immunosuppressants were associated in three (5%) studies (Greenstein & Siegal, 1998; Butler et al., 2004; Griva et al., 2012). Two (3.3%) studies suggested perceiving immunosuppressants disruptive or having a negative impact on daily life is associated with non-adherence (Gremigni et al., 2007; Chisolm et al., 2012). Additionally, those who perceived low social support were more likely to be non-adherent. This was identified in three (5%) studies (Rosenberger et al., 2005; Chisolm et al., 2010; Pabst et al., 2015). Furthermore, greater experience of barriers (Chisolm et al., 2012; Weng et al., 2013) and concerns about the treatment regimen (Griva et al., 2012; Weng et al., 2017) were associated with non-adherence. Perceptions of less autonomy in treatment management (Gremigni et al., 2007) and less control over taking immunosuppressants (Chisolm et al., 2007) were also associated.

Table 4.2: Summary characteristics of included studies

Authors	Country of origin	Study design	Method of assessment	Sample size	Mean age (years)	Men (%)	NA rates % (N)	Factors associated with NA
<b>Adhikari et al., (2016)</b>	India	Longitudinal observational	Self-report (MMAS)	110	38.1 (12.8)	65.50%	26.4% (29)	No significant correlations
<b>Burkhalter et al., (2014)</b>	Switzerland	Cross-sectional	Self-report (BAASIS); self-report via visual analogue scale 0-100	926	59.7 median (IQR 50.26-67.77)	63%	35%	Younger age, male gender, greater transplant vintage, depression
<b>Butler et al. (2004)</b>	UK	Cross-sectional, observational	Electronic monitoring	58	48.0 (13.0)	66%	12% (7) missed at least 20% of days medication	Living donor transplant, low belief in need for immunosuppressants
<b>Butler et al., (2004)</b>	UK	Cross-sectional	Self-report (MMAS & MARS); Electronic monitoring; cyclosporine levels	153	48.0 (13.0)	59% in sample without EM, 66% subsample with EM	EM 12% (n=7); 37% MARS; 33% MMAS; Cyclosporine levels (range of the last six levels median 108.0, IQR 63.8–187.3)	Forgetting
<b>Calia et al., (2015)</b>	Italy	Cross-sectional	Self-report (how many times failed to take prescribed dose)	43	53 median (IQR 46-55)	55.80%	58% (25)	High levels of alexithymia
<b>Cheng et al., (2012)</b>	Taiwan	Cross-sectional	Self-report (ITAS)	412	51.5 (12.0)	52.90%	21.4% (88)	Side effects and complications of immunosuppressants

<b>Chisholm et al., (2000)</b>	USA	Observational	Pharmacy refill collected for 12 months (<80% refill characterised as non-adherent)	18	48.1 (9.3)	83.30%	At 5 months 5% NA each month, at 7 months 25%, at 12 months 52%	Low target blood levels
<b>Chisholm et al., (2005)</b>	USA	Cross-sectional	Self-report (ITAS) - whole sample; blood levels, refill records - sub-sample	137 (sub-sample 65)	52.52 (14.02)	64%	35% (48) ITAS; (sub-sample ITAS 23%, refill records 37%)	Older age, female, tacrolimus immunosuppressant, higher income, poor refill record, further since transplantation, experience of rejection episode
<b>Chisholm et al., (2005)</b>	USA	Observational	Pharmacy refill (<80% refill characterised as non-adherent)	33	50.4 (8.8)	72.70%	12% ciclosporin and 5% tacrolimus. At 12 months post-transplant, approx. 58% NA	Cyclosporine immunosuppressant
<b>Chisholm et al., (2007)</b>	USA	Cohort	Pharmacy refill (<80% refill characterised as non-adherent)	158 (subsample 70)	51.0 (12.4)	60.10%	27% of subsample	Less favourable attitudes, less control over taking immunosuppressants, weaker subjective norms, lower intentions
<b>Chisholm et al., (2016)</b>	USA	Cross-sectional	Medication possession ratio (Pharmacy refill data <80% refill characterised as non-adherent)	17181	50.2 (14.3)	59.1%	16.8% MPR <.80. At 12 months mean MPR 0.91 (0.17)	Male gender, not medication therapy management eligible, taking fewer prescription drugs, older age

<b>Chisolm-Burns et al., (2008)</b>	USA	Retrospective observational	Pharmacy refill	70	51.61 (12.53)	58.60%	12.9%	Older age, greater transplant vintage
<b>Chisolm-Burns et al., (2010)</b>	USA	Cross-sectional	Self-report (ITAS)	61	48.85 (11.44)	47.50%	Mean score 11.1 (2.0) (Total score 12 - higher score indicates high adherence)	Low social support, forgetfulness
<b>Chisolm-Burns et al., (2012)</b>	USA	Cross-sectional	Self-report (ITAS)	512	52.37 (10.74)	60.27%	34.5% (177). Average ITAS score 11.27 (SD =1.15)	Forgetting, greater experience of barriers, younger age, perceiving immunosuppressants disruptive to life, lower life satisfaction
<b>Couzi et al., (2013)</b>	France	Observational cohort	Self-report (MMAS)	312	49.5 (13.2)	68.30%	increase in NA over time: 17.3% (Month3), 24.1% (M6), 30.7% (M12), and 34.6% (M24)	Forgetting, younger age, simple treatment regimens, adverse events
<b>de Fatima et al., (2016)</b>	Brazil	Cross-sectional	Self-report (ITAS)	151	40.33 (11.7)	51.7%	60.3% (91)	Living donor transplant, higher serum creatinine
<b>Demian et al., (2016)</b>	Canada	Observational	Self-report (TxEQ)	96	52.77 (12.56)	56.20%	TxEQ M = 20.89 (SD = 3.77), 75% (74) score indicating less than 'perfect' self-reported adherence	Younger age, male gender, higher levels of employment, lower health literacy
<b>Denhaerynck et al., (2007)</b>	Switzerland	Prospective longitudinal	Electronic monitoring	249	53.6 (12.7)	56.60%	Taking 1.6%, dosing 3.8, timing 8.1%. Mean number of drug holidays per 100 monitored days was 1.1 days (SD=3.2).	Younger age, male gender, low self-efficacy, high self-reported NA, busy lifestyle, living related donor, symptom distress

<b>Eisenberger et al., (2013)</b>	Switzerland	Observational	Ingestible sensor system (electronic monitoring)	20	51.7 (8.8)	75%	Taking NA overall 0.06%; timing NA overall 15.5%	Not reported
<b>Feldman et al., (1999)</b>	USA	Observational	Electronic monitoring	25	47.9 (11.6)	48%	On average 6.8% of cyclosporine doses, 9.8% of azathioprine doses	Twice daily regimen
<b>Gelb et al., (2010)</b>	Canada	Cross-sectional, observational	Self-report (TxEQ); pharmacy refill; blood levels	103	50.07 (12.38)	52.4	Mean self-reported adherence score 20.8 (SD = 3.60); serum concentrations 15.5% (16) NA; refill 5.98% NA	Younger age, depressive symptoms, poorer everyday problem solving
<b>Goldfarb-Rumyantzev et al., (2011)</b>	USA	Observational	Self-report (MMAS)	199	43 (14.2)	67%	Taking NA 21%, timing NA 33%	Younger age, greater comorbidity, having a living donor, full time employment
<b>Gorevski et al., (2013)</b>	USA	Cross-sectional	Self-report (ITAS)	86	50.3 (12.4)	67%	43% (37)	High scores on PHQ-9, low openness
<b>Greenstein &amp; Siegal (1998)</b>	USA	Cross-sectional	Self-report 8-point Likert scale	1402	46.6 (12.5)	49.40%	22.4% (314)	Younger age, greater transplant vintage, higher education level, employed, white collar occupation, living related donor transplant, history of infections, low beliefs in necessity of immunosuppressants

<b>Gremigni et al., (2007)</b>	Italy	Cross-sectional	Self-report 2 items	34	48.0 (12.0)	61.80%	forgetting 24%, taking exactly as prescribed 24%	Younger age, perceptions of less autonomy in treatment management and higher negative impact of medication in daily life, active coping style
<b>Griva et al., (2012)</b>	UK	Cross-sectional	Self-report (MARS); blood levels	218	49.67 (12.28)	59.60%	51.4% (112) admitted less than perfect adherence ( $\leq 23$ MARS-Total); 25.4% (52) NA by blood levels	Forgetting, concerns about treatment regimen, younger age, male gender, lower education, employment, cohabiting/marital relationships, low belief in necessity of medication, high medication concerns, shorter dialysis vintage, depression, living related donor graft, low ESRD severity index, greater transplant vintage, cyclosporine
<b>Hamedan &amp; Aliha (2014)</b>	Iran	descriptive correlational	Self-report (ITAS)	230	41.69 (12.17)	55.20%	57.8%	Low quality of life, younger age, greater transplant vintage
<b>Israni et al., (2011)</b>	USA	Cohort	Electronic monitoring	243	47.7 (11.9)	63%	At 6 months: 68% <15% NA, 20% 15-50% NA, 12% >50% NA	No significant correlations
<b>Lalic et al., (2014)</b>	Serbia	Cross-sectional	Self-report (SMAQ)	60	44.45 (11.37)	63.30%	28.3% (17)	Forgetfulness, feeling worse

<b>Lehner et al., (2017)</b>	Germany	Longitudinal	Self-report (BAASIS); investigator rating; blood levels	153	51.1 (12.3)	62.70%	Composite score: 67.7% (88). Self-report: 44.9% (57). Investigator rating as "poor": 1.5% (2). Tacrolimus concentration: 49% (75)	Female gender, aged <50, living donor, prior rejection episode
<b>Lennerling &amp; Forsberg (2012)</b>	Sweden	Cross-sectional	Self-report (BAASIS)	250	54 median (range 19-77)	69%	54 % (135)	No significant correlations
<b>Little et al., (2017)</b>	USA	Cross-sectional	Self-report (ITAS)	39	51.0 (16.0) perfect adherence group; 56.0 (12.0) not perfect adherence group	56.40%	31% (12) not perfect adherence	Higher BDI scores, positive donor specific antibody
<b>Liu et al., (2015)</b>	China	Cross-sectional	Self-report (MMAS)	209	41.7 (10.3)	63.2%	31.3% (65)	Shorter transplant vintage, male gender
<b>Marsicano et al., (2015)</b>	Brazil	Cross-sectional	Self-report (BAASIS); collateral report; blood levels	100	45.0 (13.5)	65%	Composite score: 51%. Self-report: 34%; collateral report: 30%; Assay: 7%	Lower family income
<b>Massey et al., (2013)</b>	Netherlands	Cohort	Self-report (BAASIS)	113	53 median (range 19-75)	64.60%	17% (19) at 6 weeks post-transplant. 27% (29) at 6 months post-transplant.	Younger age, re-transplantation, increase in perceived longevity of graft

<b>Massey et al., (2015)</b>	Netherlands	Cross-sectional	Self-report (BAASIS); self-report via visual analogue scale 0-100	62	25.6 (2.9)	66.10%	64.5% (40)	Issues with taking and timing
<b>Massey et al., (2015)</b>	Netherlands	Cohort	Self-report (BAASIS)	113	53 median (range 19-75)	64.60%	31% (26) at 18 months follow up	Younger age, being in paid employment, low goal importance likely to be NA over time
<b>Morales et al., (2012)</b>	Spain	Cross-sectional	Self-report	1983	53.0 (11.9)	60.70%	7.4% NA	Barriers: having to take immunosuppressants too many times per day, having to take too many tablets at one time.
<b>Ortega et al., (2013)</b>	Spain	Cross-sectional	Blood levels; physician judgement	207	53.35 (12.8)	61.20%	Blood levels: 31.1%, physician judgement 29.1%	Low levels of satisfaction, total doses of medications, treatment regimen inconvenience
<b>Pabst et al., (2015)</b>	Germany	Cross-sectional	Self-report (BAASIS, TxEQ); physician rating	238	53.15 (13.66)	65%	37.4% (89) BAASIS; TxEQ M=4.37 (SD=0.66); 9.2% (22) physician rating	Female gender, non-native language speakers, depression, anxiety, lower social support
<b>Reber et al., (2016)</b>	Germany	Cross-sectional	Self-report (BAASIS)	74	54.1 (12.8)	66.20%	24.3%	Higher depression and anxiety levels
<b>Rosenberger et al., (2005)</b>	Slovak Republic	Cross-sectional	Self-report; physician rating	139	47.7 (11.7)	58.10%	Self-report: 31.7% (44); physician rating: 41% (57); Combination of patient self-report and physician rating: 54% (75)	High stress from adverse effects of immunosuppression, less satisfaction with social support, fair self-reported health, male gender

<b>Russell et al., (2006)</b>	USA	Longitudinal	Electronic monitoring	44	51.73 (11.39)	45%	25% (score <.90)	No significant correlations
<b>Russell et al., (2009)</b>	USA	Prospective descriptive	Electronic monitoring	73	61.37 (5.6)	58%	Mean medication score for patients who perceived MEMS had negative/neutral effect on medication taking 0.76 (0.13) (max 1), patients who perceived MEMS had a positive effect 0.70 (0.18)	Forgetfulness
<b>Russell et al., (2010)</b>	USA	Descriptive, Longitudinal	Electronic monitoring	37	60.38 (4.46)	62%	86% (score <.90)	No significant correlations
<b>Russell et al., (2013)</b>	USA	Longitudinal, Correlational	Electronic monitoring	121	51.12 (12.35)	63%	61% adherence score <0.90 and 41% <0.80.	Younger age, low self-efficacy
<b>Schafer-Keller et al., (2008)</b>	Switzerland	Longitudinal	Electronic monitoring, self-report (Siegal scale), collateral report, blood levels	249	53.6 (12.7)	56.60%	EM 17.3%, blood levels 33%, self-report 12.4%, collateral report range 0.9%-23.9%,	Not reported
<b>Scheel et al., (2017)</b>	Germany	Cross-sectional	Self-report (BAASIS)	267	52.8 (13.7)	65%	33% (89)	Rejection associated with younger age at transplantation and higher percentage of sub-therapeutic immunosuppressant trough levels
<b>Schmid-Mohler et al., (2010)</b>	Switzerland	Cross-sectional	Self-report (BAASIS); collateral report	114	53.6 (11.9)	64.90%	Self-report: 23.7% (27); 3.8% (4) collateral report; composite score 26.4% (28)	Forgetfulness, interruption to daily routine

<b>Siegal &amp; Greenstein (1997)</b>	USA	Cross-sectional	Self-report	519	45.0 (13.0)	56%	18% (96)	Forgetfulness when away from home, younger age, post-transplant physical symptoms: weight gain, ongoing feelings of sadness, greater transplant vintage
<b>Siegal et al., (2002)</b>	USA	Cohort	Self-report 6 items	3676	Not reported	47.60%	57% (NA reported at least some of the time)	Low life satisfaction index
<b>Silva et al., (2016)</b>	Brazil	Cross-sectional	Self-report (BAASIS); collateral report; blood levels; composite score	88	47.2 (12.9)	63.60%	70.5% (62) NA through at least one method. BAASIS 46.6% (41) NA; collateral report 38.6% (34); blood levels 34.1% (30)	Lower self-efficacy, chance health locus of control, lower intrinsic religiosity
<b>Spivey et al., (2014)</b>	USA	Retrospective observational	Medication possession ratio (Pharmacy refill data)	31913	48.0 (13.7)	58.6%%	Mean MPR for the sample 0.56 (0.29) with a median of 0.58 (risk of graft failure when <0.80)	Younger age, male gender, non-white ethnicity, living donor transplant, not taking tacrolimus
<b>Teng et al., (2015)</b>	China	Cross-sectional	Self-report 4 items	231	44.91 (10.75)	60.60%	89.2% had at least one aspect of NA	Higher level of symptom distress
<b>Tielen et al., (2011)</b>	Netherlands	Cross-sectional, observational	Self-report (Siegal scale 4 items)	26	73 median (range 67-82)	80.80%	30.8% (8)	Not reported
<b>Tielen et al., (2014)</b>	Netherlands	Cross-sectional, observational	Self-report (BAASIS)	113	Not reported	64.60%	16.8% (19)	Lower 2 year graft survival

<b>Tsapepas et al., (2014)</b>	USA	Longitudinal	Self-report (ITAS)	808	51.7 (13.2)	64%	49.8% (402)	African American ethnicity
<b>Weng et al., (2005)</b>	USA	Cohort	Electronic monitoring	278	48 median (IQR 39-57)	61.20%	Average daily percentage adherence: >95 to 100% 114 (41%); >80-90% 90 (32.4%); >50-80% 36 (12.9%); 0-50% 38 (13.7%)	Black ethnicity, transplant centre, renal disease cause, original dosing frequency of medication
<b>Weng et al., (2013)</b>	USA	Cross-sectional	Self-report (ITAS)	252	54.7 (median, IQR 44.6-62.9)	59.90%	14.3% (36)	Depression, increased perceived stress, lower household income, lack of employment, greater perceived barriers,
<b>Weng et al., (2017)</b>	Taiwan	Cross-sectional, correlational	Self-report 7 items	145	45.5 (11.8)	45.50%	Mean score 29.73 (SD 4.01). (Total score 35 - higher score indicates higher adherence).	Male gender, low income, low education level, greater transplant vintage, high level of concerns

#### 4.3.2 Meta-analysis

A one group meta-analysis was conducted to estimate the pooled non-adherence prevalence rate across studies using self-report measures only. As self-report measures were the most commonly used measure used across studies, there was a large number of studies that could be included in the analysis. Additionally, most authors using self-report measures provided a prevalence rate (%) for those categorised as non-adherent by that measure. Only studies providing a prevalence rate for the total measure were included (whereas some studies provided prevalence per question of the measure or a mean score on the measure). Where longitudinal studies using self-report measures were included, non-adherence prevalence at the final time point was used. Additionally, where studies used more than one method of assessment to measure adherence, only the reported non-adherence rate on the self-report measure was recorded for the analysis. It was not possible to run an analysis on studies using electronic monitoring or prescription refill, as definitions of non-adherence/cut-off points via that measure was not always clear (studies reported score or % for refill/medication taking). A random effects model was used based on the assumption that studies are likely to differ in ways that may impact the results, and the true effect size will likely vary from study to study therefore we cannot assume a common effect size (Borenstein et al., 2010).

Of the 60 studies included in the review, 38 were eligible for inclusion, which used the proportion of non-adherent patients from each study to give an estimate of the pooled non-adherence prevalence rate across studies. The overall pooled estimate was 0.376 (95% CI 0.30 to 0.45,  $P < .001$ ), meaning across studies the pooled prevalence of non-adherence was 37.6%. The studies were heterogeneous,  $Q(37) = 4244.03$ ,  $P < .001$ , with an  $I^2$  value of 99.13. The forest plot is shown in figure 4.2.

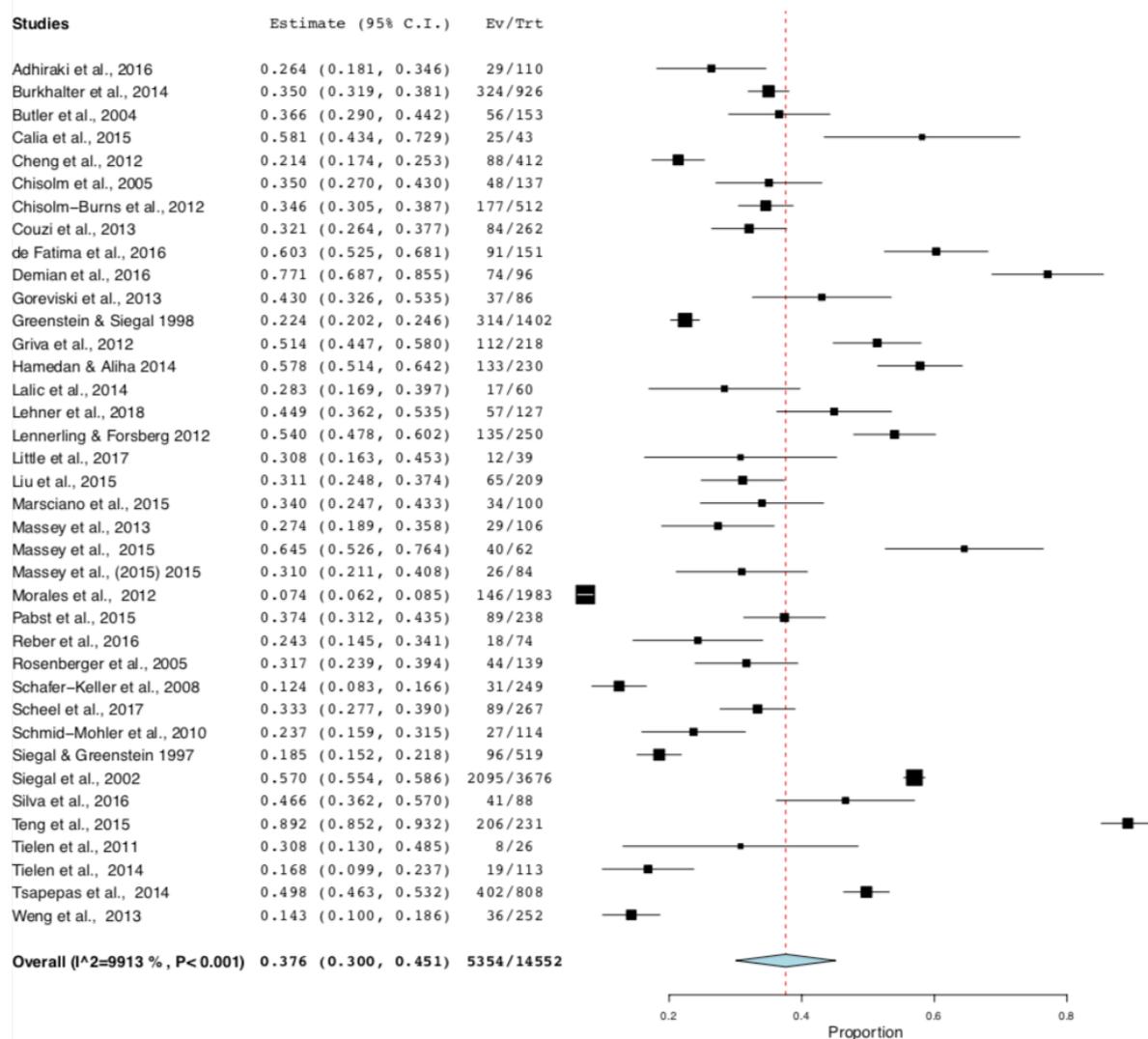


Figure 4.2: Forest plot of non-adherence to immunosuppressants prevalence rates

### 4.3.3 Quality Assessment

All studies included in this review were assessed for quality using the Downs and Black quality assessment checklist (Downs & Black, 1998) (see figure 4.3). Generally, the studies were good quality, with almost all reporting clear aims, patient characteristics and outcome measures. Studies were representative of the renal transplant population. Appropriate analyses were conducted across the majority of studies, however, over half of the studies did not report adjusting for confounding variables in final analyses.

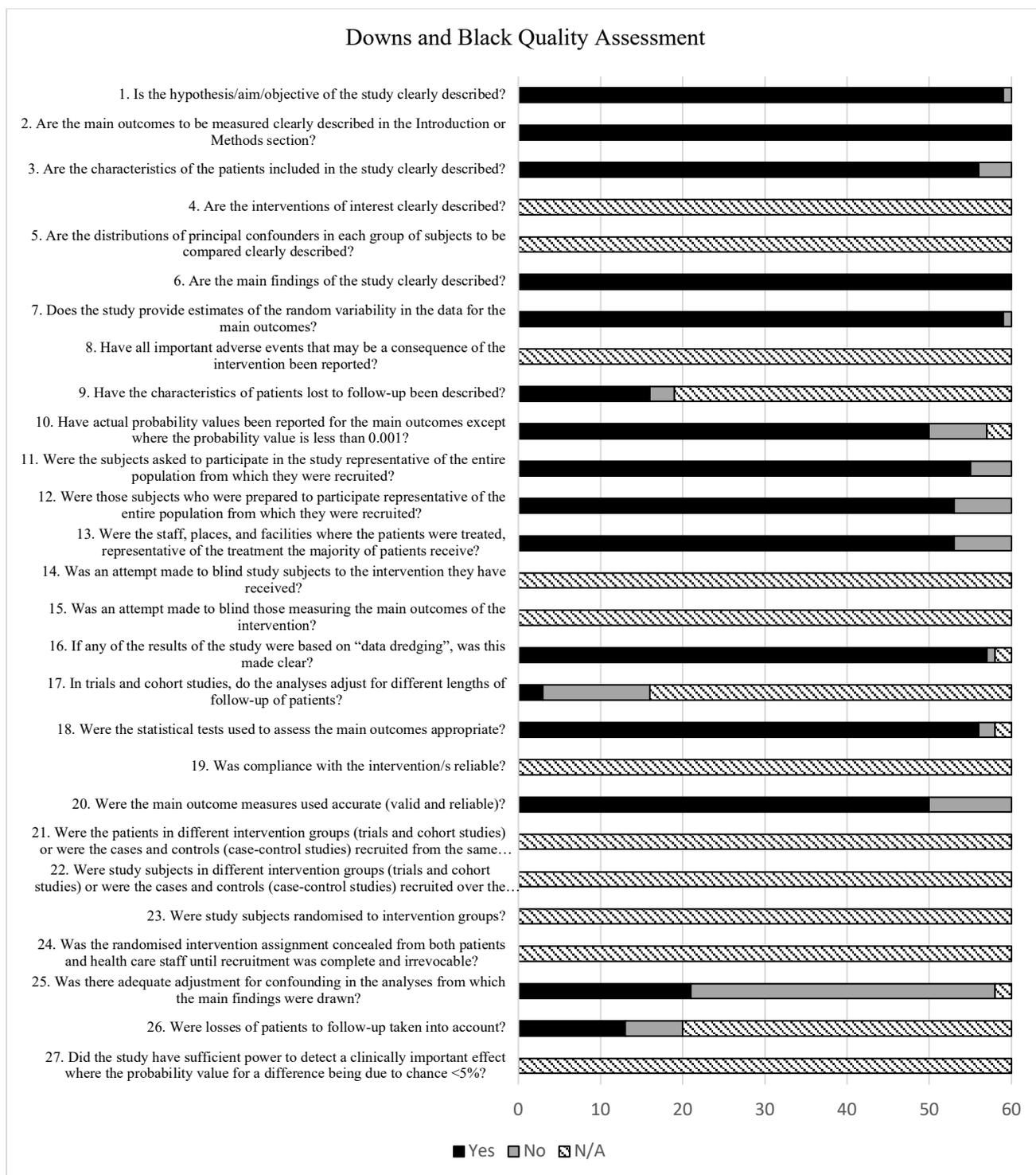


Figure 4.3: Figure of each item of the Downs and Black Quality Assessment

#### 4.4 Discussion

This systematic review and meta-analysis aimed to assess studies exploring non-adherence to immunosuppressants among renal transplant recipients. The aims were to provide a summary of the methods used to measure and assess adherence, identify the prevalence rate of non-adherence,

identify factors associated with non-adherence including psychological correlates and explore the impact of non-adherence on graft failure.

This review highlights a variation of measurement methods used to assess adherence, including self-report, electronic monitoring, immunosuppressant blood levels, pharmacy refill and physician rating. Self-report was most commonly used as a method of measuring adherence across studies. This is similar to that of previous literature reviews (Denhaerynck et al., 2005; Belaiche et al., 2017). This is likely due to their ease of administration, lack of cost and feasibility in clinical settings (Schafer-Keller et al., 2008).

Findings highlight a wide non-adherence prevalence rate of studies included, ranging from 0.06% to 89.2%. This was dependent on the type of measurement method utilised, supporting DiMatteo (2004) who indicated measurement method used can impact non-adherence prevalence rates reported. When exploring this within each type of measurement method, prevalence rates remained wide in range. Self-report ranged from 7.4% to 89.2%. This is likely due to the fact that studies are using different self-report measures to assess adherence, each with differing items and scoring systems to classify adherent/non-adherent patients. There are a number of questionnaires available to assess adherence, some specific to immunosuppressants and some more broad to assess the medication regimen. A clear and standard definition of adherence/non-adherence is needed. Additionally, further research is needed to explore the reliability of existing self-report measures in terms of their use within the renal transplant population. Researchers should be encouraged to utilise reliable and valid self-report measures to assess adherence within this patient population, to improve accuracy of prevalence rates and allow for clearer comparisons to be made across studies.

Similarly, clearer guidance in defining non-adherence by other measurement methods is also needed. Although electronic monitoring provides a more accurate representation of non-adherence (Kreys, 2016) clarity in how to interpret the data in order to identify and categorise non-adherent patients will assist in consolidating outcomes to make comparisons across studies. Some studies have attempted to

do this (Butler et al., 2004; Schafer-Keller et al., 2008), however, this is limited and not consistent across studies. This is similar for studies using pharmacy refill data, with one author applying the same definition of non-adherence across studies conducted (Chisolm et al., 2000; 2005; 2007; 2016), however, wider implementation of this across studies is limited. Use of immunosuppressant blood levels are accompanied by similar limitations in terms of how to define and categorise non-adherent patients. Clearer guidelines on expected immunosuppressant blood levels should be provided for use in research in order to identify target ranges. However, it is important to note that target ranges may be individualised to a patient, consider patient factors such as transplant vintage or differ based on local trust target ranges.

Findings from this review also highlight areas that could be targeted for intervention in order to improve adherence rates. Patients that are younger in age were identified as more likely to be non-adherent, similar to findings in other literature and reviews (Raiz et al., 1999; Denhaerynck et al., 2005; Belaiche et al., 2017). Adherence has also been shown to increase with age (Chisolm et al., 2007; Lin et al., 2011). This may be due to a busier lifestyle at a younger age, such as work and family life. Additionally, older aged patients may have other health conditions to manage alongside their transplant which may engage them more closely with treatment regimens. Other sociodemographic characteristics associated with non-adherence included male gender and employment status. Similarly to age, patients in full or part-time employment may balance busier lifestyles and may be at risk of non-adherence due to this. Encouraging patients to utilise reminders such as via mobile phone alarms or use of diaries may avoid unintentional non-adherence, such as forgetting.

As patients move further from date of transplantation, likelihood of non-adherence increases. This may be due to complacency and forgetting (unintentional adherence) or may be due to patients intentionally not taking medication where function has been stable over a long period of time. Often non-adherence is unintentional and occurs when patients forget or find themselves outside of their daily routine (Griva et al., 2012). Qualitative studies have shown how perception of medication

necessity is important for ensuring successful medication taking (Ruppar & Russell, 2009). Patients may benefit from education sessions once they reach a certain number of years post-transplant to remind them of the necessity of the immunosuppressant medications they are taking to encourage/promote continued adherent behaviour. The majority of studies included in the review didn't report or distinguish between intentional and unintentional non-adherence. Greater understanding in relation to this breakdown in adherent behaviour may be captured via qualitative work, which wasn't in the scope of this review.

Some studies included in the review identified an association between donor type and adherence, with patients receiving a living donor graft to be more at risk of non-adherence. Denhaerynck et al., (2014) reported patients who received a living related donor graft had lower adherence. Patients receiving living unrelated donor and deceased donor transplantations had similar adherence levels, indicating that relatedness may be an important characteristic. This may be due to dynamics in relationships between donor and recipient, and/or significant pressure to be adherent following receiving an organ from a relative, which may prove counterproductive. Additionally, it may be due to patient beliefs that those receiving a living donor transplant require less immunosuppression e.g. due to a better HLA-matched kidney and are less likely to experience rejection (Denhaerynck et al., 2014). However, it must be noted that some studies report no differences in adherence between recipients of living and deceased donor transplants (Griva et al., 2012; Massey et al., 2013; Tielen et al., 2014).

Patients who experience psychological distress may also benefit from intervention in order to improve adherence. Depression and anxiety were associated with non-adherence in some of the studies included in the review. Previous literature has shown psychological distress (Achille et al., 2006; Lee et al., 2015), emotional distress (Jindal et al., 2003) and higher frequency of stress (Brito et al., 2015) is experienced by renal transplant recipients and can lead to lower adherence levels. Symptoms of depression may also lead to intentional non-adherence (Griva et al., 2012). Additionally, experiencing side effects of immunosuppressants (Rosenberger et al., 2005; Cheng et al., 2012) and symptom burden (Low et al., 2015) may also lead to non-adherence. Patients often consider transplantation as a

treatment that will allow them to return to a more normal life (Tucker et al., 2019) and therefore experiencing side-effects or adverse events, such as graft rejection, may be unexpected and challenging for patients. Interventions to help patients manage expectations may be beneficial to assist in coping with adjusting to life post-transplant.

This review will be updated for publication. Around 1000 citations have been identified from the databases following searches for literature published in 2018-2019. Based on the screening process reported in the PRISMA flow chart, we can likely expect 1% of the citations to be potentially relevant for inclusion.

#### 4.4.1 Strengths and limitations

This review included a wide range of databases in order to try and capture all relevant existing literature eligible for inclusion in the review. Additionally, a comprehensive search strategy was devised utilising both free text terms and MeSH terms. Furthermore, this review provides an updated synthesis of the literature exploring non-adherence to immunosuppressants among renal transplant recipients, updating reviews conducted in 2003 (Jindal et al., 2003), 2004 (Butler et al., 2004) and 2017 (Belaiche et al., 2017). Measurement methods and definitions of adherence/non-adherence were assessed which provides important considerations for the development of future research in this field. Additionally, factors associated with increased risk of non-adherence were highlighted, providing potential areas for future interventions. Finally, the review was pre-registered, therefore considering open and transparent science practice.

Despite these strengths, some of the intended analyses were not feasible due to data related issues such as heterogeneity in methods of non-adherence assessment, reported outcomes across studies and statistical analysis. Not enough data was available for impact on graft failure, therefore this was not explored. However, a pooled estimate of non-adherence prevalence rates using self-report measures was included. Additionally, the majority of studies included in the review utilised self-report measures to assess adherence. This could impact the accuracy of reported adherence/non-adherence

due to the reliance on recall and potential for social desirability response bias (Schafer-Keller et al., 2008). However, as the most common method used, it is likely that these current estimates are the most pragmatic and clinically useful. Finally, we only explored factors identified as associated with non-adherence. We did not explore studies reporting no significant associations. Further research is needed to verify factors associated with non-adherence to confirm these are representative of the patient population.

#### 4.4.2 Conclusion

It is clear from the literature identified in this review that non-adherence remains a prevalent issue within the renal transplant population. When assessed using the most common type of measurement, self-report, it can be expected that an estimated 37.6% of patients will be identified as non-adherent, however, prevalence rates vary across measures used. There is a lack of consistency in how adherence is measured and defined across studies and so it is likely that clear guidelines or consensus would be useful for clinical practice to identify which patients are at risk of poorer outcomes. This is necessary for all types of measurement methods, including across the different self-report measures available and widely used. Additionally, guidance is also needed on how best to combine different measurement methods for a more reliable non-adherence prevalence rate using e.g. subjective and objective measures. In accordance with previous findings, the review exposed that younger age, greater transplant vintage, living related donor grafts, and symptoms such as side-effects and psychological distress, are useful targets for intervention in order to improve non-adherence rates. Multicomponent interventions are likely to be needed to address the intersection of these factors for patients.

## Chapter 5: Adherence behaviour in patients on haemodialysis is not a clear predictor of post-transplant adherence

### 5.1 Introduction

Non-adherence is common in both haemodialysis (HD) patients and kidney transplant recipients. HD regimens are complex and demanding, necessitating attendance at HD sessions, adherence to prescribed medications, fluid and dietary restrictions (Kammerer et al., 2007; Kim & Evangelista, 2010). Poor adherence to treatment can lead to complications, poor clinical outcomes, increased risk of mortality (Leggat et al., 1998; Saran et al., 2003) as well as adding to healthcare and treatment related costs (Cleemput et al., 2004; Kugler, Maeding & Russell, 2011). Due to the high demand of HD and associated restrictions, patients may not adhere to the prescribed treatment regime (Denhaerynck et al., 2007).

There is a lack of consensus on definitions, which contributes to widely varying non-adherence rates in the HD population. A review of previous research examining non-adherence rates to aspects of the HD treatment regimen found reported non-adherence rates in this population to vary (Kim & Evangelista, 2010). The authors reported ranges in rates of attendance (0-32.3%), medication adherence (1.2-81%), fluid adherence (3.4-74%), and diet restrictions (1.2-82.4%). This large variation in adherence rates is likely due to inconsistency in the measures used, such as self-report or clinical data, a lack of consistency in clinical definitions of non-adherence, and the time period over which data is collected (Kim & Evangelista, 2010). Therefore, as is the case in transplant, the measurement of adherence in HD is nuanced.

There have been some attempts to achieve consensus. A US renal data system (USRDS) study (Leggat et al., 1998) defined non-adherence in the following ways: 1) skipping HD sessions; 2) shortening HD sessions by ten minutes or more; 3) an interdialytic weight gain of more than 5.7% of patient dry weight; and 4) serum phosphate of greater than 7.5mg/dL. Skipping and shortening HD sessions was measured over a one-month period, where patients were classified as non-adherent if

they skipped or shortened one or more sessions. These were considered good indicators of adherence with HD treatment itself, and as common manifestations of non-adherence to dialysis (Kutner et al., 2002). The researchers suggested that adherence to HD was almost entirely controlled by patient behaviour (Leggat et al., 1998). Phosphate was used as a measure of medication and dietary adherence. As HD does not fully remove the extra phosphorous in the blood, most patients are required to adhere to dietary requirements or to take phosphate binder medication to control phosphorous levels. High levels of phosphorous could indicate non-adherence to dietary requirements or medication. Although these measures of non-adherence are criticised due to occurring within a narrow timeframe, longitudinal research has shown that patients classified as non-adherent in one month were continuously non-adherent, and those classified as adherent when measured in one month remained adherent (Sherman et al., 1994). However, it is important to note that adherence could change, and patients categorised as non-adherent during the one-month period of in question could become adherent in following months and vice versa. Overall, Leggat et al., (1998) found that non-adherence ranged from 8.5% - 22.1%, dependent on the measure used. The highest rates of non-adherence were found for shortening HD by ten or more minutes (20.3%) and serum phosphate of greater than 7.5mg/dL (22.1%). A high correlation was found among the different measures of non-adherence suggesting consistency in outcome. The strongest predictors of non-adherence were younger age and smoking status.

Further research exploring non-adherence in HD has utilised the USRDS methodology (Saran et al., 2003; Hecking et al., 2004) namely as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS). DOPPS provided in depth reviews of adherence using European and global data. Similar non-adherence levels were found, ranging from 3.8-19.6% for the overall sample and 0.6-20% for the European sample only (Saran et al., 2003), and from 0.6-23.8% for the overall sample and 0.8-21.9% for the UK sample only (Hecking et al., 2004). Again, the variation in rates was dependent on how non-adherence was defined and measured. Saran et al., (2003) also found the following were associated with increased odds of non-adherence: younger age; female gender; disabled status; living alone; African-American race; smoker; depression; time with ESRD. These determinants support

those found by Leggat et al., (1998) and demonstrate that at least in a 4-5 year period, little has changed in terms of clinical interventions to enhance adherence behaviour.

Compared with HD patients, kidney transplant recipients have improved quality of life, a less restrictive diet, longer life expectancy (Jindal et al., 2003) and less psychological symptoms such as depression (Cukor et al., 2009). Nonetheless, these patients are also required to make adjustments in their lifestyle such as adherence to immunosuppressants to prevent rejection, alongside attending clinic for regular check-ups and generally maintaining a good diet and activity level (National Kidney Federation, 2000). However, non-adherence in this context remains common and resultant ill health is costly for the NHS and individuals, as services required for dialysis are more expensive than services required to support patients with a functioning transplant (Jindal et al., 2003). It is therefore important to address issues of non-adherence to ensure graft survival following transplantation.

Non-adherence is a major risk factor for poor outcomes including graft survival (Loghman-Adham, 2003). Reported rates of non-adherence to immunosuppressants in transplant patients vary and again definitions and methods of assessment are inconsistent. Methods such as self-report, electronic monitoring, reports from family or healthcare professional observations are most common (Denhaerynck et al., 2005). Use of clinical data to assess non-adherence in this setting is less frequently used.

It is important to consider how adherence behaviour may transfer from one modality to another. For example, if poor adherence in HD patients pre-transplant could be identified and addressed, could post-transplant adherence be improved and with it the risks of graft loss? Less research has been conducted exploring the relationship between pre and post-transplant adherence among renal transplant recipients. Douglas et al., (1996) conducted a longitudinal retrospective chart audit to examine this relationship, specifically considering pre-transplant adherence and post-transplant outcomes in 126 renal transplant recipients over a three-year period. They defined non-adherence as having at least one note indicating pre or post-transplant non-adherence with a therapeutic regimen in

the clinical chart. Findings revealed that 61% of patients identified as non-adherent prior to transplantation experienced graft loss or died. This research indicated a relationship between pre-transplant adherence and post-transplant outcomes; however, this method of defining non-adherence is not particularly stringent despite being related to severe consequences for patients.

More recently, Dobbels et al., (2009) prospectively followed 141 heart, liver and lung transplant recipients, examining pre-transplant predictors of post-transplant outcomes. Patients were followed from pre-transplant until one year post-transplant. Independent predictors of non-adherence with immunosuppressant's one-year post-transplant were pre-transplant non-adherence with medication taking; lower social support with medication taking; higher education status; low scores on personality trait "conscientiousness". Higher education status, for example, may seem counter intuitive as one might consider higher education to be associated with greater understanding for medication necessity, however, it may be that those with higher education levels have busier work lifestyles which interferes with adherence to treatment regimes. A meta-analysis of 122 studies also suggested poor social support with medication taking is a key determinant of non-adherence (DiMatteo, 2004). In addition, pre-transplant medication adherence was found to be the only predictor of late acute rejection. Although this research was not conducted in the renal transplant population, it signals the importance of attending to pre-transplant behavioural patterns in predicting post-transplant outcomes.

Research in the renal transplant population has identified socio-economic factors related to non-adherence similar to those found by Dobbels et al., (2009), including perceiving low social support as well as younger age and being unmarried (Denhaerynck et al., 2005). It is also fair to assume that transplantation in all of these contexts, as with kidney disease, improves outcomes versus any other interim symptom relief. There are parallels therefore to be drawn about the level of non-adherence that persists despite a need to preserve and do justice to organs. Moreover, Dobbels et al., (2009) lead to the curious question of whether non-adherent HD patients go on to become non-adherent transplant recipients without any form of meaningful behaviour change attempts. This would have implications

for how patients are prepared for transplantation and beyond. We need, for clinical utility, to therefore baseline rates of non-adherence within patients across modalities of treatment and to consider suitable points for intervention to be more fruitful.

### 5.1.1 Aims and objectives

To our knowledge, there is little previous literature examining the relationship between clinical measures of pre-transplant adherence to HD and clinical measures of post renal transplant adherence in the renal transplant population. This is important as a high percentage of HD patients go on to receive a transplant. Although previous literature has highlighted predictors of non-adherence to HD and post-transplant adherence separately, there is little exploration of whether there is a relationship that could help clinicians identify aspects of pre-transplant non-adherence that act as potential risk factors for post-transplant non-adherence. Additionally, this could highlight patients that need to be targeted for intervention to address adherence concerns prior to transplantation in order to modify adherence behaviour post-transplant. It is clear from the literature that non-adherence both pre-transplant when on HD, and post-transplant, is a major risk factor for poor clinical outcomes and hence important to address. As such, the current study was designed to address whether non-adherent HD patients become non-adherent transplant recipients. It also considers whether there are particular patterns of non-adherence to HD, which are more likely to associate with poor adherence following transplantation. This question is of interest not only for patient quality of life, but arguably since there is a justice issue for donated organs to advance the most benefit.

## 5.2 Method

### 5.2.1 Setting and participants

This was a retrospective study carried out in a regional renal unit. Data was collected from an electronic patient system held at the NHS Trust about adherence to HD regimens in the six months prior to transplantation, and for one-year post-transplantation following return transfer to the post-transplant clinic from the transplanting centre. The system on which data is recorded is unique to the

Trust and allows for the recording of data such as clinical tests and patient notes from clinic visits and telephone consultations with health care staff. As this data was readily available, it made it a pragmatic and cost-effective means through which to address the association between pre-transplant and post-transplant adherence.

The study population consisted of 88 adult (aged 18 years and over) kidney transplant patients transplanted between 2006 and 2016, who had received HD for a minimum of six months prior to transplantation. A minimum of six months was required as this was considered an appropriate time-period to account for observation of natural behavioural occurrences and to ensure typical behaviour (adherent/non-adherent) was captured. Data was obtained from the renal plus database at East and North Herts NHS trust for six months prior to transplantation, and for one-year post-transplantation following return transfer to the East and North Herts NHS trust renal post-transplant clinic from the patients transplanting hospital.

#### 5.2.2 Inclusion/ exclusion criteria

Patients that returned to the post-transplant clinic prior to 2006 were excluded, as the hospital database did not upload electronic notes from clinic visits prior to this year. In addition, patients were excluded if they were transferred later than one-year post-transplantation back to the East and North Herts NHS Trust transplant clinic from the transplanting hospital. Further exclusions included: patients who received HD for less than six months prior to transplantation; patients that received home HD or peritoneal dialysis in the six-month period prior to transplantation; patients who did not take tacrolimus as their post-transplant immunosuppressant.

Of a sample of 204 kidney transplant patients who had received HD as a treatment at some stage prior to transplantation, 88 were eligible for inclusion in the study analysis. The remaining 116 patients were excluded, as they did not meet the inclusion criteria. The flow diagram (figure 5.1) illustrates the number of patients excluded from inclusion and why:

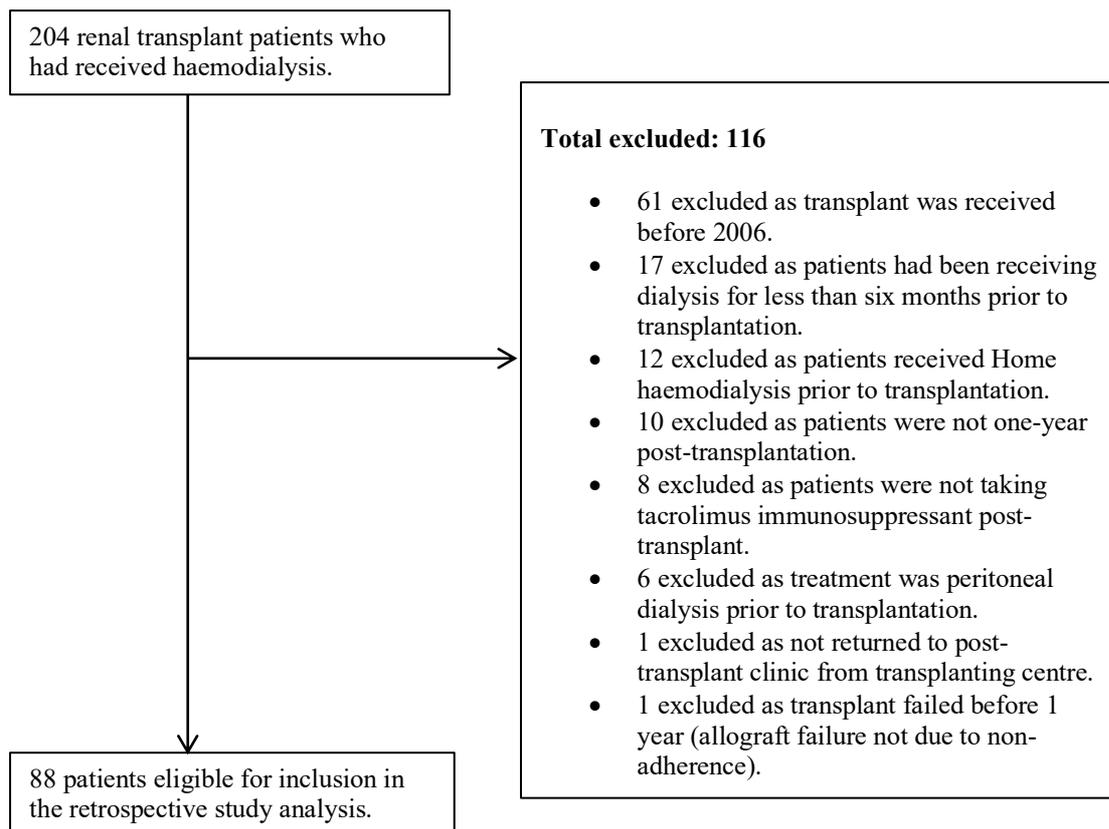


Figure 5.1: Flow diagram of participant study inclusion/exclusion.

### 5.2.3 Demographic and clinical data

A retrospective analysis compared non-adherence in renal transplant recipients prior to transplantation when on HD. Data was retrieved on the six-month period prior to transplantation.

Demographics retrieved for each patient included age, sex, ethnicity, age at first dialysis session, age at transplant and index of multiple deprivation (IMD) as calculated using patient postcodes via gov.uk.

### 5.2.4 Pre-transplantation

Clinical data collected as part of routine care was retrieved that could provide indicators of non-adherence. Pre-transplant information was retrieved on the following for the six-month period prior to transplantation:

- Most recent dialysis prescription (in minutes of session length)

- Mean dialysis prescription (in minutes of session length)
- Mean time spent on dialysis per session (in minutes of session length)
- Variance from dialysis prescription (in minutes of session length)
- Number of missed dialysis sessions
- Dialysis vintage
- Residual kidney function (KRU)
- Most recent patient dry weight
- Phosphate
- Parathyroid hormone (PTH)
- Interdialytic weight gain (IDWG)

#### 5.2.5 Post-transplantation

Post-transplantation, the following information was retrieved for one-year following return transfer to the East and North Herts NHS Trust transplant clinic from the transplanting hospital:

- Mean Tacrolimus levels and their standard deviation
- Number of missed clinic appointments
- Immunosuppression regimen
- Donor type (Living or deceased donation)
- Experience of delayed graft function

From collecting the above data, direct comparisons could be made to assess patients adherence levels pre-transplant when receiving dialysis, and post-transplant in order to identify if there were any change in levels of adherence following transplantation. As different markers were used to measure adherence pre-transplant compared to post transplant, a narrative comparison of the data was reported using appropriate statistical analyses.

## 5.2.6 Outcome measurements

### *Pre-transplantation:*

#### *Variance from dialysis prescription*

To calculate the variance from dialysis prescription, the mean dialysis prescription and mean time spent on dialysis per session were calculated for the six-month period prior to transplantation. To calculate the *mean dialysis prescription*, dialysis prescription times for the six-month period prior to transplantation were recorded, the mean was calculated for each month, and the monthly means were then used to calculate the mean dialysis prescription. To calculate the *mean time spent on dialysis per session*, the time spent on dialysis during each session was recorded in minutes for the six-month period prior to the date of transplantation. The mean was then calculated using these values to provide an average length of dialysis per session. These two values were used to create the variance from dialysis prescription, by subtracting the mean time of dialysis per session from the mean dialysis prescription. This showed the mean difference in minutes between the dialysis prescription, and the time spent on dialysis for the six-month period prior to transplantation.

#### *Missed dialysis sessions*

Missed dialysis sessions were recorded as the number of sessions missed in the six-months prior to transplantation until the date of transplantation (in six months the average number of dialysis sessions is 72, based on patients dialysing on a thrice weekly regime). Missed sessions due to hospitalisation or periods of dialysis away from base (e.g. holidays) were not included as this was not considered non-adherence.

#### *Phosphate*

Mean phosphate for the six-month period prior to transplantation was calculated. Phosphate measurements were taken on a monthly basis as part of routine medical care. According to the 2016 renal registry report, the recommended serum phosphate level therapeutic range is between 1.1-1.7mmol/l (Methven et al., 2017). Previous research which included serum phosphate as a clinical measure of non-adherence took a level of >1.8mmol/l to indicate non-adherence (Wileman et al.,

2011). Based on clinical guidance and previous research, phosphate levels above 1.8mmol/l were considered non-adherent in this study.

#### *Parathyroid hormone (PTH)*

Mean PTH was calculated for the six-month period prior to transplantation using the measurements taken as part of routine medical care. PTH measurements were recorded every 3-6 months. Patients would therefore either have one or two PTH readings for the six months prior to transplantation, of which the mean was recorded. PTH is monitored as secondary hyperparathyroidism (high levels of PTH) can cause bone disease and can also cause calcium to build up on organs and tissues.

#### *Residual kidney function (KRU)*

Mean residual kidney function for the six-month period prior to transplantation was calculated. KRU measurements were recorded on a monthly basis as part of routine medical care, of which the mean was recorded for this period.

#### *Interdialytic weight gain (IDWG)*

IDWG is the weight increase between the end of one dialysis session and the start of the next. The extent of IDWG in HD patients is usually related to the level of adherence with fluid restriction. The mean IDWG for the six-month period prior to transplantation was automatically calculated using the database at East and North Herts NHS Trust by entering two dates: start date - six-months prior to transplant date, end date – date of transplantation. The mean IDWG was then calculated.

#### *Post-transplant:*

##### *Tacrolimus*

Mean tacrolimus levels were calculated for the one-year period post-transplantation, following patient return transfer to the East and North Herts NHS Trust post-transplant clinic. Immunosuppressant levels are recorded prior to clinic appointments, as part of routine medical care. Patients were categorised as adherent if they had tacrolimus levels within the therapeutic range of 5-10ng/mL. This

range was used based on clinical advice and previous literature (Schafer-Keller et al., 2008) for expected ranges within the first two years following transplantation.

#### *Missed clinic appointments*

Missed clinic appointments were recorded as the number of appointments a patient had not attended (DNA) in the first year post-transplant following return transfer to the East and North Herts NHS Trust transplant clinic from the transplanting hospital (from the date of the first clinic appointment at East and North Herts NHS Trust renal post-transplant clinic). Missed clinic appointments due to hospitalisation were not included. The frequency of post-transplant clinic appointments is determined on a case-by-case basis. This can generally vary from every 4 weeks, 8 weeks, or 12 weeks.

#### *Delayed graft function*

Delayed graft function was recorded for any patient who experienced an episode that may or may not have required treatment (including dialysis) or an episode(s) of acute rejection post-transplant, from the time of transplantation to the end of the first year following return transfer to the East and North Herts NHS Trust post-transplant clinic.

#### 5.2.7 Defining adherence

There is no agreed way of defining adherence pre and post-transplant, therefore, using previous literature (Leggat et al., 1998; Saran et al., 2003; Hecking et al., 2004; Schafer-Keller et al., 2008) and clinical experience, different cut off points were applied to assess the data to uncover any relationships between pre and post-transplant adherence.

Pre-transplant (six-month period prior to transplantation) definitions of non-adherence included if patients:

1. On average shortened their dialysis prescription by >10 minutes;
2. On average shortened their dialysis prescription by >15 minutes;
3. Missed two or more haemodialysis sessions;

4. Had mean serum phosphate levels  $>1.8\text{mmol/l}$ .

Post-transplant (one-year period following return transfer from the transplanting hospital) definitions of non-adherence included if patients:

1. Mean tacrolimus levels outside of the expected range within the first two years of 5-10 ng/mL following transplantation;
2. Missed one or more post-transplant clinic appointments.

For this study, we used a six-month period to assess non-adherence pre-transplant, whereas previous studies (Leggat et al., 1998; Saran et al., 2003; Hecking et al., 2004) defined non-adherence in a narrower time frame of one month. Differences were therefore made to some of the pre-transplant measures of adherence accordingly. A longer time frame would account for natural changes in behaviour overtime that shorter frame measurement cannot untangle. In addition to using shortening dialysis prescription by  $>10$  minutes used in previous research as a definition of non-adherence, we also used  $>15$  minutes as a cut-off point, as this represented the top 25% of variance in dialysis prescription times for patients in this study. Furthermore, previous studies used a higher non-adherence cut off point for serum phosphate levels of  $7.5\text{mg/dL}$  (this equates to roughly  $\sim 2.42\text{mmol/l}$ ). For this research, we chose to use a cut-off point in line with previous research using serum phosphate as a measure of non-adherence (Wileman et al., 2011) and in line with the recommended renal association serum phosphate level of  $1.1\text{-}1.7\text{mmol/l}$  in the UK (Methven et al., 2017). Post-transplant tacrolimus therapeutic range was determined by clinical advice and previous research, which used this range (Schafer-Keller et al., 2008).

#### 5.2.8 Statistical analysis

As different markers were used to measure adherence pre-transplant compared to post transplant, a narrative comparison of the data is reported. Demographic data is reported for the study sample using means and frequencies. Comparisons of the data were completed using McNemar's test and Cochran's Q for categorical data and t-tests for continuous data. P-values of less than 0.05 were

considered to be significant. Logistic regressions were used to determine potential predictors of non-adherence both pre and post-transplant. McNemar's test was used to explore relationships between pre and post-transplant adherence. The data was analysed using SPSS version 25.

### 5.2.9 Approvals

This study was considered by the institutional review team at East and North Hertfordshire NHS Trust (RD2016-82) and determined to be a service evaluation. Departmental agreement was provided for the service evaluation to be completed.

## 5.3 Results

### 5.3.1 Patient characteristics

Patient characteristics for the sample are shown in Table 5.1. Ethnicity is shown for the overall sample and by gender. Of the 88 patients, the sample included more males (62.5%) than females (37.5%). Mean age at transplant for the overall sample was 48.5 years (SD=12.7), with no significant differences between genders. Across the overall study population, 54.5% were from white European ethnic backgrounds, although a considerable proportion were from other ethnic groups (45.5%). Breakdowns of the different patient ethnicities are shown in Table 5.1. Comparisons were made between males and females, and both groups had a fairly equal split of patient ethnic heritage.

Chronic glomerulonephritis (21.6%: N=19), diabetic nephropathy (20.5%: N=18), polycystic kidney disease (13.6%: N=12), chronic pyelonephritis (9.1%, N=8), and hypertension (4.5%: N=4) accounted for the majority of causes of ESRD in the sample. Aetiology was uncertain for over a quarter of the sample (28.4%, N=25).

Table 5.1: Demographics for the study sample including ethnicity and comparisons by gender.

		N=88 (100%)	Male N=55 (62.5%)	Female N=33 (37.5%)
<i>Ethnicity n (%)</i>	White European	48 (54.5)	30 (54.5)	18 (54.5)
	Non-white European	3 (3.4)	2 (3.6)	1 (3.0)
	South Asian	24 (27.3)	17 (30.9)	7 (21.2)
	Black	11 (12.5)	5 (9.1)	6 (18.2)
	Other Ethnic	2 (2.3)	1 (1.8)	1 (3.0)
	Minority Ethnic total	40 (45.5)	25 (45.5)	15 (45.5)

Deprivation index was also recorded for all patients to examine if there were any differences in social deprivation between white and non-white patients (Table 5.2). The indices of deprivation rank every postcode in England from 1 (most deprived) to 32, 844 (least deprived). These are split into deciles of 1-10 from most deprived to least deprived dividing them into 10 equal groups. The most deprived 10% is represented by 1 and the least deprived 10% by 10. Table 5.2 shows the deprivation deciles for the overall sample, and a comparison between white European and patients from minority ethnic groups. Across the overall sample, 23.9% (n=21) of patients live in neighbourhoods that fall in the 20% most deprived small areas in England. Findings differed across ethnicity, with 40% (n=16) of minority ethnic patients shown to live in neighbourhoods that fall in the 20% most deprived small areas in England, compared to 10.4% (N=5) of white European patients.

Table 5.2: Deprivation index: comparing white European and minority ethnic patients

	Total (N=88)	White European (N=48)	Minority ethnic (N=40)
<i>Index of multiple deprivation decile</i>			
1	2 (2.3)	1 (2.1)	1 (2.5)
2	19 (21.6)	4 (8.3)	15 (37.5)
3	9 (10.2)	5 (10.4)	4 (10.0)
4	10 (11.4)	3 (6.3)	7 (17.5)
5	5 (5.7)	3 (6.3)	2 (5.0)
6	8 (9.1)	6 (12.5)	2 (5.0)
7	8 (9.1)	5 (10.4)	3 (7.5)
8	4 (4.5)	4 (8.3)	0
9	14 (15.9)	11 (22.9)	3 (7.5)
10	9 (10.2)	6 (12.5)	3 (7.5)

### 5.3.2 Clinical pre-transplant data

Non-adherence ranged from 25% to 42% dependent on how it was operationalised. When non-adherence was defined as shortening dialysis prescription by more than 10 minutes, 39.8% of patients were identified as non-adherent. This percentage reduces as the definition of adherence becomes more stringent (>15mins = 25% non-adherent). When defining non-adherence using the number of missed HD sessions as two or more, 27.3% of patients were identified as non-adherent. When using phosphate level as greater than 1.8mmol/l to define non-adherence, 42% of patients were defined as non-adherent (Table 5.3). There were no significant demographic differences between groups across measures, with the exception that patients categorised as non-adherent based on phosphate levels were significantly younger age at transplantation, ( $t(86) = 1.99, p = .049$ ) than those categorised as adherent (Table 5.3). Cochran's Q was used to determine if there were any differences in patients identified as non-adherent across the four pre-transplant measures. There was a statistically significant difference in the proportion of non-adherent patients across the four non-adherence measures ( $\chi^2(3) = 9.79, p = .020$ ), indicating differences in patients identified as non-adherent across the four pre-transplant measures.

We explored whether pre-transplant clinical data predicted pre-transplant adherence. Dialysis vintage, KRU, serum phosphate, PTH and IDWG were compared independently across adherent and non-adherent patients using the four pre-transplant adherence measures. All measures were skewed with the exception of serum phosphate. There was a significant difference for KRU between adherent and non-adherent patients, when adherence was defined as shortening dialysis by >10 minutes ( $U = 684.5, p = .035$ ), adherent patients having lower residual kidney function than non-adherent (Table 5.3). No other significant differences were observed between adherent and non-adherent patients when adherence was defined as shortening dialysis by >10mins or by >15mins. Significant differences were observed when adherence was defined using serum phosphate levels. Patients categorised as non-adherent based on their phosphate levels had lower KRU,  $U = 648, p = .011$ , and higher parathyroid hormone levels,  $U = 545.5, p = .002$  (Table 5.3).

Table 5.3: Demographic comparison of adherent and non-adherent patients pre-transplant. KRU = Urea clearance (ml/min), PTH = Parathyroid hormone (pmol/l), IDWG = Interdialytic weight gain (kg)

	N=88 (%)	Pre-transplant shortening dialysis prescription >10mins		Pre-transplant shortening dialysis prescription >15mins		Pre-transplant missed dialysis sessions 2 or more		Phosphate $\geq$ 1.8mmol/l	
		Adherent	Non-adherent	Adherent	Non-adherent	Adherent	Non-adherent N=24 (27.3%)	Adherent	Non-adherent
		N=53 (60.2%)	N=35 (39.8%)	N=66 (75%)	N=22 (25%)	N=64 (72.7%)		N=51 (58%)	N=37 (42%)
Age at transplant M (SD)	48.5 (12.7)	49.2 (13.4)	47.5 (11.6)	49.1 (13.1)	46.9 (11.4)	48.4 (12.8)	48.9 (12.6)	50.8 (11.7)	45.4 (13.4)*
Age at first dialysis M (SD)	44.9 (13.0)	45.3 (13.7)	44.3 (12.0)	45.1 (13.6)	44.2 (11.2)	44.7 (13.3)	45.5 (12.4)	47.2 (12.3)	41.7 (13.4)
Gender N (%)									
Male	55 (62.5)	32 (60.4)	23 (65.7)	41 (62.1)	14 (63.6)	39 (60.9)	16 (66.7)	31 (60.8)	24 (64.9)
Female	33 (37.5)	21 (39.6)	12 (34.3)	25 (37.9)	8 (36.4)	25 (39.1)	8 (33.3)	20 (39.2)	13 (35.1)
Ethnicity N (%)									
White European	48 (54.5)	29 (54.7)	19 (54.3)	39 (59.1)	9 (40.9)	32 (50)	16 (66.7)	28 (54.9)	20 (54.1)
Minority ethnic	40 (45.5)	24 (45.3)	16 (45.7)	27 (40.9)	13 (59.1)	32 (50)	8 (33.3)	23 (45.1)	17 (45.9)
Index of multiple deprivation (IMD) M (SD)	5.5 (2.9)	5.3 (3.0)	5.9 (2.8)	5.6 (3.0)	5.2 (2.7)	5.3 (3.1)	5.9 (2.6)	6.0 (3.0)	4.8 (2.7)
<i>Dialysis</i>									
Dialysis vintage (months) Median (IQR)	26 (16, 49)	26 (16.3, 54)	26 (15, 40)	26 (17, 51)	24 (13, 39)	25 (16, 48)	27 (16, 50)	28 (15, 55)	24 (17, 40)
KRU Median (IQR)	.42 (.01, 2.2)	.30 (.01, 1.2)	1.28 (.07, 2.7)*	.41 (.01, 1.9)	.64 (.01, 2.6)	.39 (.01, 2.2)	.81 (.01, 2.3)	1.1 (.01, 2.8)	.10 (.01, .86)*

PTH Median (IQR)	37 (25, 57)	35 (22.2, 57)	43 (25, 59)	36 (25, 57)	43 (25, 60)	38 (26, 57)	30 (14, 70)	30 (17, 51)	50 (34, 72)*
IDWG Median (IQR)	1.79 (1.24, 2.4)	1.8 (1.4, 2.4)	1.8 (1.1, 2.4)	1.8 (1.2, 2.4)	1.8 (1.1, 2.5)	1.8 (1.2, 2.4)	1.9 (1.3, 2.5)	1.7 (.94, 2.4)	1.8 (1.6, 2.5)

\* $p < .05$

Logistic regression analyses were conducted to identify possible predictors of non-adherence among pre-transplant patients. Factors included in the models were age at transplant, gender, ethnicity, index of multiple deprivation and dialysis vintage. No significant predictors of non-adherence were identified for any of the non-adherence measures (Table 5.4).

Table 5.4: Predictors of non-adherence pre-transplant.

	<i>Odds ratio and 95% CI by non-adherence measure</i>			
	Pre-transplant shortening dialysis prescription >10mins	Pre-transplant shortening dialysis prescription >15mins	Pre-transplant missed dialysis sessions 2 or more	Phosphate >1.8mmol/l
Age at transplant (years)	0.99 (0.95, 1.03)	0.99 (0.94, 1.03)	1.00 (0.96, 1.05)	.97 (0.93, 1.01)
Male (vs. female)	1.17 (0.45, 3.04)	1.23 (0.41, 3.68)	1.75 (0.58, 5.30)	1.15 (0.43, 3.13)
White European (vs. minority ethnic)	0.71 (0.26, 1.91)	0.45 (0.15, 1.38)	1.71 (0.56, 5.16)	1.03 (0.37, 2.88)
Index of Multiple Deprivation	1.06 (0.89, 1.26)	0.98 (0.80, 1.19)	1.00 (0.83, 1.22)	0.87 (0.72, 1.04)
Dialysis vintage (months)	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)

### 5.3.3 Clinical post-transplant data

Patients with tacrolimus levels outside the range expected within the first two years of 5-10ng/l were highlighted. Of the 88 patients, 14 (15.9%) had tacrolimus levels outside of the expected range of 5-10ng/l. Within this, ten were male and four were female, and there were an equal number of white European and minority ethnic patients (N=7). There were no significant demographic or clinical differences between adherent and non-adherent patients defined in this way.

When non-adherence was defined using the number of missed post-transplant clinic appointments as one or more, 20 patients (22.17%) were identified as non-adherent (Table 5.5). No significant demographic differences were observed between groups when post-transplant adherence was defined in this way except that non-adherent patients were significantly younger when transplanted,  $t(86)=2.14$ ,  $p=.035$ , and significantly younger when starting dialysis,  $t(86)=2.07$ ,  $p=.041$ , than those categorised as adherent (Table 5.5).

Table 5.5: Demographic comparison of adherent and non-adherent patients post-transplantation.

	Post-transplant tacrolimus levels		Post-transplant missed clinic appointments 1 or more	
	Adherent N=74 (84.1%)	Non-adherent N=14 (15.9%)	Adherent N=68 (77.3%)	Non-adherent N=20 (22.7%)
Age at transplant M (SD)	48.8 (12.9)	46.8 (11.7)	50.0 (12.1)	43.3 (13.4)*
Age at first dialysis M (SD)	45.1 (13.3)	43.50 (11.7)	46.4 (12.2)	39.7 (14.6)*
Dialysis vintage (months)	35.9 (27.6)	29.8 (16.7)	35.4 (26.4)	33.1 (26.2)
Gender N (%)				
Male	45 (60.8)	10 (71.4)	42 (61.8)	13 (65.0)
Female	29 (39.2)	4 (28.6)	26 (38.2)	7 (35.0)
Ethnicity N (%)				
White European	41 (55.4)	7 (50)	37 (54.4)	11 (55.0)
Minority Ethnic	33 (44.6)	7 (50)	31 (45.6)	9 (45.0)
Index of multiple deprivation (IMD) M (SD)	5.7 (2.9)	4.6 (2.9)	5.69 (3.1)	4.9 (2.4)

\* $p < .05$

Across the overall sample, more patients received a deceased donor transplant (80.7%). Most patients took a combination of two or three immunosuppressants, and around one third of the sample experienced delayed graft function following transplantation (see Table 5.6).

Table 5.6: Transplant comparison of adherent and non-adherent patients.

	Total N=88 (100%)	Post-transplant tacrolimus levels		Post-transplant missed clinic appointments 1 or more	
		Adherent N=74 (84.1%)	Non-adherent N=14 (15.9%)	Adherent N=68 (77.3%)	Non-adherent N=20 (22.7%)
<i>No. immunosuppressants</i>					
1	1 (1.1)	1 (1.4)	0	1 (1.5)	0
2	44 (50.0)	38 (51.4)	6 (42.9)	32 (47.1)	12 (60.0)
3	43 (48.9)	35 (47.3)	8 (57.1)	35 (51.5)	8 (40.0)
<i>Donor type</i>					
Deceased	71 (80.7)	62 (83.8)	9 (64.3)	53 (77.9)	18 (90.0)
Living	17 (19.3)	12 (16.2)	5 (35.7)	15 (22.1)	2 (10.0)
<i>Delayed graft function</i>					
Yes	31 (35.2)	28 (37.8)	3 (21.4)	24 (35.3)	7 (35.0)
No	57 (64.8)	46 (62.2)	11 (78.6)	44 (64.7)	13 (65.0)

Logistic regression analyses were conducted to identify possible predictors of non-adherence among post-transplant patients in this study. No significant predictors for non-adherence to tacrolimus immunosuppressant medication were identified. Phosphate levels  $\geq 1.8$ mmol/l pre-transplant were identified as predicting higher odds of non-attendance to post-transplant clinic appointments (Table 5.7).

Table 5.7: Predictors of non-adherence post-transplant.

	<i>Odds ratio (OR) and 95% CI by non-adherence measure</i>	
	Post-transplant tacrolimus levels	Post-transplant missed clinic appointments 1 or more
Age at transplant (years)	0.99 (0.93, 1.05)	0.98 (0.94, 1.04)
Male (vs. female)	2.09 (0.49, 8.88)	0.80 (0.23, 2.86)
White European (vs. minority ethnic)	0.89 (0.23, 3.46)	1.40 (0.34, 5.82)
Index of Multiple Deprivation	0.85 (0.66, 1.09)	0.89 (0.70, 1.14)
Dialysis vintage (months)	0.99 (0.96, 1.02)	1.00 (0.97, 1.02)
Variance in dialysis time from prescription (mins)	1.01 (0.97, 1.04)	1.05 (0.99, 1.11)
Missed dialysis sessions >2 (vs. <2)	0.86 (0.19, 3.84)	0.60 (0.14, 2.58)
Phosphate $\geq 1.8$ mmol/l (vs. <1.8mmol/l)	0.69 (0.17, 2.80)	4.19 (1.15, 15.24)*
Donor type deceased (vs. living)	0.28 (0.06, 1.19)	2.42 (0.41, 14.29)

\* $p < .05$

In addition to looking at tacrolimus using the mean levels, the standard deviation and co-efficient of variation (CV) was also calculated to examine the variation in tacrolimus levels for each patient for the one-year period recorded post-transplantation. A non-adherence cut-off point of SD >2.0 was used in line with previous research (Shemesh et al., 2004), and tacrolimus CV% cut-off point of 41% was used, again in line with previous research (Hsiao et al., 2011). Logistic regression analyses were conducted to identify potential predictors of these parameters. No significant predictors were identified. There was no difference between the proportion of non-adherent patients defined in terms of highly variable tacrolimus levels (tacrolimus CV% > 41%) and defined in terms of missed clinic appointments ( $p = .47$  by McNemar's test).

#### 5.3.4 Comparing pre and post-transplant adherence

In general the prevalence of non-adherence was greater pre-transplant than post-transplant. The prevalence of pre-transplant non-adherence defined by shortened dialysis by >10mins was greater than post-transplant non-adherence defined by both tacrolimus levels and by missed post-transplant clinic appointments ( $p = .001$  and  $.029$  respectively; McNemar's test). Likewise the prevalence of pre-transplant non-adherence determined by phosphate levels was greater than the prevalence of post-transplant non-adherence determined by both tacrolimus levels ( $p < .001$ ) and by missed post-transplant clinic appointments ( $p = .003$ ). No other significant differences were found when comparing pre and post-transplant groups (Table 5.8).

We explored the relationship between pre-transplant demographic and clinical data to post-transplant adherence. Of the 28 patients categorised as non-adherent to either one ( $N=22$ ) or both ( $N=6$ ) post-transplant measures, 46.4% ( $n=13$ ) were non-adherent to two or more pre-transplant measures, compared with 32.2% ( $n=9$ ) who were non-adherent on a single pre-transplant measure. The remaining 21.4% ( $n=6$ ) of non-adherent patients post-transplant were adherent to all pre-transplant measures. In general there was only a weak relationship between pre-transplant data and post-transplant adherence. The exception was that patients who had missed one or more post-transplant clinic appointments had higher mean pre-transplant phosphate levels ( $M=1.92$ ,  $SD=.41$ ) compared with those who had missed none ( $M=1.69$ ,  $SD=.40$ ;  $t(86) = 2.25$ ,  $p = .027$ ). This finding suggests that patients with higher phosphate levels pre-transplant are more likely to miss clinic appointments post-transplant. There was no relationship of interdialytic weight gain with post-transplant adherence even when the analysis was confined to patients with no residual kidney function pre-transplant.

Table 5.8: Comparing pre-transplant adherence to post-transplant adherence measures.

		Pre-transplant shortening dialysis prescription >10mins			Pre-transplant shortening dialysis prescription >15mins			Pre-transplant missed dialysis sessions 2 or more			Phosphate $\geq$ 1.8mmol/l		
		Adherent	Non-adherent	<i>p</i>	Adherent	Non-adherent	<i>p</i>	Adherent	Non-adherent	<i>p</i>	Adherent	Non-adherent	<i>p</i>
		N=53 (60.2%)	N=35 (39.8%)		N=66 (75%)	N=22 (25%)		N=64 (72.7%)	N=24 (27.3%)		N=51 (58%)	N= 37 (42%)	
Post-transplant determined by tacrolimus levels	Adherent N=74	45	29	.001*	55	19	.20	53	21	.11	43	31	<.001*
	Non-adherent N=14	8	6		11	3		11	3		8	6	
Post-transplant missed clinic appointments 1 or more	Adherent N=68	40	28	.029*	48	20	.87	49	19	.61	45	23	.003*
	Non-adherent N=20	13	7		18	2		15	5		6	14	

\* $p < .05$ ; McNemar's Test

## 5.4 Discussion

The primary aim of this single-centre retrospective study was to explore whether patterns of adherence behaviour when on HD are indicative of patterns of adherent behaviour post-transplantation. Our findings do not support the likelihood of a strong direct relationship between these behaviours. However, the possibility remains of some overlap of non-adherent behaviours in these two settings as evidenced by our finding of a relationship between pre-transplant phosphate control and subsequent attendance for post-transplant follow-up. Additionally, the findings do suggest there are a proportion of patients that have: (a) missed dialysis sessions, shortened their dialysis prescription in the six months leading up to transplantation and have serum phosphate levels outside of the recommended therapeutic range; (b) missed post-transplant clinic appointments in the year following transplantation; (c) have tacrolimus levels outside of the suggested therapeutic range post-transplant. This has important implications for patients in terms of their overall health status even if there are not always immediate consequences of these behaviours.

The number of patients categorised as non-adherent was dependent on how non-adherence was defined. Pre-transplant non-adherence ranged from 25% to 42%, and post-transplant non-adherence ranged from 15.9% to 22.7%, dependent on definition. Clearly the general trend seen is that adherence behaviour improves on average with a narrower margin across outcome types from pre to post transplant. Our finding of a higher non-adherence rate for phosphate control than that quoted in the literature (Leggat et al., 1998; Saran et al., 2003) is highly likely to be due to our using a lower cut-off point for non-adherence in line with previous research from our unit (Wileman et al., 2011) and UK clinical practice guidelines (Methven et al., 2017).

Defining pre-transplant adherence in terms of phosphate control, non-adherent patients were found to be younger age at transplant, to have less residual kidney function and to have higher PTH levels. Both latter factors have well-established effects on phosphate control. Previous studies have also demonstrated negative correlations between age and phosphate control. Longer dialysis vintage was also associated with lower phosphate levels (Kim & Evangelista, 2010). In addition, self-reported

patient adherence to medication was associated with lower phosphate levels. Nevertheless, our findings may help define a group of patients in whom targeted intervention may improve aspects of adherence pre-transplant and potentially post-transplant. No other significant findings were observed when exploring predictors of non-adherence pre-transplant using clinical data. This is in contrast to previous literature.

However, serum phosphate levels are affected by clinical variables and diet, therefore the reliability as a measure of non-adherence should be interpreted with caution (Wileman et al., 2015). There are multiple factors that could influence adherence to phosphate treatment, such as complex treatment regimen, high pill burden, side effects and lack of immediate symptomatic benefit (Wileman et al., 2015). It has been suggested that dietary and fluid restrictions may require more patient willpower in order to adhere. A study found that 57.6% of patients reported difficulty adhering to dietary prescription, and 56.3% reported this was due to an inability to resist favourite foods (Kim & Evangelista, 2010). In addition, in the same study 62% reported some difficulty adhering to fluid restrictions, and 43.7% were unable to control their desire for fluid. This suggests that these aspects of the treatment regimen may be more challenging to adhere to and could explain why non-adherence rates are higher for these measures of pre-transplant non-adherence. This could indicate that phosphate is a better indicator of pre-transplant non-adherence than other measures because of the multi-faceted nature of the behaviours required to manage phosphate levels, which encompass dietary restriction, phosphate binder medication adherence, and adherence with dialysis protocols. Age may be a factor in this relationship as non-adherent patients judged by this parameter pre-transplant were significantly younger as were those who missed post-transplant clinic appointments. On the other hand, the absence of other significant predictors of post-transplant non-adherence increases the possibility that this association was a chance finding.

Post-transplant predictors of non-adherence - defined in terms of number of missed clinic appointments - similarly indicated that non-adherent patients were significantly younger at transplant and at dialysis initiation. These patients also had higher phosphate levels pre-transplant, above the

Renal Association recommended range, indicating inadequate phosphate control. Previous literature using serum phosphate as a clinical measure of non-adherence also indicated phosphate control as a major issue for HD patients (Wileman et al., 2011; Wileman et al., 2015). This is similar to our findings, which showed a mean phosphate level of 1.74 (SD=.41) for the overall sample. Logistic regression identified phosphate levels  $\geq 1.8$ mmol/l predicted higher odds of non-attendance to post-transplant clinic appointments.

We found that the prevalence of non-adherence was greater pre-transplant by some but not all measures. This may suggest that adherence with treatment post-transplant is more manageable than adherence to treatment pre-transplant which involves both HD and associated medications. However, the measures of adherence used in these setting are, of necessity, very different, so this interpretation needs to be treated with caution.

Although clinical data can provide indications of non-adherence both pre and post-transplant, previous research has shown that other factors, such as socio-economic, psychological, patient-related, may lead to non-adherence occurring. Cukor et al., (2009) suggested that depression may play an important role in non-adherence among both HD and transplant recipients. HD patients were found to be more depressed than patients with an active transplant. In addition, higher depression scores significantly correlated with low medication adherence in both HD and transplant recipients.

Furthermore, HD patients reported lower medication adherence, however, this could be explained by the complex aspect of HD treatment and restrictions accompanying the treatment process in patients with ESRD. So, it is perhaps unsurprising that non-adherence is more variable in this patient group than in transplant recipients.

Overall, these findings suggest that pre and post-transplant adherence are only weakly associated. The relationship is complex. The challenges that patients experience with adherence pre-transplant may be different following transplantation. There are multiple potential factors. For example, whether a patient has received a living or deceased donor organ may play a role in behaviour modification

(Terasaki et al., 1995; Denhaerynck et al., 2007). In addition, anxiety, depression (Achille et al., 2003; Cukor et al., 2009) and socio-economic factors (NHS BT, 2017) have been associated with non-adherence. This highlights the complexity of what could contribute to non-adherence, and the potential need for a multi-disciplinary intervention to address adherence both pre and post-transplant. Pre-transplant, patients on HD are usually entitled to free prescriptions. However, although post-transplant clinic appointments are covered via the National Health Service (NHS), post-transplant medication is not (unless patients meet the criteria for prescription payment exemption). This additionally could contribute to differences in non-adherence rates. Our findings do support existing literature pertaining to adherence in specific renal replacement therapy (RRT) modalities, for example, the relationship between younger age and non-adherence.

#### 5.4.1 Strengths and limitations

Whilst our study suggests the possibility of a complex relationship between pre and post-transplant adherence, the findings should be interpreted with caution. The sample size was small and single-centred. A power calculation was not performed prior to retrieving the data. As this is a specific patient population and data was only available from one NHS site, data was collected for as many patients that met the inclusion criteria as possible, however, it is possible findings may have been underpowered due to the small sample size. Additionally, this study only included patients that had an active transplant and had been attending the post-transplant clinic for one year. As a result of this, graft loss and survival differences between adherent and non-adherent patients with aspects of the HD treatment were not explored, as in previous studies (Leggat et al., 1998; Saran et al., 2003). As this study used patients from one hospital, it is important to consider that this could have impacted our findings, as treatment support with non-adherence available to patients can vary from site to site.

Younger age predicted high phosphate levels pre-transplant. We found no other major associations. However, the time frame in which non-adherence was assessed pre-transplant was over one month in the previous literature (Leggat et al., 1998; Saran et al., 2003; Hecking et al., 2004), whilst this study assessed pre-transplant non-adherence over a period of six months prior to transplantation. Our six-

month assessment of non-adherence may provide a more stable picture of patient behavioural patterns. Additionally, a follow-up of one year may be too shorter period for exploring post-transplant non-adherence, as research suggests rates of non-adherence can increase as time from transplantation increases (Nevins & Thomas, 2009).

Whilst we have attempted to delineate clinically relevant indices of non-adherence in the transplant population, there may be other parameters, which may be more relevant. There is limited research indicating how non-adherence should be defined clinically pre and post-transplant, therefore it is possible that the measures we used to define non-adherence post-transplant were not the most reliable and valid. This could indicate the need to identify clinically relevant definitions that accurately measure non-adherence rates to ensure this is reported reliably in future research. Notwithstanding these limitations, our study is one of the few to consider how patterns of adherence vary within patient groups as they transition between RRT modalities.

Certain aspects of the HD treatment regimen, such as diet and fluid restrictions, and symptoms, side effects and high pill burden experienced may make regimes more challenging to adhere to, and could explain why non-adherence rates are higher for these measures of pre-transplant non-adherence. In addition, the challenges that patients experience with adherence pre-transplant may be different or even eradicated following transplantation. Further research to identify a clinically relevant, reliable and valid definition of non-adherence both pre and post-transplant adherence is needed to help address the variation in non-adherence rates reported in the literature.

#### 5.4.2 Future research

Future research could consider more efficient ways of measuring and defining non-adherence pre-transplant to help further understand what mediates the relationship between pre and post-transplant adherence. Further research with renal transplant recipients via quantitative or qualitative work should be considered to explore in more detail why patients are not adhering to particular medications, and therefore what areas should be targeted via intervention. Findings highlight serum phosphate levels as

a potentially more effective clinical measure of pre-transplant non-adherence and indicate that younger patients are more likely to be non-adherent to phosphate medication. This highlights a potential target area for intervention to improve pre-transplant medication taking, which could also improve post-transplant adherence behaviour. In addition, findings highlight the complexity of contributors to non-adherence, and the importance of a multi-disciplinary intervention to address this issue in patients both pre and post-transplant.

#### 5.4.3 Conclusions

Poor phosphate control pre-transplant was associated with some aspects of adherence post-transplant. However, our findings do not indicate a strong direct relationship between pre and post-transplant adherence. Whatever measure of adherence used pre-transplant, non-adherence is less post-transplant and, in some cases, significantly so. However, the only adherence parameter that predicted post-transplant adherence was pre-transplant phosphate control. Although some patients do improve adherence to treatment post-transplant, non-adherence remains an issue for a proportion of patients post-transplant. Non-adherent patients pre-transplant should be reviewed on a case-by-case basis for transplant eligibility, to determine if adherence behaviour could change following transplantation or if interventions are needed pre-transplant prior to wait listing. These findings require confirmation and further work to assess whether interventions in relation to pre-transplant adherence may enhance adherence post-transplant and hence improve outcomes. Furthermore, enhancing patient understanding about the importance of medication and engaging with treatment regimens could help improve adherence post-transplant.

## Chapter 6: Understanding clinician attitudes towards the importance of adherence in decisions to list patients for transplantation

### 6.1 Introduction

Qualitative studies in health-related settings allow researchers to highlight participants' experiences and thought processes (Rohleder & Lyons, 2015), and can be used to understand about treatment and medication adherence. A recent systematic review of qualitative studies (Tong et al., 2011) explored the perspectives of renal transplant recipients on medication taking, as gleaned from studies using focus groups and interviews. The following themes were identified: 1) *Attitudes to medicine taking* – this comprised of a range of patient views including major life events, lifestyle, responsibility for maintaining health, protecting life and the relationship with the renal donor and health care professionals; 2) *Unintentional non-adherence*; 3) *Medication properties* – for example, patients often altered dosage or requested changes in medications due to side effects. However, patients who viewed dialysis treatment as worse than medication side effects would be more likely to adhere to taking medication as prescribed; 4) *Structure of healthcare services* – patients were sometimes conflicted by clinical appointments that asked them to alter medication taking for blood testing; 5) *Personal efforts in managing medications* – including strategies to try and improve memory and reminders; 6) *Availability of external support* – patients with strong social support from family members shared a sense of accountability which encouraged adhering to prescribed medication regimen. Research from quantitative studies support these findings, with non-adherence more often being due to patient forgetfulness (Griva et al., 2012), perceiving low social support (Denhaerynck et al., 2005; Denhaerynck et al., 2007), lifestyle (Muduma et al., 2016), high emotional distress and high transplant related stress (Jindal et al., 2003).

Research exploring patient perspectives on medication taking could lead to the development of more effective strategies to improve adherence, resulting in improved treatment outcomes for renal transplant recipients (Tong et al., 2011). However, it is not clear from the literature whether clinicians

have similar understandings or beliefs about types of factors that influence medication taking, and whether research findings inform efforts to improve patient care. Clinician understanding of adherence behaviour is important to ensure optimal patient experience and response to treatment, and that treatment regimens are adjusted and prescribed with this in mind (Tong et al., 2011; Williams et al., 2014; Muduma et al., 2016) to improve patient quality of life and prolong graft survival.

Few studies have explored clinician understanding and attitudes of non-adherence among renal transplant recipients. An interview study with nephrology nurses (Muduma et al., 2016) sought to understand reasons for non-adherence in this patient population. Nurses identified patients under the age of 25 years to be the most non-adherent and suggested that this was due to the transition from adolescent to adult care. They also indicated that young people's lifestyles conflicted with good adherence, leading to forgetting to take medication, particularly the evening dose. Young people were also suggested to be less aware of the consequences of non-adherence (Muduma et al., 2016). This could be due to parents managing medication, resulting in young patients having less awareness of the importance of adherence for maintaining their health and wellbeing post-transplant. Elderly patients were also highlighted as often forgetting to take their evening dose of medication. However, these patients were more adherent with the morning dose (Muduma et al., 2016). Middle-aged patients were indicated to be most adherent, notably those with social support from family and partners. Reasons for non-adherence were ranked in the following order: 1) Forgetting (unintentional non-adherence); 2) Pill burden; 3) Lifestyle (Muduma et al., 2016).

Williams et al., (2014) conducted a qualitative exploratory study focusing on medication taking. They interviewed nine renal transplant coordinators from five hospitals in Australia. Staff members emphasised the importance of early education in relation to immunosuppressant medication to ensure graft survival. Patients started receiving education on medication taking from when they were added to the waiting list to receive a deceased donor kidney transplant, or when the "work up" began in preparation for a live donor transplantation. Pre-transplant education sessions were run with various members of the multidisciplinary team every 2-4 months, covering areas such as renal transplant

surgery, staying healthy, medications specific to transplantation, psychosocial aspects and risks of renal transplantation. Leaflets on immunosuppressant medication and side effects were also provided. Most of the education relating to immunosuppressant medication began following transplant surgery when medication taking had started, with renal nurses explaining the function and importance of each tablet and the treatment regimen. Post-transplant booklets were also provided detailing the prescribed medications, their importance and possible side effects, as well as what to do if patients missed a dose. The authors extensively detail the importance of medication education, however, the effectiveness of this on adherence levels among their patients was not reported (Williams et al., 2014).

This limited existing literature highlights the need for further research exploring clinician attitudes and understanding of non-adherence in this patient population. This will help to identify whether providers are aware of factors that are likely to result in non-adherence to medication, and how they might work with patients to address this issue in order to improve adherence, patient satisfaction and ensure graft survival. Research has shown that patient participation is associated with positive outcomes, and clinicians that dominate clinical appointment discussions reduce patient involvement (Stevenson et al., 2004). This indicates the importance of shared decision-making. Through understanding clinician attitudes to non-adherence, this will provide some evidence of whether “shared understanding” and agreement exists between patients and health care professionals.

There is also a need to understand the importance of patient adherence in determining patient eligibility for transplantation. Guidelines on pre-transplantation assessment focus mainly on medical fitness, including cardiovascular health, obesity, exposure to infections, previous cancers etc. (Dudley & Harden, 2011). How adherence behaviour pre-transplant, with for example dialysis or pre-transplant work-up, is considered as part of this process is less clear. Currently, there is limited existing literature exploring the relationship between pre and post-transplant adherence. Some of the issues relating to dialysis adherence such as attendance to HD, fluid and diet restrictions (Kammerer et al., 2007; Kim & Evangelista, 2010) may be reduced post-transplant, however, the issue of medication adherence and clinic attendance remains. It is not yet clear if non-adherence behaviour

transfers across treatment modalities. Due to the risks to graft function (Loghman-Adham, 2003) and treatment related costs associated with graft failure (Jindal et al., 2003) it is important whether non-adherent behaviour should be more heavily considered when determining whether patients are eligible for transplantation. Additionally, how clinicians may target patients at greater risk for non-adherence post-transplant as part of transplant assessments in order to improve chances of graft survival is also unclear. It is important to identify why such a prevalent number of patients have issues with adherence post-transplant and how clinicians are considering and addressing this issue. There is of course a moral reason to understand further whether clinicians take pre-transplant adherence into consideration prior to listing for a donor organ. Most if not all healthcare systems are likely to have a higher demand for organs than supply. The morality of giving an organ to a candidate who already seems to be disengaged from optimising treatment may therefore lend itself to with-holding treatment until there are signs of improved adherence. Similar practice already operates for factors such as weight, as obese patients are at greater risk of peri and post-operative complications (Dudley & Harden, 2011). There is some evidence to suggest that patients who are not suitable for transplant waiting lists also favour an efficacy argument to give the donated organ its best chance (Lawrence, Sharma, Da Silva-Gane, Fletcher, & Farrington, 2013).

#### 6.1.1 Rationale

Clearly there is a lack of research into whether or not clinicians feature pre-transplant adherence into their decision making as to whether or not to list a patient for transplantation. Yet, such considerations about “risk” to the donated organ might shape practices aimed at further encouraging patients to engage with treatment modalities to the best of their ability. The current study was designed to explore this issue further, importantly taking a qualitative approach to endeavour to gain a rich understanding of decision making in this context.

### 6.1.2 Aims and objectives

The aim of the study was to complete semi-structured interviews with clinicians working closely with renal transplant recipients to elicit their:

- Understanding of the term “non-adherence” in relation to renal transplant recipients;
- Views on factors that influence adherence to treatment regimens following transplantation;
- Attitudes towards the importance of patient adherence when determining eligibility for transplantation;
- Views on whether non-adherent patients pre-transplant are likely to be non-adherent post-transplant.

## 6.2 Methods

### 6.2.1 Participants

Thirty-six staff members who work closely with renal transplant recipients were recruited from across two NHS Trusts: East and North Herts NHS Trust (Lister Hospital) and Royal Free London NHS Foundation Trust. Twenty-one were recruited from Lister Hospital and 15 from Royal Free London. Staff members included nephrologists, transplant surgeons, registrars, transplant nurse specialists and pharmacists. Table 6.1 provides a breakdown of participants across the two NHS sites. In total, the sample consisted of 20 (55.6%) females and 16 (44.4%) males. Across the two sites, eight (61.5%) consultant nephrologists were male, and five (38.5%) were female. Two (66.7%) transplant surgeons were male, and one (33.3%) female. Five (62.5%) renal registrars were male, and three (37.5%) were female. Seven (87.5%) of the transplant nurses were female, and one (12.5%) was male. The renal pharmacists and dialysis and research nurse were female. Years of experience working with renal transplant recipients varied across participants, ranging from less than 1 year to more than 20 years.

Table 6.1: Breakdown of clinical staff recruited for interviews

Lister Hospital	Royal Free London
N=21	N=15
Consultant Nephrologists N=6	Consultant Nephrologists N=7
Renal Registrars N=8	Transplant surgeons N=3
Transplant nurse specialist N=4	Transplant nurse specialist N=4
Pharmacists N=2	Pharmacists N=1
Dialysis and research nurse N=1	

### 6.2.2 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied to ensure that participants had expert knowledge to provide in depth and detailed responses during the interview, and to engage with the study materials independently.

#### Inclusion Criteria:

- Employed by the NHS;
- Member of the renal transplant team with regular contact with renal transplant patients.

#### Exclusion Criteria:

- Staff who were not employed directly by the NHS;
- Staff with less than six months experience.

### 6.2.3 Design

One to one semi structured interviews were conducted with participants. A qualitative methodology was considered the most appropriate in order to gather rich data to address the study aims. Interviews were digitally recorded and transcribed verbatim. The transcripts were analysed using thematic analysis (Braun & Clarke, 2006). This method of analysis allowed the research team to highlight prevalent themes from within the data. Two sites were included to ensure that data was representative across more than one NHS trust. One site was a transplanting centre (Royal Free London) and the other was a long-term follow up service (Lister Hospital) where patients return for follow-up care

after transplantation at a transplanting centre. Staff members were recruited until data saturation was achieved across the two sites, therefore meaning that no new themes were highlighted from conducting further interviews. A detailed summary of the qualitative method used in the study can be found in chapter three of this thesis.

#### 6.2.4 Data collection

All staff members involved with the renal transplant process both pre and post-transplant, with regular contact with patients, were contacted via email and informed of the study aims by a consultant nephrologist who was a member of the research team. They were provided with the participant information sheet with the researchers contact details. This was then followed up with an email by the researcher, to determine whether or not they were interested in participating in the study. A convenient time and place were arranged to conduct the interview. All interviews were conducted face-to-face in offices at the Lister Hospital and Royal Free London, to ensure privacy and confidentiality. Consent was gained prior to starting the interview. Participants were informed that the interview was to be recorded, with their permission, however, any resulting data would be anonymised when transcribed.

Interviews were conducted using an interview topic guide compiled of questions based on a review of the existing literature. Alongside discussion within the project team, this led to a topic guide that addressed interpretations of what it means to be non-adherent, the reasons underlying non-adherence rates and how these may be managed. In addition, the topic guide considered factors influencing the decision of whether a patient is eligible for transplantation, and the importance of pre-transplant non-adherence in this decision-making process was also covered. All in all, the topic guide not only aimed to explore the level of consistency between what patients report as barriers and facilitators of non-adherence, it also covered the important element of clinician decisions on wait-listing and whether this does or should feature within this process. Staff were encouraged to expand on their responses to allow the interviews to go into areas that were not foreseen or could be anticipated. Demographic information was also collected at the time of conducting the interview, to allow the homogeneity of

the sample to be identified and acknowledged in the analysis. Interviews lasted on average 30 minutes.

#### 6.2.5 Data analysis

Interviews were transcribed verbatim. Transcripts were analysed using Thematic Analysis (Braun & Clarke, 2006). This systematic method allows researchers to identify recurrent themes within the data, demonstrating the issues relevant to clinicians regarding renal transplant recipients in relation to eligibility for transplantation and factors associated with non-adherence. Transcripts were read and allocated initial codes and themes by the researcher (AH) who also conducted the interviews. These codes and themes were discussed and confirmed with the research team. Constant reference to the original transcripts throughout the analysis process ensured that the resulting themes were true to the data. All analysis was conducted in NVivo version 12. The researcher's positionality within the process was considered in relation to interviews and analysis, recognising that this will impact the way the "story" told by clinicians unfolds. Constant reference back to and self-evaluation of being a psychologist completing a PhD on non-adherence was required, as well as acknowledging what the thesis had shown so far so as to be aware of any biases that might influence interpretation of narrative from clinicians. Hosking & Pluut (2010) refer to this as "sources of subjectivity" (p.64-65). As a researcher there was constant reflection also on acknowledging that clinical staff make themselves vulnerable when sharing their beliefs about what could be a contentious issue, especially whether or not they take adherence into account when making decisions about wait-listing. The interview process was highly supportive and non-judgemental by constantly reflecting on language, tone etc., and analysis paid attention to representing participants accurately.

#### 6.2.6 Ethical considerations

Approval was given from the renal departments at the Lister Hospital and Royal Free London to conduct this research since low risk research with NHS staff required local approval as opposed to Research Ethics, which is required when researching with patients. This study received ethical

approval from the University of Hertfordshire Health, Sciences, Engineering and Technology ethics committee with delegated authority (UH protocol number: LMS/PGR/UH/03192).

### 6.3 Results

Five main themes were identified, which underpin clinician understanding of patient adherence behaviour and the role of this in their own transplantation assessment. The themes and their associated sub-themes are presented in Table 6.2. A narrative overview of themes follows, which includes illustrative quotes to evidence consistency between what participants said and the extraction of meaning.

Table 6.2: Summary of themes extracted from clinician interviews on understanding of adherence

<b>Theme</b>	<b>Sub-theme</b>
<b>Barriers to adherence</b>	<ul style="list-style-type: none"> <li>- <i>Predisposing risk factors</i></li> <li>- <i>Language barriers</i></li> </ul>
<b>Striving for normality</b>	<ul style="list-style-type: none"> <li>- <i>Regaining day-to-day autonomy</i></li> <li>- <i>Aversion to dialysis</i></li> </ul>
<b>Mutuality in maximising patient adherence</b>	<ul style="list-style-type: none"> <li>- <i>Multidisciplinary input in treatment management</i></li> <li>- <i>Addressing amenable barriers to treatment engagement</i></li> <li>- <i>Promoting adherence autonomy</i></li> <li>- <i>Facilitating social capital</i></li> </ul>
<b>Complexity of shining light on adherence in wait listing</b>	<ul style="list-style-type: none"> <li>- <i>Complexity of subjective assessment</i></li> <li>- <i>Predictability of future behavioural patterns</i></li> <li>- <i>Justice to scarce resource</i></li> </ul>
<b>Post-transplant normalization</b>	<ul style="list-style-type: none"> <li>- <i>Perceptions of wellness</i></li> <li>- <i>Risks driven by fallacy of bodily intuition</i></li> </ul>

## **Barriers to adherence**

There was a clustering of risk factors for non-adherence, which featured consistently across all interviews. Additionally, clinical staff identified barriers to the formation of a meaningful patient-physician relationship, which acted to reduce confidence or control in whether or not patients were aware of how to adhere. Within this theme, “predisposing risk factors” and “language barriers” were identified as sub-themes.

### *Predisposing risk factors*

The majority of clinicians highlighted age and chaotic lifestyle as major risk factors for non-adherence. Patients of younger age were considered to be at greater risk of non-adherence, as well as those who were trying to manage a busy lifestyle with, for example, work and family commitments.

*“I think that patients who have had additional big life events, whether that’s going from child into adulthood, or a breakup of a long-term relationship so suddenly they are more isolated or they’ve lost their job, those patients tend to be quite vulnerable to non-adherence.” (P007, Consultant Nephrologist)*

*“Young patients I know are at higher risk and chaotic lifestyles, those and any drug or alcohol use would be flags that I would maybe be concerned about.” (P023, Consultant Transplant Surgeon)*

*“How stable they are in their life etc. how chaotic their life is and there is a difference between someone who is let’s say elderly retired etc. who has a good financial backing and owns their own house etc. compared to someone who might be young, single mother, might have children to look after, has a lot of other things going on to try and balance as well as their health.” (P025, Consultant Nephrologist)*

Young patients with transplantations may be more at risk of non-adherence due to the challenge of managing a serious health condition and having to take medication, alongside wanting to have a

normal life similar to that of their friends. Additionally, the presence of chaotic lifestyles lead to patients experiencing barriers on a daily basis, whether that is a busy work schedule or family pressures that impacts their ability to attend clinics, or commonly finding themselves outside of a regular routine impacting remembering to take medication.

### Language barriers

Some clinicians described how language barriers and communicating via professional or informal translators can cause concern. When family members or friends are used as translators, accuracy of translation and information relayed is not known. Such factors acted to reduce confidence and control in whether or not patients were well informed about adherence - an added challenge in clinical practice.

*“So we have to use one of the family members to translate, so it is out of our control exactly what information is being delivered to that patient, so it can be difficult sometimes” (P023, Consultant Transplant Surgeon)*

*“Ideally you would have a professional translator when you see some of these patients but in many cases you are using a family member to translate, and so whether or not what you are saying is actually being translated correctly is a bit unknown to us”. (P010, Consultant Nephrologist)*

*“I think sometimes if family members who are translating back to their parents for instance and I do find that challenging because you can never be entirely clear about what the patients understanding is of that” (P011, Renal registrar)*

Relying on unofficial translators can be challenging for clinicians when managing language barriers. Employing other methods of information transference, such as pictorial materials and information leaflets in their own language, could help with this, which was mentioned in some of the interviews. Patients where English is not their first language may be at greater risk of non-adherence if there is a

lack of understanding, therefore it is important to provide the best support where possible to ensure the importance of medication taking is understood. Despite the challenge, a minority of staff had considered proactive ways in which to address this barrier, which relates to a theme described later in the results section about “mutuality in maximising patient adherence”.

*“I think sometimes we need to make sure our information is culturally appropriate, sometimes to consider having it translated into, you can’t have it translated into every language, but there are definitely some. And then making sure that we also provide content in a non-written format so, something again that can be replayed for people, so either videos...” (P024, Consultant Nephrologist)*

*“I think moving to some of the more modern ways of people getting information, electronic resources etc. videos... Finding different ways of what’s appropriate not just for different cultures but also different ages and health literacies and IT skills” (P025, Consultant Nephrologist)*

### **Striving for normality**

Clinicians described patients as viewing transplantation as a desirable treatment for their kidney failure. On the whole, most patients sought transplantation in the hope for a better quality of life. Additionally, those who had received dialysis prior to transplantation were often viewed as wanting to avoid having to return to that treatment. Within this theme, “regaining day-to-day autonomy” and “aversion to dialysis” were identified as sub-themes.

#### Regaining day-to-day autonomy

As well as being considered the best treatment option for treating ESRD, clinicians described how patients valued transplantation as an opportunity to regain freedom and independence, and an ability to live a more normal life.

*“I think most patients would say they want it to happen because I think it’s a more life changing event for them and essentially they get their lives back....it’s as close as they’re going to get” (P023, Consultant Transplant Surgeon)*

*“They see it as something that’s going to give them near normality, live life, work, go on holidays, do normal activities as other people.” (P009, Consultant Nephrologist)*

*“So a lot of them say “at least I can have my life back”, especially if they’ve got families.” (P035, Transplant nurse specialist)*

Transplantation was viewed as an opportunity to regain independence and return to daily life activities, such as returning to work or participating more easily in family commitments.

#### *Aversion to dialysis*

Patients who had experienced dialysis were described as often viewing transplantation as a superior and better treatment, and therefore wanted to avoid having to return to receiving dialysis treatment.

*“I think the majority of patients who have been on dialysis for them a transplant will completely change their lives .....if they have a transplant they can now live normal lives, they can go back to work they can go on holidays and all of this. So for those that are on dialysis they do see it as life changing basically.” (P034, Renal Pharmacist)*

*“If they have been on dialysis before and then they have had the transplant, some patients don’t want to go back to that phase of where they were on dialysis so they will be quite good with the adherence” (P006, Transplant nurse specialist)*

*“...most of them like they’re really really grateful that they have the transplant and they don’t want to go back on dialysis anymore” (P004, Transplant nurse specialist)*

Patients were described as being grateful for a transplant and the ability to lead a better life compared to life when on dialysis. Some described this as a motivator for adherence.

### **Mutuality in maximising patient adherence**

The majority of participants described responsibilities they considered they have in ensuring that patients are prepared and enabled to be adherent to their treatment regimens. This encompassed a variety of elements from ensuring patient support was provided via a multidisciplinary team, adjusting treatment and follow-up to allow engagement and providing patient education to ensure that patients are prepared for managing transplant aftercare. Within this theme “multidisciplinary input in treatment management”, “addressing amenable barriers to treatment engagement”, “promoting adherence autonomy” and “facilitating social capital” were identified as sub-themes.

#### *Multidisciplinary input in treatment management*

The majority of participants described how patient information surrounding post-transplant treatment is conveyed via a multidisciplinary team. This was considered important as patients can gain input and expertise from different members of the team and engage with staff with differing regularity, all the time hearing consistent messages.

*“So most of that (how patients are educated about their medicines and health/wellbeing) is done usually by the multidisciplinary team, so we’ve got our pharmacists usually who get involved...especially in the transplant centres to go through medications.....nurses are very involved, the post-transplant nurse who is a good link for them to have outpatient communication. Usually these are the people that provide education for them and tends to be more the doctors consulting if they have side effects or issues when they come and see them in the clinic itself.” (P009, Consultant Nephrologist)*

*“Involving other people to ensure that their patients are being adherent, so transplant co-ordinators, and other people involved in the follow up process. And even things like involving the pharmacist to*

*ensure the medications are you know, package them all together you know so it's easier for patients to take them.” (P013, Renal registrar).*

*“So that comes from both the doctors they see in clinic but we also have support from a post-transplant nurse specialist and support from a renal pharmacist. And so they have the opportunity to see all 3 of those people at each clinic visit.” (P007, Consultant Nephrologist).*

The role of pharmacists in the transplant centre was also emphasised with patients receiving pictorial aids to understand the different medications and dosages that their regime consists of. This alongside verbal communication was utilised to ensure that patients understood their medications before being discharged.

*“The pharmacy we always go through, what's called a Meds card, which is basically a list of all their medicines they're on, what times to take it, what it's for, some of the common side effects. And every transplant patient will get counselled by us before they go home.” (P034, Renal pharmacist)*

Utilising a multidisciplinary team was considered best practice for ensuring patients were prepared for post-transplant life and with the knowledge to enact adherent behaviour. Interacting with multidisciplinary team members allows patients to gain support with different aspects of their treatment management. Regular monitoring and revisiting of medications from different members of the team allows for greater monitoring of adherence and potential for engagement. Some participants indicated that transplant nurses may have more time to speak with patients, allowing for support and guidance to be provided but also opportunities for issues to be highlighted to the wider treatment team if necessary. Some patients may additionally feel more comfortable speaking to certain members of the treatment team than others, and having a multi-disciplinary team allows for patients access to a range of health care professionals with whom they may feel comfortable discussing their follow-up care.

### Addressing amenable barriers to treatment engagement

Clinicians discussed how it was important to establish reasons for non-adherence and provide reasonable adjustments to treatment where possible to allow patients to be more engaged. This was discussed in terms of medication and clinics, with some suggestions specifically related to the previously identified pre-disposing risk factors and some more general. Consideration of telephone clinics or off-site clinics were suggested to allow people greater flexibility in managing follow-up care alongside commitments such as work.

*“...trying to facilitate for instance telephone clinics if that’s appropriate and offering the patient as many chances and opportunities to adhere.” (P011, Renal registrar)*

*“You can certainly do things like tele-clinics to try and speak to people directly at the house or when they are at work, make things easier for them. I think a lot of it is about making things as easy as possible for the person.” (P010, Consultant Nephrologist)*

*“Whether you could do more tele-clinics or virtual clinics, or maybe doing satellite clinics in areas where patients tend to be, so there is less travelling. Out of hours clinics. Those might be innovative ideas to try to see patients, so we can keep communications, so that they can lead a normal life.” (P009, Consultant Nephrologist)*

With patients struggling with adherence to immunosuppressants, treatment could be altered in an attempt to improve this. This could include changes to dosage, such as from a twice day regimen to a once daily regimen in cases where certain medication doses are regularly forgotten or are difficult to incorporate alongside daily lifestyle pressures.

*“I think we can try to make it easier for them by having things like once a day medication, maybe even by combining pills together.” (P026, Consultant Nephrologist)*

*“...Or it could be that they find it difficult to take medication twice a day whereas if we switch them to a once a day regimen that might help because they might remember first thing but not in the evening...”. (P006, Transplant nurse specialist)*

One participant noted the cost-burden associated with this, however, which is often considered and presents restrictions in terms of the number of patients that can be allocated to this regimen.

*You do find that if they're really non-compliant and they can't take medicines twice a day or whatever there are preparations that they can go onto once a day slow release tacrolimus but again it's more expensive, so we have to look at cost burden as well. So those we would reserve for the really non-compliant. (P034, Renal Pharmacist)*

Alternatively, side effects of medications can be addressed by spreading doses across the day or changing the immunosuppressant medication that is being taken.

*“some of the once of a day ones, you get a high trough which is associated with a lot of tremor, so can we put them on a twice a day regime where they get a less peak of the drug and less side effects.”*  
(P015, Renal pharmacist)

Clinicians acknowledged a responsibility to monitor adherence behaviour and consider approaches to target and address barriers to adherence to ensure patients have the best opportunity to engage with their treatment. Additionally, this involves having discussions with patients to explore how patients are managing their treatment, however, it was noted that it is not always possible to do this at length. Addressing barriers and ensuring regimes are as clear and simple as possible allows patients the best opportunity to engage and adhere, without experiencing confusion or having to navigate around challenges that might impede on their adherence.

### Promoting adherence autonomy

Almost all clinicians emphasised the importance of patient engagement and communication to promote patient understanding and self-management of their treatment regime, whether that was continuing education that was already being implemented or considering improvements that could be beneficial.

*“They have to be in control essentially. And ideally from day one, they know what they were given, not just give them a cup of tablets to take. They have to understand them.” (P18, Renal registrar)*

*“Patients taking charge of their health to a certain extent, so they are interested in knowing the blood result, their blood pressure, diabetic control, how to manage their tablets. I think a lot of it you need the patient to be very involved in their care post-transplantation.” (P009, Consultant Nephrologist)*

*“...there are a lot of things patients can do looking after themselves, taking their medications, making sure to have blood tests and attending clinics. If they do you know own these, there are things that we can pick up early on, rather than after something has happened.” (P006, Transplant nurse specialist)*

*“I think it comes down to communication.....clear and good communication, making sure your patients understand the importance of it and spending that time talk them openly about it” (P019, Consultant Nephrologist)*

It was considered that improving understanding of treatment necessity would lead to greater engagement with the treatment process and as a result, adherence. Encouraging patients to feel in control of their health, treatment and having the power to influence the outcome of their kidneys was considered important for promoting independence with treatment management.

### Facilitating social capital

Some participants highlighted the benefits of peer support, and how speaking with other patients that have experienced transplantation, whether a positive or negative journey, might be beneficial for transmitting adherence messages to prospective or newly transplanted patients, rather than just hearing them from clinicians. As such, clinicians were making efforts to enhance the social capital of patients by recognising the power of peer support.

*“It’s interesting when patients come to the support evening they won’t remember anything that the clinician said, but they will remember what the other patients have said that have been through it and I think that’s really powerful and if you choose the right peer support I think that’s a really good way of people understanding it.” (P025, Consultant Nephrologist)*

*“To have patients to be able to speak to another patient who has gone through the transplant, what the journey has been, to see it from another patient but in a similar situation can give them some insight into not just what they think has gone really but to actually see someone for whom it’s not gone really well as well”. (P006, Transplant nurse specialist)*

*“I think one of the main ways we could do is peer support actually speaking to other patients who have had a transplant, patients who have had a failed transplant and back on dialysis....What they need is peer support. Doctors can bang on about things but in many times it will not go into the patients head actually. They would be more receptive if someone who’s had a transplant is speaking to them” (P008, Consultant Nephrologist)*

Hearing from other transplant recipients may provide patients with a more realistic understanding and appreciation of the process when hearing experiences from someone who has actually undergone the

process and treatment. However, this would need to be structured and monitored to ensure appropriate advice and support was being provided and not encouraging negative beliefs.

### **Complexity of shining light on adherence in wait listing**

Discussions surrounding the relationship between pre and post-transplant adherence resulted in differing views across clinicians in relation to the role of adherence as part of the transplant eligibility assessment and whether adherence to dialysis can be viewed as an indicator of post-transplant adherence. Despite this, some clinicians did consider the importance of ensuring the potential organ resource was respected and given the best chance of survival- recognising the scarcity of organs. Within this theme, “complexity of subjective assessment”, “predictability of future behavioural patterns” and “justice to scarce resource” were identified as sub-themes.

#### *Complexity of subjective assessment*

Clinicians described differing views in the role of non-adherence as part of the transplant assessment process in determining eligibility for listing. A few indicated it would have little impact in determining suitability.

*“For me it would have very minimal influence on them being suitable to be on the transplant list, other than them not engaging with the process of assessment to confirm that there is not a medical reason why they wouldn’t be able to have the transplant safely.” (P007, Consultant Nephrologist)*

*“All patients are put forward for transplantation, so if we have concerns about their adherence we would see them in clinic and we would discuss them at a multidisciplinary team level, so I wouldn’t expect anybody just to be knocked out because they maybe haven’t turned up to clinics or they haven’t turned up to dialysis sessions. That would certainly raise red flags and therefore it would be discussed at the MDT level but it wouldn’t be a knock out for transplantation.” (P023, Consultant Transplant Surgeon)*

*“obviously the evidence of their adherence pre-transplant is relevant, but it’s not the be all and end all.” (P010, Consultant Nephrologist)*

Others recognised that perhaps it is overlooked and should be considered as part of the wider transplant work-up.

*“The psychological assessments may be overlooked and so you may actually just go through with someone transplant work-up and then actually realise they might be non-adherent without really working that out beforehand.” (P013, Renal registrar).*

*“Do you know I think it (adherence) gets lost. I think it gets lost and we don’t focus on it and it is incredibly important. I think it only really gets looked at when it’s the second time around.” (P025, Consultant Nephrologist)*

A number of clinicians described how non-adherence to certain aspects of the treatment regimen pre-transplant would have cause for concern, however, this might lead to patients not being listed until they could demonstrate an improved level of adherence.

*So if you’ve got someone who’s not adherent to the treatment their creatinine is going to be way high, and they may not be suitable for them to be put through to the transplant list, so the transplant team would usually advise that they demonstrate some degree of adherence before they get transplanted. (P006, Transplant nurse specialist)*

*I think it depends how bad their noncompliance was beforehand. We’ve certainly had people where we have felt that they need to kind of understand what it would involve a bit better and be compliant for a while before we put them through it. (P026, Consultant Nephrologist)*

*“So yes we will stop patients from being transplanted if we don’t think they are going to be adherent and we do ask them to demonstrate adherence and we do write that on their clinic notes and will say not to be activated until can demonstrate adherence to dialysis and actually write that on their letters.” (P029, Consultant Nephrologist)*

It seems that the role of adherence as part of the transplant assessment process and eligibility for listing is unclear, and clinicians may take a differing view based on prior experience of patient cases. Among those who considered demonstrating a period of adherent behaviour appropriate prior to listing, this time period was often set individually with patients in mind, but often six months was considered suitable to confirm longer term adherence.

#### *Predictability of future behavioural patterns*

Clinicians considered the relationship between pre-transplant dialysis adherence and adherence post-transplantation in different ways. Some considered the treatments were very different and therefore not comparable in terms of viewing as a predictor of future behavioural patterns.

*“I think sort of coming to dialysis for instance they are coming to the hospital three times a week for dialysis four hours at a time that’s a very different scenario I guess to coming for a clinic appointment post-transplant.” (P011, Renal registrar)*

*“Now for me if someone is on dialysis and they’re not very good at taking their kidney medications and they’re not great at turning up for dialysis that tends not to worry me so much, because I think when you are transplanted it’s different. And I don’t think past performance is a guide to the future you know, when it comes to dialysis patients.” (P022, Consultant Transplant Surgeon)*

*“But having a history of non-adherence doesn’t mean they’re not going to be adherent after they’ve had the transplant.” (P035, Transplant nurse specialist)*

On the other hand, some clinicians felt that adherence to aspects of the pre-transplant treatment could be taken as indicators of non-adherence, and considered that this behaviour would likely, but not always, continue post-transplant.

*“So I think some are, many are. Some change their pattern because they realise they have been given an opportunity, but many are, many remain non-compliant to some extent, and I think it’s the extent of it that is the problem.” (P026, Consultant Nephrologist)*

*“Most of them I would say yes in one way or another, it’s how bad they will be non-adherent post-transplant. On the whole I would say mostly yes, some people less so.” (P025, Consultant Nephrologist)*

*I think it’s likely but not a given. I think we have patients where there has been evidence of non-adherence, but they seem to be reformed characters and then they are put on the list, transplanted, and then there is clear evidence of non-adherence post. But that’s not always the case. (P024, Consultant Nephrologist)*

Clinicians recognised that we can use adherence to aspects of pre-transplant treatment, such as dialysis attendance, phosphate binder/blood pressure medication adherence, attendance at clinic appointments/assessments etc. but the influence of these elements on transplant outcomes and transplant adherence is unclear. It was considered that elements of non-adherence may translate, however, there are instances where patients appreciate the “gift” of transplantation and recognise the importance of adherence for preserving graft function. Therefore, the predictability of future behavioural patterns remains unclear.

### Justice to scarce resource

Some of the clinicians considered adherence in transplantation eligibility in relation to the organs as a precious resource. Due to a limited availability of organs, it was considered that these should be distributed not only to a patient that was going to get the best use out of them, but also in respect to the donor themselves.

*“Many centres of course do think about compliance issues as well which is very important because you are taking an organ from someone else and giving it to someone, especially people who have been very non-compliant to dialysis more centres will think twice before thinking about giving a transplant” (P008, Consultant Nephrologist)*

*“It is also not ethical because then maybe this kidney could have gone to someone else. So you know I think it is our job to make sure that whoever is put through is suitable for it.” (P018, Renal registrar)*

*“...it’s normally the people who stand out as non-compliant that you would worry about, and that’s a sort of red flag, and then that’s something I do worry about in terms of what’s going to happen afterwards. Especially if you are taking a, it’s all about resources being limited” (P026, Consultant Nephrologist)*

However, it was interesting that some participants commented on this in relation to live donation, indicating that the issue relating to use of resource is removed when you have a living related donor.

*“that’s partly overcome if they have got someone in their family donating to them, although I think you would need to make it clear to the person donating that this is what happened the last time, this could happen again, and they understand that.” (P022, Consultant Transplant Surgeon)*

*“It’s slightly different if you’ve got a relatively non-adherent patient where someone is a live donor, say a family donor who is willing to donate, because they are not reducing the pool of organs*

*generally. And we do occasionally get that, so you've got somebody who is relatively non-adherent, but their family member wants to give them a kidney and you know, so that aspect of it is much less relevant then.” (P010, Consultant Nephrologist)*

Considering the scarcity of the organ resource should be an important factor when assessing patients at risk of non-adherence post-transplant. This is particularly notable in relation to deceased donor transplants as organs could go to someone else, however, how this is viewed in relation to living related donation is less clear. It might be considered that it should be viewed in the same way as every kidney is a precious resource, and living donors are healthy individuals putting themselves at risk of an operation that is not to their benefit.

### **Post-transplant normalization**

Most of the participants considered that non-adherence to immunosuppressants and clinic attendance increases with transplant vintage due to patients becoming complacent in how closely they monitor their treatment regimen. This was considered due to established stability of kidney function meaning medical input is reduced over time and patients returning to what they perceive to be a more normal life. Within this theme, “perceptions of wellness” and “risks driven by fallacy of bodily intuition” were identified as sub-themes.

#### *Perceptions of wellness*

The majority of participants described how successful transplantation leads to patients feeling well again. This experience of feeling well coupled with the ability to return to a more normal life post-transplant, such as returning to work, may result in a busy lifestyle where treatment management is not considered as important or necessary.

*“There are a few who just think that oh I feel fine not realising that you have to take this for the rest of your life even though we've informed them.” (P035, Transplant nurse specialist)*

*“I think it comes down to, as I said, people feel better over time and if they haven’t had any problems within the first couple of years. I think that probably ascends this feeling of well things are going well and actually so far so good and everything’s been fine.” (P019, Consultant Nephrologist)*

*“I think they start to feel well, they start to go back to work, start to do things they weren’t able to do before, generally life starts to get busy again in that respect for them and it just becomes another pill I think.” (P012, Transplant nurse specialist)*

*“If their condition is stable and there’s not much exciting things happening, they sometimes forget about, you can forget about the transplant.” (P004, Transplant nurse specialist)*

Due to the complexity of pre-transplant treatment, particularly the debilitating nature of HD, patients who have successful transplantation and an uncomplicated adjustment in terms of renal function may forget or place less emphasis on the importance of the medication in terms of its role in preventing rejection as time progresses. Many patients consider transplantation as an opportunity to “get their life back” and as they transition back into how their life was before ESRD or HD they may focus on enjoying greater freedom and opportunities they have, with medication management taking less precedence. As medical appointments and interventions become less frequent with graft stability, there are additionally fewer opportunities for clinicians to monitor this behaviour.

#### *Risks driven by fallacy of bodily intuition*

Perceiving a lack of consequences with graft function was considered by the majority of participants as explanations for reduced adherence with immunosuppressants over time. Patients will likely experience at some stage a situation where they accidentally forget to take a tablet or take it late, and as a result may perceive that when nothing happens and they remain feeling well, the medication has little impact. This could occur as missing a tablet may not have immediate consequences.

*“I assume that some people get more confident in their transplant working well and that occasionally may be in a position where they miss a medication or miss an appointment and not had a serious consequence and that’s made them feel less concerned about that happening again in the future.”*  
(P007, Consultant Nephrologist)

*“So they will rapidly learn that if they miss one tablet, not much happens and so, whereas at the start after a transplant they probably, their anxiety levels are quite high, and they are much less likely to do things like miss medications and miss clinics.”* (P010, Consultant Nephrologist)

*“And also there will be a degree of experimentation, so they will have possibly accidentally forgotten to take it one time and nothing bad happened, so you feel less stressed about you know if you forget again”.* (P022, Consultant Transplant Surgeon)

Over time patients become less anxious about the transplant function as it has been working well for a long period of time. Circumstances that have led to occasional forgetting or late taking of medication may have resulted in minimal perceived consequences or symptoms leading to repetition of this behaviour. This may be particularly notable for patients who experience other issues relating to their medication, such as side effects. As patients are followed up less frequently, there are less opportunities for transplant function to be monitored and checked, therefore the patient continues thinking their function is fine based on their treatment taking behaviour, perpetuating non-adherence. However, this may be a fallacy. Patients are also told that their body adjusts to the transplant and that clinicians wean down their immunosuppression over time and this may further add to their confidence in adjusting treatment regimens. In addition to this, they may speak to other patients at clinic who have had their medication dosage reduced who are still experiencing stable function and consider the same will be suitable for themselves.

#### 6.4 Discussion

The aim of this study was to explore clinician understanding of non-adherence among renal transplant recipients, including factors associated with adherence to treatment and the role of adherence in transplant eligibility. The study yielded a range of findings. Clinicians reported predisposing risk factors for non-adherence consistent with previous literature, citing younger age and chaotic lifestyle as major barriers (Denhaerynck et al., 2005; Muduma et al., 2016). Managing medications in light of lifestyle events was also discussed by patients and highlighted in a systematic review by Tong et al., (2011). Interestingly, language barriers were also considered challenging in ensuring messages of adherence are conveyed accurately to patients when using a family member as a translator, and introduces a third person into the patient-physician relationship that has to be managed. The proportion of patients from minority ethnic groups at the centres where clinicians were recruited from is higher than the overall proportion of renal service users from minority ethnic groups across the UK (Gilg, Methven, Casula & Castledine, 2017). As such, it is noteworthy but perhaps unsurprising that participants in this study considered the ability to directly form a relationship with patients as a major barrier to adherence as they simply could not be sure that patients had access to the right information.

Clinicians perceived patients as viewing transplantation as an opportunity for a better quality of life and to regain day-to-day autonomy, close to how their life was prior to ESRD. This was captured by the ability for patients to return to work and re-engage with activities they were once unable to due to, e.g. HD. This finding supports recent literature in transplant recipients where transplantation was associated with improvements in health and lifestyle in the majority of patients (Tucker et al., 2019). Other studies of renal patients have shown the majority report the ability to re-establish everyday life following transplantation (Nielson et al., 2019).

Many of the clinicians described feeling a sense of responsibility to ensure patients are prepared to manage expectations associated with transplantation and educated in order to adhere appropriately to prescribed treatment regimens. As such, there is mutual responsibility towards supporting adherence. The value of multidisciplinary input in delivering information was considered essential in educating

patients. Different health care professionals can all provide expertise to assist patients in managing their transplant follow-up care and also consistently share similar messages about self-care. Transplant nurses were considered to perhaps having more time to spend with patients to discuss transplantation, and pharmacists were essential in providing detailed education on prescribed medications. Clinicians also felt a responsibility to address amenable barriers patients experience, such as side-effects or challenges impacting adherence, in order to facilitate the ability to engage. This was considered through altering medication doses or flexibility with clinics. Peer support was also considered a method they should utilise to encourage adherence behaviour. Although it was not termed so by participants, what they perhaps have not realised is that by encouraging peer support, they are helping patients to build “social capital”, with social support consistently aiding strategies and motivation for managing treatment regimens (Parker, Ferreira, Vernon & Cardone, 2017). This emphasis on education mirrors that of Williams et al., (2014) where patient education was implemented both pre and post-transplantation verbally and through the use of information leaflets, ensuring patients have the best opportunity to be adherent and are aware of how to look after their kidney graft.

The notion that patients become more non-adherent over time with transplant vintage was considered by clinicians as normalization relating to perceptions of wellness and experiencing a lack of consequences when tablets or doses are missed. This view supports similar patient findings among the renal transplant population (Griva et al., 2012; Nevins, Nickerson & Dew, 2017). Additionally, due to feeling well and the ability to return to a more normal life, patients may want to forget that they have been transplanted or have been unwell, identifying as a “normal person”. This doesn’t involve taking tablets on a daily basis. Jamieson et al., (2016) reported that patients want to free themselves from the patient role following transplantation and from continuous contact with health care professionals, which places them at risk for non-adherence. Patients reliance and need for regular contact with health care professionals also decreases over time (Nielson et al., 2019). All in all, changes in regularity of health service contact alongside a lack of bodily feedback may render a fallacy that “all is well”, which was seen as a concern by participants for future adherence.

Finally, the importance and role of pre-transplant adherence as part of the transplant assessment was contentious. Clinicians considered this aspect as having different levels of importance. Where the medical work-up has clear and concrete guidelines in regard to suitability for transplantation (Dudley & Harden, 2011), how adherence fits into this is less clear cut. Some clinicians reported pre-transplant adherence as having minimal input when assessing patient eligibility, and others recognised that it is perhaps overlooked. A larger number of clinicians discussed how certain pre-transplant non-adherence behaviours are potential indicators of post-transplant adherence, such as attendance at dialysis, adherence to medications, such as phosphate binders or antihypertensives, or attendance at pre-transplant work-up. In these cases, patients would be asked to demonstrate a period of adherence before being listed, often reported as around 6 months. It is important to note, however, this was evaluated on a case-by-case basis and considered alongside the risks of prolonged dialysis on patient outcomes. This was viewed as appropriate not only for the patient in terms of graft outcomes once transplanted, but to ensure the best use of the organ due to the limited number of deceased donor transplants as a resource. So, clinicians were aware of medical ethics in their practice.

In addition, although clinicians could identify potential pre-transplant predictors of post-transplant adherence behaviour, the relationship between pre and post-transplant adherence remains unclear. There is limited existing literature in this area to evidence if adherence behaviour is transferred across modalities. Some clinicians suggest it might, but it is not always the case. One study, completed within this programme of work, exploring relationships between HD and post-transplant adherence did not support the likelihood of a strong direct relationship between these behaviours (Hucker et al., 2019). However, this was a small sample and the most effective objective measures of adherence are not yet clear. Despite this, it highlights a need for greater understanding in this area coupled with greater agreement among clinicians. Further research is needed to establish the relationship between pre and post-transplant adherence behaviour to allow this to be appropriately considered as part of the transplant assessment process. Additionally, consistent agreement is needed for transplantation in how best to manage pre-transplant non-adherence in order for transplanted kidneys to be given the best

chance of survival, but also to ensure patients are treated equally and fairly. So whilst it appears that there may be some strength in the suggestion that pre-transplant non-adherence could indicate issues post-transplantation, without further evidence and concrete guidelines driving consistency across patients, it is unsurprising that clinicians are fragmented in how much importance they place on adherence behaviour. But, this in itself indicates that patients may not be getting a consistent experience as some clinicians might expect a change in behaviour over 6 months, whilst others only look to medical “fitness”. There is clearly room for further consensus work on the role of adherence, if at all, in transplant listing.

#### 6.4.1 Strengths and limitations

There were a number of strengths to this study. Firstly, a range of clinicians covering different roles and responsibilities in working with renal transplant recipients were recruited. This ensured that wide experiences were shared to contribute to the understanding of the topic area. Secondly, few studies have been conducted with clinicians to unearth their understanding of non-adherence; much of the literature has focused on understanding patient experiences. In doing so, the study has demonstrated consistency in some of the barriers and facilitators of adherence, but also uniquely been the first to raise the contentious issue of what clinicians additionally may place emphasis on in the wait-listing processes. As such, the research has identified a number of avenues for future research, including the reduced sense of ethical obligation that some clinicians voiced when managing living related organs.

There are still a number of caveats that should be considered when interpreting the findings.

Participants were recruited from two NHS sites only, and therefore views may not be generalisable to the wider community of clinicians working in this setting, especially as geographically, the Trusts were both located in either central or greater London. However, the study included a large sample size for a qualitative investigation including a range of employees within clinical teams. The data reflected a degree of shared and individual thoughts, which could be explored further in a larger scale quantitative study by drawing on trends within this in-depth exploration.

#### 6.4.2 Conclusions

Non-adherence post-transplant is a prevalent issue that clinicians have to manage with their patients. This study demonstrates that clinicians recognise and understand the barriers that patients can face with adherence, and often attempt to work on individual circumstances and find options for making treatment management easier. Enhancing patient understanding and engagement was considered an effective way to promote adherence, and clinicians felt a sense of duty in doing so alongside providing continued patient education and implementing greater use of peer support. Agreement on how adherence is viewed as part of transplant eligibility is lacking, with clinicians managing pre-transplant non-adherence in different ways. This is a juxtaposition since on the one hand, clinicians felt that non-adherence is a subjective judgement, but at the same time, it is already being used in different ways and possibly leads to inconsistency in patient management, even if over a short duration of time (e.g. 6 months). Although the patterns of beliefs, attitudes, and behaviours exposed in this qualitative study could be helpfully followed up with a quantitative approach, it is likely that the findings signal need for consensus in the renal community about how non-adherence features in the decision-making process for wait-listing.

# Chapter 7: The relationship between self-reported adherence and clinical parameters in transplant recipients

## 7.1 Introduction

Non-adherence among renal transplant recipients is a complex issue. It is a major risk factor for poor outcomes, including health complications and mortality (Leggat et al., 1998; Saran et al., 2003; Denhaerynck et al., 2007). It brings with it added healthcare and treatment related costs (Cleemput et al., 2004; Kugler, Maeding & Russell, 2011). For example, non-adherence has been identified as the second most common cause of late graft failure in renal transplant patients (Loghman-Adham, 2003).

There is little previous research exploring the relationship between self-reported adherence and adherence recorded as part of routine care. It is common practice for transplant clinics to record serum levels of immunosuppressants in order to gauge how well patients are maintaining their treatment regimen. Self-reported non-adherence is often inaccurate and under-reported (Massey et al., 2013). Measures such as electronic monitoring are regarded as the most reliable and accurate form of measuring non-adherence (Schafer-Keller et al., 2008). However, as discussed earlier, even this method of measurement can be inaccurate as patients could open the bottle therefore recording medication as being taken but not actually take the medication itself. Electronic monitoring is also expensive, and so self-report is the most pragmatic alternative.

Schafer-Keller et al., (2008) investigated the diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressants in renal transplant recipients. The researchers found a significant association between adherence reported via blood assay and self-reported adherence. This suggests that whilst some research argues that self-reported adherence may fall short of objective assessment, there is reasonable concordance between the two. Importantly, Schafer-Keller et al., (2008) also advanced the idea that combining measurement methods was in fact the most optimal option. Given that transplant clinics routinely record serum levels of medications such as tacrolimus, this offers the opportunity to further explore both agreement between self and objective reports of

adherence, and to further scope the usefulness of combining different outcome measures. There is a caveat that clinical methods of measuring adherence require careful interpretation (Schafer-Keller et al., 2008). Nonetheless, combining methods of measurement could allow for better evaluation of whether patients have a good and in-depth understanding of how they should be following their treatment regimen.

Surprisingly, there is also a dearth of previous research exploring the role of psychosocial factors, such as medication beliefs and illness perceptions, in treatment and medication adherence among renal transplant recipients. Illness perceptions/ representations can be understood through the self-regulation model (Leventhal, Nerenz & Steele, 1984), and refer to organised beliefs surrounding a health condition. The SRM suggests these beliefs then guide coping procedures in an attempt to control the illness threat, suggesting how patients perceive their illness may influence how they then manage it, including adaptation, coping and health behaviour. Research has identified the cognitive representations and behaviour that form illness representations (Moss-Morris et al., 2002; Broadbent, Petrie, Main & Weinman, 2006). The model consists of five key components of illness representations (Cameron & Moss-Morris, 2013). These include illness identity, consequences, timeline, control or cure and cause, with later versions of the model (Illness perceptions questionnaire-Revised: IPQ-R) including further components representing perceptions in relation to illness coherence, the cyclical timeline of illness and emotional representation (Moss-Morris et al., 2002). Illness concern has also been included in refined versions of the scale (Brief IPQ) (Broadbent, Petrie, Main & Weinman, 2006). Previous literature has highlighted that patient behaviour is influenced by illness representations and could therefore be used to inform interventions in chronic illness groups (Petrie, Broadbent & Meechan, 2003).

Illness perceptions have been explored in the context of a variety of chronic health conditions, including dialysis patients and to a lesser extent in renal transplant recipients. Among HD patients, previous literature has reported higher scores in a number of the illness perceptions domains (timeline, consequences, personal and treatment control and emotional perceptions) (Kim &

Evangelista, 2010). Relevant to the current research, patients believed that they could control their illness by receiving treatment (dialysis) to some extent. Therefore, it is plausible that patients perceiving low treatment control, curability or consequences could be non-adherent to their treatment regimen. In terms of treatment adherence, patients with more negative illness perceptions were more likely to be non-adherent to diet restrictions (Kim & Evangelista, 2010). The extent to which illness perceptions has been seen as crucial to illness experience in dialysis is further signalled by a systematic review which found five studies on the topic (Parfeni, Nistor & Covic, 2013).

Some previous literature in renal transplant recipients has explored the association between illness perceptions and quality of life (Griva et al., 2009). Illness perceptions have also been explored in relation to treatment transitions between dialysis and transplantation (Griva et al., 2012). Changes in treatment from dialysis to transplantation are highlighted as having a significant impact on illness perceptions and quality of life. Receiving a kidney transplant was shown to lead to greater positive perceptions of illness identity, consequences, intrusiveness and controllability (Griva et al., 2012). This likely reflects the 'gold-standard' nature of transplantation over dialysis as a treatment modality that restores most normality for patients due to the reduction in symptoms, reduced treatment demands and improvements in kidney function (O'Connor et al., 2009). Griva et al., (2012) also note that positive illness perceptions post-transplant are associated with improved quality of life. Graft failure or graft loss was associated with decreased quality of life and negative changes in illness perceptions. Negative illness perceptions, poor health status and engagement in maladaptive coping techniques have also been associated with lower levels of quality of life and psychological distress, including anxiety and depression (Knowles et al., 2016).

Research exploring the role of illness perceptions in self-reported adherence following renal transplantation (Massey et al., 2013), assessed patients six weeks following transplantation and again at six months using the Brief IPQ. At six weeks post-transplant, patients who perceived their graft to have a longer timeline reported higher adherence. Higher adherence was also associated with greater perceived personal control and emotional response. Perceived consequences were rated significantly

higher among patients categorised as non-adherent using the “Basel assessment of adherence to immunosuppressive medications scale” (BAASIS) (Dobbels et al., 2010). The authors changed the open-ended causes of illness question on the Brief IPQ to perceived causes of graft rejection. Non-adherence to immunosuppressants was reported as a cause of graft rejection by 83% of the patients at both six weeks and six months post-transplant. These findings demonstrate that patient beliefs and perceptions about their illness may have an impact on medication adherence and a decline in adherence over time. This puts patients at greater risk of poor clinical outcomes. Further research by Massey et al., (2015) identified that patients who have good illness coherence relating to the transplantation process also have high perceptions of treatment and personal control. Low perceptions of symptoms and emotional response were reported, with emotional response reducing over time. All in all, such data suggests that illness perceptions are essential when trying to unpack patient responses to kidney disease and their treatment engagement. This becomes even more apparent given that illness perceptions have been shown to be amenable to change and so may offer a useful mechanisms for patient support (Jansen et al., 2013).

Previous literature has also explored associations between patient beliefs about medication (BMQ) and adherence. Beliefs about medication in relation to adherence are suggested to be more strongly associated with specific medications prescribed, with a cost-benefit analysis of the necessity of medications for maintaining health assessed against concerns regarding adverse effects of medications (Horne & Weinman, 1999). It is suggested that decisions regarding adherence behaviour are influenced by this assessment. In a study of asthmatic, dialysis, cardiac and oncology patients, strong beliefs about the necessity of medications for maintaining health were identified (Horne & Weinman, 1999). Patient beliefs about medication explained a significant proportion of the variance in adherence alongside type of illness and patient age. Dialysis and oncology patients were more adherent than asthmatic or cardiac patients. This may be due to perceptions of medication concerns outweighing the necessity (Horne & Weinman, 1999). Additionally, beliefs about medication were stronger predictors of adherence than sociodemographic or clinical variables. Patients who reported higher scores on the

concern scale compared to the necessity scale in relation to prescribed medication had lower levels of adherence.

In a meta-analysis of the necessity-concerns framework in predicting adherence to medication, Foot, Caze, Gujral and Cottrell (2016) assessed this in relation to a variety of different conditions, which included studies of dialysis and transplant patients. Adherence to medication was positively correlated to necessity beliefs and negatively correlated to concern beliefs via the BMQ, with those perceiving their medication as necessary for maintaining health and wellbeing were more adherent compared with those who do not. Patients who perceive greater concerns from medications, such as increased side effects, disruption to daily life and normal routines and medication dependency are more likely to be non-adherent. This supports the findings reported by Horne & Weinman (1999) in relation to the cost-benefit analysis.

Among renal transplant recipients, patients report higher levels of perceived necessity of immunosuppressant medication and lower levels of concern, with the perceived benefits of the medication outweighing the costs in treating and managing post kidney transplant care (Massey et al., 2013; Massey et al., 2015). This is similar to literature that has explored a variety of health conditions (Horne & Weinman, 1999; Foot et al., 2016). Over time, perceptions of immunosuppressant medication necessity were shown to significantly decrease, however, this did not impact the cost-benefit view towards immunosuppressants. No significant differences were reported between adherent and non-adherent groups in beliefs about medication. Lennerling & Forsberg (2012) report similar findings within this patient population, with perceptions of immunosuppression necessity found to be high and for concerns, low. Additionally, this study measured adherence via the BAASIS self-report measure and reported high levels of adherence among renal transplant recipients, which is reflected through the high perceptions of immunosuppressant medication reported via the BMQ necessity scale. Patients demonstrated understanding of this medication and the importance of taking it for maintaining health and wellbeing. However, despite this, no significant relationships were observed between the BAASIS and the BMQ, which suggests that medication beliefs and actual adherence may

be independent to some degree. This was supported by Massey et al., (2015) who additionally found no significant relationships between adherence and medication beliefs. The feeling of low social support from family and friends was the only factor related to self-reported adherence.

#### 7.1.1 Rationale

Adherence behaviour is essential for maintaining kidney function, including for transplant recipients in order to prevent decline or rejection of grafts. The best measure of adherence behaviour remains a key question for clinical providers, with some suggestion that combining objective measures such as routine blood serum/ assay levels of immunosuppressants with self-reports offering a useful avenue to explore. At the same time, whilst there is some research on the importance of illness perceptions and medication beliefs for transplant populations, still less is known about how these factors impact on engagement with treatment and crucially, whether they form a basis for patient support. This study was designed to explore these considerations.

#### 7.1.2 Aims and objectives

The first aim of the study was to determine whether self-reported adherence is associated with markers of adherence obtained from clinical data. The second aim was to determine which illness perceptions are associated with adherence to immunosuppressants in a sample of kidney transplant recipients. The third aim was to determine whether medication beliefs are associated with adherence to immunosuppressants in this patient group. The final aim was to investigate how patients conceptualise their post-transplantation treatment.

### 7.2 Methods

Adult patients from the renal service of the East and North Hertfordshire NHS Trust were invited to participate in the study. Eligible renal transplant recipients who attend the post-transplant clinic at Lister Hospital were approached for inclusion in the study. The weekly post-transplant clinic was

attended by the researcher over a period of 7 weeks throughout April and May 2019. Clinical data was retrieved from the patient electronic database following completion of the study questionnaire.

### 7.2.1 Participants

Of 160 participants approached, 128 consented and completed the questionnaires, of which 109 were returned fully complete. Thirty participants declined/refused to take part when approached in clinic and two participants contacted the researcher prior to their clinic date asking not to be approached for participation. A power calculation was performed for sample size estimation. With up to five covariates for a linear regression model, an alpha of  $=.05$ , power  $=0.80$  and effect size  $= 0.15$ , the projected sample size needed was approximately  $N=92$ . Therefore, our sample size collected was adequate for the study.

### 7.2.2 Inclusion/exclusion criteria

The following inclusion and exclusion criteria were used to ensure all participants could engage with the study materials independently and to ensure that clinical data was available for all participants via patient electronic records at the Trust.

Inclusion criteria included:

- Aged 18 years or over;
- Good English language skills;
- Renal transplant recipient attending the post-transplant clinic at Lister Hospital
- Capacity to consent

Exclusion criterion:

- Patients who did not have sufficient English language skills to access study materials or to complete self-report questionnaires accurately

### 7.2.3 Design and procedure

A cross-sectional design was used. Potential participants were informed about the study via letter prior to their clinic appointment date. They were advised that a researcher may approach them during clinic. The participant information sheet was included with the information letter for potential participants to read in their own time ahead of clinic. Eligible patients were approached during their transplant clinic appointment waiting time. The study aims and implications of participation were explained to patients. Patients were asked if they had received and read the participant information sheet sent to them via post, and were provided with a participant information sheet to read again if necessary and given time to decide whether to participate. They were informed that the study was voluntary, and that they could withdraw from the study at any time without explanation. Potential participants were informed via the information sheet that clinical data collected as part of routine care would be accessed as part of the research, and provided consent for this via the consent form to indicate they were happy for their clinical data collected as part of routine care to be accessed as part of the study. Patients were also informed and assured of the confidentiality of their data.

Patients provided informed consent by signing a consent form, to show they understood the research they were participating in and consented to take part. Patients were given an anonymity code to use on their questionnaires, to ensure data was collected anonymously and could be identified should the participant wish to withdraw. Once consented, patients completed the questionnaires. They were provided with instructions on how to do so and were asked to complete them on their own.

Questionnaires were completed via paper copy, allowing patients to complete questionnaires during clinic whilst waiting for their appointment with the consultant nephrologist.

Data was also retrieved from the patient record database at Lister Hospital for each patient, in order to compare self-reported adherence from the questionnaires to clinical measures recorded as part of routine care. This included immunosuppressant levels from routine blood tests, attendance at post-transplant clinic appointments, and a range of other information that was deemed useful for further

analysis namely: donor type and whether patients were transplanted pre-emptively or following receiving dialysis.

#### 7.2.4 Materials/ Measures

The following self-report measures were completed: demographics (including date of birth, gender, ethnicity, level of education attained, work status/occupation and relationship status), the medication adherence report scale (MARS-5) (Horne & Weinman, 2002), the beliefs about Medicines Questionnaire (BMQ) (Horne, Weinman & Hankins, 1999) and the brief illness perceptions questionnaire (Brief IPQ) (Broadbent, Petrie, Main & Weinman, 2006). The measures were adapted to fit the context of what was being specifically measured among renal transplant recipients. All scales were brief and easy to complete i.e. tick box only and have been widely used with patients with ESRD. Detailed summaries of each of the measures used (MARS-5, BMQ, Brief IPQ) can be found in chapter three of this thesis.

#### *Open-ended questions*

Additional open-ended questions were included for patients to provide detailed written responses relating to adherence to treatment. Developed through discussion within the research team, the questions were aimed at providing more depth of understanding about trends within the quantitative data that was being collected. The items received feedback from members of the public involvement in research group (PIRg) hosted within the school of health and social work at the University of Hertfordshire in order to assess clarity. Suggested revisions were included and the final questions were:

1. Were you on a different renal replacement treatment modality prior to your kidney transplant? (e.g. haemodialysis, peritoneal dialysis). If yes, what Renal Replacement Therapy did you receive?
2. Can you describe how you found following/sticking to that treatment regime?

3. Can you describe how you find following your post-transplant treatment regime?  
(Immunosuppressant medication, clinic appointments etc.)
4. Do you think that you have got better or worse in how well you follow your treatment regime over time?
5. Has how you engage with treatment and advice you have been given changed over time?

### *Clinical Data*

Clinical data collected as part of patient routine care was retrieved from the patient electronic database for analysis in the study to compare to the questionnaire study data. This included transplant donor type, number of immunosuppressants taken for treatment regimen, immunosuppressant blood levels (tacrolimus or ciclosporin), number of missed clinic appointments and whether patients were transplanted pre-emptively or following receiving dialysis. For immunosuppressant blood levels, an average was taken for the 6 months prior to completing the questionnaire or at least three readings if this was under 6 months. The number of missed clinic appointments was also recorded for the 6 months prior to completing the questionnaire or at least three appointments if this was under 6 months. Clinical expected therapeutic ranges of immunosuppressant blood levels were also used in order to calculate the percentage of readings outside the expected range during the data collection period (6 months prior to completing the questionnaire). These were determined via input from the project team, which included two Consultant nephrologists, local practice protocol and cross checking with previous research. For tacrolimus, a therapeutic range of 5-10ng/mL in the first year following transplantation was used (Schafer-Keller et al., 2008) and a therapeutic range of 5-8ng/mL for those >12 months post-transplant (NHS Royal Berkshire, 2014). For ciclosporin, a therapeutic range of 50-100ng/mL was used for patients >12months post-transplant based on local practice protocol. No patients in the study taking ciclosporin were <12 months post-transplantation.

### 7.2.5 Ethical Approvals

This study received NHS and HRA ethical approval (IRAS number 254246) and was approved by East and North Hertfordshire NHS trust to commence. Ethical approval was also granted by the University of Hertfordshire (UH protocol number LMS/PGR/NHS/02924). Permissions were sought from the author for use of the MARS-5 and BMQ. The brief-IPQ is freely available within the public domain.

#### *Risk Assessment for Patient Participants*

The risks for patients in completing these questionnaires were deemed minimal. It was unlikely that completing the questionnaires would be sensitive or upsetting for participants as we were only asking about their treatment and medication experiences. However, the researcher was available whilst participants were completing the questionnaires should they have had any questions or queries they wished to discuss. In addition, participants were given a study debrief form and provided with details of the research team and a member of the local post-transplant team should they have had any questions following participation.

#### *Risk Assessment for Researcher*

There was minimal risk to the researcher. The researcher had undergone the relevant GCP training to take consent from patients and had experience of conducting research with this patient population.

### 7.2.6 Confidentiality

Questionnaires were completed via paper versions to aid ease of participation during clinic time. Questionnaires and consent forms were kept in a locked filing cabinet in separate files at the University of Hertfordshire. The data was anonymised and password-protected in excel, and anonymised in a statistics package when entered for analysis, to ensure that patients were not identifiable. Clinical patient data was retrieved from patient records using an NHS computer at the Lister Hospital, East and North Hertfordshire NHS Trust. This data was also anonymised and

password-protected in excel, and anonymised in a statistics package for analysis, to ensure that patients were not identifiable. Patients were only identifiable via an anonymity code used on the consent form and questionnaires, to ensure questionnaires could be identifiable should a participant have wished to withdraw their data following participation.

### 7.2.7 Statistical Analysis

Descriptive statistics were used to characterise the study sample and to calculate mean adherence, beliefs about medicines and illness perceptions rates. Correlation analyses was used to explore relationships between self-reported adherence (MARS-5) and adherence recorded in clinical data (1: Immunosuppressant blood levels [as immunosuppressant mean scores, z-scores of the mean, variability via z-scores of standard deviation of immunosuppressant levels and percentage outside expected immunosuppressant blood level ranges]; 2: post-transplant clinic attendance) for renal transplant recipients. For example, self-reported immunosuppressant medication adherence was compared to immunosuppressant levels to assess if there was a correlation between what patients report and their recorded adherence level via routine blood tests. Linear regression models were used to determine whether illness perceptions predict adherence among renal transplant recipients. Additional regression analyses were used to determine whether beliefs about medication predict adherence among renal transplant recipients. All tests were two-tailed and p-values of less than 0.05 were considered to be significant. The data was analysed using SPSS version 25. Feedback on open-ended questions were reviewed and analysed using thematic content analysis, and anonymised quotes were used to support quantitative findings. Thematic content analysis was conducted using NVIVO version 12.

## 7.3 Results

### *Patient Characteristics*

Patient characteristics are shown in Table 7.1. Mean age for the sample was 55.5 years (SD=13.34; range 20 – 86 years). The majority of the sample were male (N=81, 63.3%), married (N=73, 57%)

and of white ethnicity (N=95, 74.2%). Patients reported mixed employment status with a roughly equal split of employed (N=61, 47.6%) or retired (N=43, 33.6%), with a range of different education levels.

Table 7.1: Demographic characteristics of patient study sample

	N=128
<i>Age M (SD)</i>	55.5 (13.3)
<i>Gender N (%)</i>	
Male	81 (63.3)
Female	47 (36.7)
<i>Ethnicity N (%)</i>	
White European	95 (74.2)
Minority ethnic	32 (25)
Missing	1 (0.8)
<i>Relationship Status N (%)</i>	
Single	28 (21.9)
In a relationship	7 (5.5)
Living with partner	8 (6.3)
Married/civil partnership	73 (57)
Divorced	9 (7.0)
Widowed	3 (2.3)
<i>Occupation N (%)</i>	
Unemployed	17 (13.3)
Employed	47 (36.7)
Self-employed	14 (10.9)
Retired	43 (33.6)
Student	3 (2.3)
Other	4 (3.1)
<i>Education level N (%)</i>	
No formal qualifications	25 (19.5)
GCSE or equivalent	33 (25.8)
A-level or equivalent	20 (15.6)
University or college degree	38 (29.7)
Post-graduate qualification	9 (7.0)
Missing	3 (2.3)

Treatment characteristics of the sample are summarised in table 7.2. The majority of the patients received a deceased donor transplant (N=94, 73.4%) and were transplanted following receiving renal replacement therapy via dialysis (N=111, 86.7%). The average transplant vintage for the sample was just under eight years (M=7.96, SD=6.43). Post-transplantation, the majority of patients were taking a combination of two immunosuppressant medications (N=70, 54.7%). In terms of clinic attendance, the sample reflected an adherent group with 89.9% (N=115) of patients having missed no post-transplant clinic appointments in the six months prior to taking part in the study. Nine patients (7%) had missed clinic appointments in the previous six months prior to taking part in the study, with only a few patients having missed more than two. The majority of patients were taking tacrolimus as their main immunosuppressant (N=109, 85.2%). Mean tacrolimus level for patients for the six months prior to the study was 5.99 ng/l (SD=1.52). Of those taking ciclosporin (N=15, 11.7%), mean level for patients for the six months prior to the study was 73.4 ng/ml (SD=31.1). Using the immunosuppressant therapeutic expected ranges, 81 (65.9%) patients were found to have blood levels outside the expected range for more than 25% of the readings during the study data collection period observed, 48 (39%) for more than 50% and 21 (17.1%) for more than 75% of the readings.

Table 7.2: Treatment characteristics of patient study sample

	N=128
<i>Donor type N (%)</i>	
Deceased	94 (73.4)
Living	34 (26.6)
<i>Transplant Vintage (years) M (SD)</i>	
	7.96 (6.43)
<i>No. immunosuppressants N(%)</i>	
1	13 (10.2)
2	70 (54.7)
3	45 (35.2)
<i>Pre-emptive vs. post-dialysis transplant N (%)</i>	
Pre-emptive	17 (13.3)
Post-dialysis	111 (86.7)
<i>No. Missed clinic appointments N (%)</i>	
0	115 (89.8)
1	9 (7.0)
2	1 (0.8)
3	1 (0.8)
4	2 (1.6)
<i>Immunosuppressant levels M (SD)</i>	
Tacrolimus ng/1 (N=109)	5.99 (1.52)
Ciclosporin ng/ml (N=15)	73.4 (31.1)
Missing (N=4)	
<i>Percentage outside immunosuppressant expected therapeutic range N (%)</i>	
>25%	81 (65.9)
>50%	48 (39)
>75%	21 (17.1)
Missing (N=5)	

#### *Data Screening*

All variables were tested for normality using the Shapiro-Wilk test. The test showed that the data did not meet the assumption of normality for most parameters, with the exception of BMQ specific-concern and BMQ necessity-concern differential (see table 7.3). All non-normally distributed variables were transformed using both log transformation and square root transformation to see if the

normality issues could be resolved. All variables remained significantly non-normally distributed, therefore further analysis was conducted using the original non-normally distributed variables.

Table 7.3: Shapiro-Wilk test of normality for questionnaire items.

	<i>p-value</i>
<i>MARS-5</i>	
MARS 1 (N=121)	<.001
MARS 2 (N=116)	<.001
MARS 3 (N=116)	<.001
MARS 4 (N=116)	<.001
MARS 5 (N=116)	<.001
MARS Total (N=114)	<.001
<i>Brief IPQ</i>	
Item 1: Consequences (N=127)	<.001
Item 2: Timeline (N=125)	<.001
Item 3: Personal control (N=125)	<.001
Item 4: Treatment control (N=127)	<.001
Item 5: Identity (N=125)	<.001
Item 6: Concern (N=127)	<.001
Item 7: Coherence (N=127)	<.001
Item 8: Emotional representation (N=126)	<.001
Brief IPQ Total (N=119)	.019
<i>BMQ</i>	
BMQ Specific: Necessity (N=125)	<.001
BMQ Specific: Concern (N=123)	.07
BMQ Necessity-Concern differential (N=123)	.38
BMQ General: Overuse (N=126)	.042
BMQ General: Harm (N=126)	.001

*NB: MARS-5 = Medication Adherence Report Scale; Brief IPQ = Brief Illness Perceptions Questionnaire; BMQ = Beliefs about Medicines Questionnaire*

#### *Reliability of the Scales Used*

The internal reliability of the scales, indicated by Cronbach's alpha, is displayed in table 7.4. The

Brief IPQ scale total had a good reliability score of 0.77. The beliefs about medicines sub-scales had

good reliability scores of above 0.70, with only the general-harm scale having a score below this of 0.66, albeit still acceptable. The MARS-5 had a poor internal reliability score of 0.38. When exploring correlations between the five items on the scale, item 1 and item 2 failed to have a correlation coefficient of above 0.30 with at least one other item in the scale. A benchmark of 0.30 is commonly used in scale development and assessment. When items 1 and 2 were removed from the scale, internal consistency improved to 0.69. It is possible that the items within the scale could be interpreted as measuring different types of non-adherence, and this may have caused lower internal reliability. Item 1 “I forget to take them” could be viewed as measuring unintentional non-adherence, whereas the other items are on intentional non-adherence. Item 2 “I alter the dose” may not be viewed as having serious consequences if patients are longer since transplantation and are therefore confident in medication taking or may have agreements with clinicians on when and how to alter doses if required dependent on patient needs. Items 3, 4 and 5 could be viewed as more serious in terms of non-adherent behaviour. It is possible in this patient sample that although patients may forget to take medication or may alter doses, they may be less likely to stop taking them for a while (item 3), decide to miss out a dose (item 4) or take less than instructed (item 5). It is therefore possible that in the context of the patient sample used in this study, patients understood the questions relating to different types of non-adherence with differing consequences of non-adherent behaviour. However, this scale has been validated in a number of long-term conditions and other previous studies using the MARS-5 have found good internal reliability of the scale, including studies of HD (Wileman et al., 2015) and transplant populations (Butler et al., 2004; Griva et al., 2012). Therefore, based on this consideration, the total scale using all five items will be used in this analysis. Analysis was conducted using the modified MARS items 3-5 only to explore if the data would change. Similar outcomes were observed in relation to multiple regression analyses.

Table 7.4: Internal consistency shown by Cronbach's alpha for each questionnaire scale

Scale	Cronbach's $\alpha$
<i>MARS-5 (N=114)</i>	0.38
MARS items 3-5 (items 1 & 2 deleted) (N=115)	0.69
<i>Brief IPQ items 1-8 (N=119)</i>	0.77
<i>Beliefs about medicine</i>	
BMQ Specific: Necessity (N=125)	0.80
BMQ Specific: Concern (N=123)	0.73
BMQ General: Overuse (N=126)	0.75
BMQ General: Harm (N=126)	0.66

*MARS-5 = Medication Adherence Report Scale; Brief IPQ = Brief Illness Perceptions Questionnaire; BMQ = Beliefs about Medicines Questionnaire*

Mean scores for the three questionnaires administered in the study are displayed in table 7.5. Scores on the MARS-5 reflect high self-reported adherence to immunosuppressants, with a total MARS-5 mean score of 24.25 (SD=1.10) out of a total score of 25. Responses on the beliefs about medicines questionnaire indicate that patients felt their illness has an infinite timeline (M=9.38, SD=1.76). Patients indicate they felt treatment is extremely helpful in helping their illness (M=8.73, SD=1.87) and that they understand their illness clearly (M=8.80, SD=1.63). Responses relating to other elements of the brief IPQ reflect a moderate view. An overall score for the brief IPQ was computed representing the degree to which illness is perceived as threatening or benign. The total score reflects a moderate threatening view of illness (M=35.57, SD=13.38). Responses on the BMQ specific-necessity indicate that patients have strong perceptions of the need for the immunosuppressant medication they are taking to maintain their kidney transplant health now and, in the future, (M=21.70, SD=3.27). Scores on the BMQ specific-concerns scale indicate patients have uncertain views about the potential negative effects of immunosuppressant medication. The relative importance of these attitudes (necessity and concerns) was obtained by calculating the necessity-concerns differential. The differential score indicates patients perceive the benefits of their immunosuppressant medication to outweigh the costs (M=9.40, SD=5.17). Responses on the BMQ general-overuse scale indicate an uncertain view about how medicines are prescribed and beliefs that they are overused by

clinicians (M=10.21, SD=2.85). Scores on the BMQ general-harm scale are low indicating a more positive view about medicines, perceiving them as less likely to be harmful (M=7.98, SD=2.47).

Table 7.5: Overall patient mean scores for adherence, illness perceptions and treatment beliefs

	M (SD)
<i>MARS-5</i>	
MARS 1 (N=121)	4.45 (0.77)
MARS 2 (N=116)	4.88 (0.42)
MARS 3 (N=116)	4.95 (0.22)
MARS 4 (N=116)	4.98 (0.13)
MARS 5 (N=116)	4.93 (0.32)
MARS Total (N=114)	24.25 (1.10)
<i>Brief IPQ</i>	
Item 1: Consequences (N=127)	4.46 (3.04)
Item 2: Timeline (N=125)	9.38 (1.76)
Item 3: Personal control (N=125)	5.90 (2.96)
Item 4: Treatment control (N=127)	8.73 (1.87)
Item 5: Identity (N=125)	4.48 (3.12)
Item 6: Concern (N=127)	5.67 (3.26)
Item 7: Coherence (N=127)	8.80 (1.63)
Item 8: Emotional representation (N=126)	4.63 (3.33)
Brief IPQ Total (N=119)	35.57 (13.38)
<i>BMQ</i>	
BMQ Specific: Necessity (N=125)	21.70 (3.27)
BMQ Specific: Concern (N=123)	12.28 (3.85)
BMQ Necessity-Concern differential (N=123)	9.40 (5.17)
BMQ General: Overuse (N=126)	10.21 (2.85)
BMQ General: Harm (N=126)	7.98 (2.47)

*MARS-5 = Medication Adherence Report Scale; Brief IPQ = Brief Illness Perceptions Questionnaire; BMQ = Beliefs about Medicines Questionnaire*

### *Correlation Analyses*

Spearman's correlation was used to explore associations between total MARS-5 adherence scores with both the illness perceptions from the brief IPQ and the BMQ sub-scales (see table 7.6).

Consequences, personal control, treatment control and emotional representation were all found to significantly correlate with total MARS-5 adherence score. Brief IPQ total score was found to significantly correlate with total MARS-5 adherence score. None of the BMQ sub-scales were found

to correlate with total MARS-5 adherence score, however specific-necessity and general-overuse were marginally non-significant. Additionally, correlations were conducted exploring associations between clinical data and MARS-5 adherence (see Table 7.6). No significant correlations were found between mean tacrolimus levels, mean ciclosporin levels or clinic attendance and total MARS-5 adherence score. In addition, standardised z-scores of the mean, z-scores of the standard deviation of immunosuppressant levels for variability comparisons and percentages outside the expected range for immunosuppressant blood levels were calculated to correlate with adherence. Similarly, no significant correlations were found between any of the immunosuppressant variables and total MARS-5 adherence score. When exploring transplant vintage, no significant correlations were observed between adherence, illness perceptions or beliefs about medications and transplant vintage.

Donor type was also considered to see if this impacted on adherence or psychological factors. Mann-Whitney U test was used due to the difference in patient numbers between the donor type groups and the non-normal distribution of the measures. No significant differences were observed in illness perceptions and beliefs about medicines between deceased donor and living donor recipients. A significant difference was found in MARS-5 adherence scores between deceased donor (M=24.11, SD=1.19) and living donor (M=24.63, SD=0.67) recipients,  $U=940.0$ ,  $p=.022$ , with deceased donor recipients having a lower total adherence score, however, this was only marginally lower.

Table 7.6: Spearmans correlations between Brief IPQ and BMQ scales with adherence

	MARS-5 Total	
	$r_s$	$p$
<i>Brief IPQ</i>		
Consequences	-0.28	.003*
Timeline	-0.002	.99
Personal control	0.26	.005*
Treatment control	0.24	.009*
Identity	-0.11	.27
Concern	-0.13	.19
Coherence	0.13	.17
Emotional representation	-0.21	.024*
Brief IPQ Total	-0.31	.001*
<i>BMQ</i>		
BMQ Specific: Necessity	0.18	.058
BMQ Specific: Concern	-0.13	.18
BMQ General: Overuse	-0.18	.055
BMQ General: Harm	-0.15	.11
Tacrolimus	.05	.61
Ciclosporin	-.50	.11
Missed clinic appointments	-.02	.85
Z-score immunosuppressant mean	-.003	.98
Z-score immunosuppressant SD	-.086	.37
Percentage outside expected range	-.130	.18

*MARS-5 = Medication Adherence Report Scale; Brief IPQ = Brief Illness Perceptions Questionnaire; BMQ = Beliefs about Medicines Questionnaire*

### *Linear Regression Analyses*

#### *Illness perceptions (Brief IPQ) and self-reported adherence (MARS-5)*

Simple linear regressions were used to determine whether illness perceptions were predictive of self-reported adherence behaviour. These were conducted exploring each illness perception independently as a predictor of adherence measured by the MARS-5. Consequences was found to be a significant predictor of adherence, with a 1 point increase in perceived consequences associated with a -.11 decrease in adherence ( $\beta = -.11, p = .001$ ). Consequences explained 9.4% of the variance in adherence. Personal control was a significant predictor of adherence, with an increase in perceived personal control associated with an increase in adherence ( $\beta = .13, p < .001$ ), explaining 11.4% of the variance in

adherence. Similarly, treatment control was a significant predictor of adherence, with an increase in perceived treatment control associated with an increase in adherence ( $\beta=.17, p=.002$ ), explaining 8.3% of the variance in adherence. Coherence was a significant predictor of adherence, with an increase in perceived coherence associated with an increase in adherence ( $\beta=.16, p=.011$ ) explaining 5.6% of the variance in adherence. Finally, emotional representation was a significant predictor of adherence, with an increase in emotional representation associated with a decrease in adherence ( $\beta= -.09, p=.006$ ), explaining 6.7% of the variance in adherence. No other illness perceptions were identified as significant predictors of adherence (timeline, identity, concern).

A multiple regression was then used to predict the combined predictive value of consequences, personal control, treatment control, coherence and emotional representation in explaining self-reported adherence. This also allowed exploration of whether these illness perceptions remained significant predictors when entered alongside the other predictor variables. These domains were found to significantly predict adherence,  $F(5, 105) = 5.79, p<.001, R^2 = .216$ . However, when looking at individual parameters, only personal control remained a significant predictor of adherence ( $\beta=.08, p=.041$ ). This means that whilst the overall model was significant, when taking into account multicollinearity, personal control was the most important predictor of adherence.

A linear regression was conducted using the Brief IPQ total score as a predictor of self-reported adherence (MARS-5). The total brief IPQ score was a significant predictor of self-reported adherence, with a 1-point increase in perception of illness as threatening is associated with a -.03 decrease in self-reported adherence score ( $\beta= -.03, p<.001$ ).

#### *Beliefs About Medicines (BMQ) and self-reported adherence (MARS-5)*

Simple linear regression was used to explore if specific beliefs about immunosuppressant medication predicted adherence. Necessity and concern were both not significant individual predictors of adherence (specific-necessity:  $p=.08$ ; specific-concern:  $p=.20$ ). This remained the same when both

variables were entered as a multiple linear regression, with the same p values. Similarly, general beliefs about medication was explored as predictors of adherence. Overuse was a significant predictor of adherence, with a 1-point increase in perceptions of overuse of general medication associated with a -.07 decrease in self-reported adherence score ( $\beta = -.07, p = .048$ ) explaining 3.5% of the variance in adherence. Harm was a significant predictor of adherence, with an increase in perceptions of harm caused by general medication associated with a decrease in adherence ( $\beta = -.08, p = .049$ ) explaining 3.5% of the variance in adherence. When both variables were entered together in a multiple regression, overuse and harm were both no longer significant predictors of adherence (general-overuse:  $p = .39$ ; general-harm:  $p = .40$ ).

### **Open-ended Questions: Qualitative Analysis**

***Question 1: Were you on a different renal replacement treatment modality prior to your kidney transplant? (e.g. haemodialysis, peritoneal dialysis). If yes, what Renal Replacement Therapy did you receive?***

Answers to this question included a response about previous treatment modality and so were straightforward to analyse thematically as there was naturally a high level of similarity in descriptions of treatment. Responses were provided to this question by 117 (91.4%) patients. The majority of patients reported receiving dialysis prior to their kidney transplant. Some patients reported receiving more than one type of dialysis, e.g. HD and peritoneal dialysis, whereas some report receiving only one type of dialysis treatment. This was confirmed via the quantitative statistics which showed 86.7% of the sample received their transplant post-dialysis.

***Question 2: Can you describe how you found following/sticking to that treatment regime?***

A total of 100 patients (78.1%) provided a response to this question. When asked to describe how they found following/sticking to their dialysis treatment regime prior to their transplant, three themes

emerged representing the majority of patient responses. These included “Physical, behavioural and mental challenges”, “Space for living a normal life” and “Bitter lifeline”.

### ***Physical, behavioural and mental challenges***

The majority of patients described the physical and mental challenges of coping with dialysis. This was raised in relation to adjusting to the restrictive nature of the treatment, particularly diet and fluid intake restrictions, and the impact the treatment requirements had on patient quality of life. This is clearly demonstrated via the quotes below.

*“Very difficult to go through. The fluid restrictions were very difficult. Emotionally and physically dialysis disrupts and is very difficult.” (P133, M, 49yrs)*

*“Very difficult, both mentally and physically. Diet and fluid restrictions impacted in social life” (P021, M, 67yrs)*

In addition to reporting the restrictions associated with dialysis and the impact of these, patients also reported the side-effects experienced as a result of treatment, notably fatigue.

*“Very restrictive ie. Diet, fluid intake, spending almost the whole day travelling to, in and home from hospital, being sick, headaches, tiredness” (P018, M, 30yrs)*

*“Very hard and I used to feel very weak when I came off the machine, I passed out sometimes. Constantly thirsty....” (P008, F, 62yrs)*

*“Very restrictive of what food and drink could be consumed, also very tiring. Also not able to move much as attached to the machines” (P136, M, 61yrs)*

It is clear from patient responses that there are a number of common challenges with following treatment requirements that have to be managed in order to adhere to dialysis treatment. These present as challenges in managing behavioural requirements as part of adhering to treatment, including diet and fluid restrictions, as well as managing side-effects as a result of treatment, such as fatigue. It is also interesting that patients talk about mental challenges, suggesting that they have a common language for expressing their difficulties. This highlights the complexity of this treatment regime, and how the presentation of these challenges can impact patient's quality of life.

### ***Space for living a normal life***

The majority of patients described how dialysis treatment disrupts routines and daily life. This is likely due to treatment demands, for example in the case of HD patients must make arrangements to attend treatment three times per week for 3-4 hours per session dependent on fluid removal needs. In the case of peritoneal dialysis, treatment is required more frequently. This is demonstrated via the quotes below.

*"It takes over your life. Everything revolves around your 3 days of dialysis" (P098, M, 71yrs)*

*"I felt this was crucial treatment so accepted the disruption to my life accordingly. My employer was very accommodating, however it was difficult holding down a senior position" (P110, M, 58yrs)*

*"...Haemo took up my entire life. I could only exist not really live" (P117, F, 29yrs)*

Patients describe how the treatment demands of dialysis can have a large impact on both work and home life. If working full-time, arrangements have to be made with employers in order to attend treatment. In terms of home life, arrangements may have to be made regarding, for example, travel, childcare and/or carer duties etc. Due to these demands and also the side-effects of receiving the treatment, some patients report this can have a debilitating effect on quality of life.

### ***Bitter lifeline***

Patients also reported feeling a lack of choice in their dialysis treatment due to the necessity of the treatment in order to maintain health and wellbeing as much as possible. This was often viewed negatively by patients. This is demonstrated via the quotes below:

*“It just became a way of life and had no choice but to have dialysis – if I wanted to stay as healthy as I could be...” (P094, F, 44yrs)*

*“Awful – it was necessary, but tiring, hard work, time consuming, life limiting, upsetting for myself and family” (P044, F, 46yrs)*

*“Very challenging at first, scary too. But it was to keep me well and alive, so you have to get over that” (P023, F, 50yrs)*

Although patients often disliked dialysis treatment, they recognised the necessity of the treatment in order to maintain their health. This highlights the patients’ attempts to see the benefits of receiving the treatment as outweighing the costs and negatives in terms of treatment demand and side-effects of what is seen as a debilitating treatment.

### ***Question 3: Can you describe how you are finding following your post-transplant treatment regime now? (Immunosuppressant medication, clinic appointments etc.)***

A total of 121 patients (94.5%) provided a response to this question. When asked to describe how they were finding their post-transplant treatment regime, two themes emerged representing the majority of patient responses. These included “Improvements in quality of life” and “Challenges adjusting to treatment”.

## **Improved quality of life**

In response to post-transplant treatment, patients often described how the treatment regime became a part of their daily routine and how receiving the transplantation had allowed them to return to what they saw as more of a normal life, particularly in comparison to dialysis. Within this theme, “normalising the life of a transplant recipient” and “regaining autonomy” were identified as sub-themes.

### *Normalising the life of a transplant recipient*

The majority of patients described how managing and following the post-transplant treatment regime had become a part of their normal daily routine.

*“Taking tablets twice a day is routine, like brushing your teeth” (P057, M, 59yrs)*

*“This has been my life for 16 years since I was 19. It’s so routine now it’s just normal. I have never missed a clinic appointment and never miss my medication. Morning and evening religiously!”  
(P031, F, 36yrs)*

*“I’m 15 years past post-transplant it’s normal now to following instructions and regime” (P061, F, 27yrs)*

*“Since it’s been a long time I find it quite easy to do. It’s now become part of a natural easy routine.”  
(P133, M, 49yrs)*

Normalising treatment could be an important process for patients in adjusting to post-transplant management but additionally to allow patients to feel less like an unwell “sick patient” and to identify as an ordinary well person who simply checks in with health care professionals every now and then to ensure renal function is stable and that there are no concerns. This could ensure there is limited

anxiety and time spent worrying about the transplant and its function and allows patients to focus on living as normal a life as possible.

### Regaining autonomy

Patients described how receiving a transplant provided a sense of freedom in escaping dialysis and feelings that they had gained their life back. This was particularly notable in comments from patients who had received dialysis treatment prior to transplantation.

*“...the transplant has given me back my life ie. Working full-time as a teacher!” (P020, F, 55yrs)*

*“...in 100% better health. Can live a more normal life.....I can just take my medication and can live a normal life. Very glad I had the transplant” (P008, F, 62yrs)*

*“Much easier and able to enjoy a normal life” (P017, M, 65yrs)*

Due to the complexities and challenges in managing a dialysis treatment regime, it is evident that transplantation can provide patients with a greater ability to live life as they once did prior to receiving dialysis. Medications are managed by patients at home and once renal function becomes stable, clinic appointments and blood tests to monitor function and medication levels can become as little as once every three or four months. This can allow patients to return to work and remove the feeling of reliance on clinicians towards positive patient self-management. This treatment option also allows fewer restrictions with diet and fluid. These changes from when receiving dialysis can be important for improving patient positivity and quality of life.

### **Challenges adjusting to treatment**

Although there are clear benefits for patients in receiving a kidney transplant, a number of patients described some of the challenges experienced in adjusting to their post-transplant treatment regime.

Within this theme, “freedom within boundaries”, “unintentional forgetting in treatment management” and “psychosocial impact of treatment side-effects” were identified as sub-themes.

### Freedom within boundaries

A large proportion of patients described the burden of being required to attend a high number of clinic appointments post-transplant. This frustration may partly be due to patient expectations of greater freedom following transplantation. Although following stabilisation of renal function appointments can become more infrequent, the burden of needing to attend the transplant clinic regularly particularly within the first-year post-transplant or during times of unstable kidney function was described as an issue by patients. In relation to this, complaints were particularly raised surrounding the time spent on travelling to and from the hospital, parking costs and waiting times when appointments can often be quite short.

*“A continuous stream of appointments and the travelling to and from – 50 mile round trip, also the cost of travel and the parking, sometimes for just 90 minutes.” (P006, M, 78yrs)*

*“...Clinic appointments sometimes are a waste of time. Very short consideration for which you travel 2 hours” (P059, M, 49yrs)*

Frustration was also raised surrounding needing to travel for blood tests prior to clinic appointments, sometimes on a different day to ensure results are available to discuss with consultants, therefore disrupting daily routines for multiple days.

*“...not being able to get tests done at Bedford locally is a pain as I have to travel to do them, not having a local clinic means an entire day is taken for 10-15 min” (P064, M, 59yrs)*

Although appointments become less frequent, as some patients have to travel a considerable distance to the hospital for their appointments, this was raised as a major negative aspect of post-transplant

care. At the trust in which this study was conducted, issues surrounding car parking limitations and cost of parking were also raised as problematic. Additionally, if blood tests could not be performed locally this was also described negatively by patients. Although these aspects were raised as a nuisance for patients, the benefits and importance of attending the clinic to monitor transplant function as part of their post-transplant care appeared to be recognised, which seemed to encourage attendance despite the irritants.

#### Unintentional forgetting in treatment management

Some patients described occasional forgetting in relation to taking their immunosuppressant medication. This was often due to lifestyle factors making tracking medication taking more challenging.

*“Hard to remember varying doses of medicines while living a busy family life” (P065, M, 73yrs)*

*“It’s hard as I seem to forget that I have medication to take. Forgetting I have appointments.” (P120, F, 20yrs)*

*“...Sometimes I forget and am late with the day time dose no more than 1.5 hours” (P057, M, 59yrs)*

Patients who were longer since receiving their transplantation described forgetting due to complacency or forgetting whether medication has already been taken as it becomes embraced as a normal part of the daily routine.

*“I often forget medication. I have been on medication for 23 years and often feel like I have already taken my medication” (P117, F, 29yrs)*

*“...sometimes I think too easy as it makes me complacent and I forget both medication and appointments quite often” (P032, F, 58yrs)*

This highlights some of the challenges in managing treatment regimes, and how simple lifestyle factors and changes to daily routines can impact on remembering to take medication at the times prescribed or to attend clinic appointments. This suggests that developing and having strategies in place to manage and remember treatment requirements, such as taking medication and attending appointments, could be beneficial for patients to promote adherence.

*Psychosocial impact of treatment side-effects*

A challenging aspect described by some patients was managing and accepting side-effects of immunosuppressant medications. Patients described the physical side effects experienced and the irregularity in feelings of health and well-being.

*“...However I get depressed with the tremors which are a severe side effect of the tacrolimus” (P086, F, 75yrs)*

*“up and down. With lots of warts” (P060, M, 49yrs)*

*“...when I first started I experienced a multitude of adverse side effects. The worst being hair loss” (P091, M, 20yrs)*

Patients also described feelings of tiredness and fatigue as a physical side effect of taking the immunosuppressant medication, but additionally the mental fatigue associated with managing multiple medications required to ensure transplant function, and the fluctuation in feelings of being well whilst following this treatment regime.

*“...I am usually very fatigued and can feel quite poorly just after taking meds a.m – so can be a bit difficult” (P096, F, 61yrs)*

*“Find the drugs very tiring. Up and down with health is very hard to take. I was on an even health level on dialysis.” (P030, M, 50yrs)*

This demonstrates that although transplantation is often considered the best treatment option for most patients with ESRD, there are still challenges both physical and psychological that may be experienced and have to be managed as a result of treatment. This can be particularly challenging for patients who have been transplanted pre-emptively and perhaps felt fairly well prior to transplantation, or for patients who experienced fewer or less notable side-effects when receiving dialysis. Additionally, if patients considered prior to transplantation that following receiving the transplant their life would return to normal and they would feel healthy and well, managing these expectations when experiencing treatment side-effects may also be challenging.

***Question 4: Do you think you have got better or worse in how well you follow your treatment regime over time? And Question 5: Has how you engage with treatment and advice you have been given changed over time?***

Analysis for question four and five were combined. When asked whether they have got better or worse in how well they follow their treatment regime over time, and whether how they engage with treatment and advice they have been given has changed over time, patients answered with brief responses. Responses were provided by 121 (94.5%) patients for question four, and by 117 (91.4%) for question five. The majority of patients identified as having always been engaged with treatment since transplantation or having improved over time. However, some patients described becoming worse in how well they follow their treatment regime.

### **The” ideal” patient**

A number of patients described following treatment in the same manner with no changes in engagement with treatment and advice over time. Any changes described were in relation to

medication dosage changes but engagement with advice and treatment was described as not changing. Some patients described this in relation to their relationship with clinicians and health care professionals and how this relationship was important for engagement with treatment and advice.

*“The same. I’m not a rule-breaker – have always and will always do as the doctors ask – it gives me the best chance of staying well” (P031, F, 36yrs)*

*“No - I’ve always been very good at taking medication and following doctors’ advice – it helps to have a doctor you trust. I think this makes you more confident in the treatment they prescribe” (P074, F, 33yrs)*

*“Not really, I’ve always been inquisitive and fully engaged with my treatment and the advice I receive” (P022, F, 57yrs)*

### **The “progressive” patient**

A large number of patients described having improved in how well they follow their treatment regime, and that this got better as time progressed since transplantation.

*“Better over time. Obviously in the beginning you don’t fully understand your condition, so you follow directions. The longer it goes on it becomes more day to day” (P133, M, 49yrs)*

*“Better – I know my medication, what it does, how to manage it effectively” (P074, F, 33yrs)*

*“Better. More you do something it becomes second nature” (P010, M, 41yrs)*

This improvement was often described in relation to gaining familiarity and understanding with post-transplant treatment requirements, allowing for improved engagement.

### ***Barriers to treatment engagement***

A few patients did describe becoming worse in how well they follow their treatment regime. This was often mentioned in relation to lifestyle factors, changes in routine, longer time since transplantation in remembering to take medication or medication side-effects.

*“As time passes, sometimes (it’s) difficult remembering medications. Stressful if going away or out for the day” (P044, F, 46yrs)*

*“Much worse. I used to take medications at a particular time of the day and now I never follow this regime” (P032, F, 58yrs)*

*“Worse!! I felt better before the transplant. Med drugs are very hard to take.” (P030, M, 50yrs)*

Challenges adjusting to treatment, side-effects/pill burden, and remembering to take medication alongside a busy lifestyle were described as barriers to engagement. A few patients described feeling more unwell post-transplant, and this impacted on how well they followed their regime.

### 7.4 Discussion

This study aimed to explore whether psychosocial factors, including illness perceptions and beliefs about medication, were predictive of adherence to immunosuppressants. Findings from this study highlight some interesting outcomes relating to illness perceptions and beliefs about medication as predictors of adherence. Increases in perceived personal and treatment control were found to predict increases in adherence to immunosuppressants. There was an inverse relationship between perceived consequences and emotional representation with adherence to immunosuppressants. These findings are similar to previous literature that has identified receiving a kidney transplant to be associated with positive perceptions of illness controllability (Griva et al., 2012), including personal control associated with improved adherence (Massey et al., 2013). Additionally, Massey et al., (2013) found perceived consequences to be rated significantly higher among non-adherent patients. This relates

closely to the study's findings where increases in perceived illness consequences predicted decreases in adherence. However, where this study identified increases in perceived emotional response to predict decreases in adherence, Massey et al., (2013) found the opposite with higher perceptions resulting in improved adherence. This may relate to the level of emotion experienced by patients and whether they are able to cope with this in the context of managing a chronic health condition. Additionally, the studies used different measures of adherence and different study designs (cross-sectional vs. longitudinal), which could contribute towards different findings. Other illness perceptions have also been associated with receiving a kidney transplant, including positive perceptions of identity (Griva et al., 2012), and longer perceived illness timeline to increase adherence (Massey et al., 2013), however, this study found no association between these items and adherence. Taken with existing research, the findings indicate that illness perceptions are essential to patients framing their illness experiences and provides consistent support for them having a role in treatment adherence.

Patients reported higher scores on the necessity sub-scale and lower scores on the concerns subscale of the BMQ, indicating a greater perception in necessity of immunosuppressant medication, and a lower perception of concerns, such as medication dependency or side-effects. This supports existing literature that has found patients report higher necessity beliefs and lower concern beliefs (Horne & Weinman, 1999; Lennerling & Forsberg, 2012; Massey et al., 2013; Massey et al., 2015; Foot et al., 2016). Findings relating to the necessity-concerns differential indicated a positive score representing patients as recognising the benefits of immunosuppressant medication as outweighing the costs. This finding is also observed in other literature using this measure (Horne & Weinman, 1999; Lennerling & Forsberg, 2012; Massey et al., 2013). Specific beliefs about immunosuppressant medication in terms of necessity and concerns, were not identified as predictors of adherence. Although Horne & Weinman (1999) found medication beliefs to be stronger predictors of adherence, compared to sociodemographic and clinical factors, other literature has found no significant associations between these two factors (BMQ and adherence) (Lennerling & Forsberg, 2012; Massey et al., 2015). When explored independently, both subscales of general beliefs about medication (overuse and harm) were

identified as significant predictors of adherence, where an increase in perceived overuse and harm of medications predicted a decrease in adherence. However, these were both only marginally significant, and when both variables were entered as a multiple regression, they were no longer significant. This is an interesting finding as it suggests that perceptions of general medication could be important in determining adherence behaviour. However, much of the previous literature exploring medication beliefs have focused on the BMQ-specific subscales, therefore exploration of these findings is needed to clarify this outcome.

No significant correlations were identified between clinical data and total MARS-5 adherence score. This included both immunosuppressant blood levels exploring mean tacrolimus and ciclosporin levels, and also clinic attendance. The same was also found when using z-score of mean immunosuppressant level, z-score of SD immunosuppressant and percentage of immunosuppressant readings outside the expected range. This is an interesting finding considering previous literature has identified combining measurement methods as more effective and reliable in defining and determining non-adherence (Schafer-Keller et al., 2008), including combining self-report with blood assay. This perhaps needs to be explored in relation to measures used to assess self-reported adherence and definitions used to assess adherence via clinical data. Additionally, a high number of patients had immunosuppressant blood level readings outside of the expected therapeutic ranges during the study data collection period (6 months prior to completing the study questionnaire) which could indicate non-adherence. However, therapeutic target ranges can often be individualised on a patient by patient basis and dependent on transplant vintage. It may be that the therapeutic ranges presented in the existing literature (Schafer-Keller et al., 2008) and by local practice at NHS trusts may not be representative or applicable to patients at all trusts providing post-transplant follow-up care. Target levels may also be individualised based on patient factors.

No significant correlations were observed between adherence or psychological factors and transplant vintage. This is of particular interest as existing literature exploring long-term adherence suggests adherence declines over time (Nevins & Thomas, 2009; Tsapepas et al., 2014), however, no

associations were found in this study which reflects this. It is possible the sample recruited were a particularly adherent group of long-term survivors, and those with poor adherence may be back on dialysis. Or arguably could suggest a need to look at practice patterns in support at different centres to understand this further. Finally, patients who received a deceased donor transplant were found to have a significantly lower adherence score compared to those who received a transplant from a living donor. This finding differs to existing literature which has suggested non-adherence levels to be higher among those with living donor grafts (Denhaerynck et al., 2007; 2014). However, it should be noted that the adherence scores between the two groups did not differ largely, with the mean score for deceased donor recipients only slightly lower than that of living donor recipients.

The qualitative comments via open-ended questions provided a mixed view towards experience of renal transplantation within this patient sample. Those who reported positive experiences in relation to transplantation described feelings of regained life and ability to return to normal routines, including work and family life, prior to other forms of renal replacement therapy, such as dialysis. This could be interpreted as an increase in quality of life, which has been identified to improve following transition to post-transplantation from dialysis (Griva et al., 2012). However, as transplantation is often viewed as better than HD or not as taxing, it's downside often gets overlooked. Therefore, for some patients it does not provide the positive outcomes expected. Of those who described negative experiences in relation to their transplant, this was often described in relation to physical and psychological challenges associated with managing treatment, including experiences of side-effects. Negative experiences of post-transplant care and graft failure or loss has been associated with lower quality of life and negative illness perceptions (Griva et al., 2012). Higher perceptions of concerns of immunosuppressant medication is associated with lower levels of adherence (Foot et al., 2016). Therefore, patients who have expressed qualitative comments of challenges with post-transplant care and treatment may be at risk of non-adherence. Additionally, aspects relating to the burden of follow-up care in relation to blood tests and clinic appointments was also noted (despite the requirements often being less demanding than other renal replacement therapy types such as HD or peritoneal dialysis). Other literature has identified patients can feel overwhelmed by medication side-effects and

health decline post-transplant (Pinter et al., 2017). This could be a determining factor in whether patients engage with the treatment regimen and clinician advisements, however, the findings from the necessity-concern differential highlight that patients recognise the benefits of immunosuppressants outweigh the costs in maintaining health, which may make them more likely to engage with, for example, medication taking, clinic appointments and blood tests.

The findings from both the questionnaire measures and open-ended questions highlight the complexity in managing treatment and adjusting to life post-transplantation. Exploring how patients are coping with medication and how they perceive their illness may be useful to signal those who may be at risk of disengagement who may benefit from support via an intervention to improve treatment adherence.

#### 7.4.1 Strengths and limitations

There is limited previous literature which has explored the role of illness perceptions and beliefs about medications among renal transplant recipients and specifically how this relates to adherence. The study adds to this growing pool of evidence exploring psychological aspects in relation to adherence. Additionally, the study utilised mixed questions, providing in depth analysis of answers as well as exploring patterns in data. As such, research of this nature has a useful contribution to make towards strategies to support patient adherence. Furthermore, the sample size exceeded the requirements identified for adequate analysis via a power calculation.

There were a number of limitations to be considered when interpreting findings. Firstly, the study relied on self-report measures, which previous literature indicated may lead to under reporting of non-adherence (Massey et al., 2013). However, in consideration of this issue, clinical data relating to adherence behaviour was also collected via immunosuppressant blood levels and clinic attendance to compare with self-reported adherence rates. Secondly, poor internal validity was identified via Cronbach's alpha for the MARS-5 total adherence score in this patient sample. This may be due to perceptions of adherence in this particular patient sample recruited for this study. The questions may

have been perceived in different ways by patients relating to different severity levels of non-adherence with differencing consequences. This could lead to different reporting rates between the items. However, analysis was conducted removing the items that were problematic, with similar outcomes shown in relation to multiple regression analyses. The MARS-5 has been used in other chronic illness contexts, including HD, but less commonly among renal transplant recipients. An alternative adherence measure may need to be considered in future studies. Thirdly, most of the variables used in the linear regression analyses were non-normally distributed. Although log and square root transformation were used, this did not resolve the issues with normality. Analyses was therefore conducted using the original non-normally distributed variables. Interpretation of the study findings should be considered with this in mind. Finally, the post-transplant clinic at the trust in which the study was conducted is not a transplanting centre, therefore patients are often more experienced transplant patients with longer transplant vintage. Patients who are longer since transplantation are more likely to be non-adherent, particularly with unintentional non-adherence (Griva et al., 2012), which could influence reporting on the measure.

#### 7.4.2 Conclusion

Certain illness perceptions may play an important role in adherence to immunosuppressants within the renal transplant population. Perceived personal control and treatment control predicts an increase in adherence. Perceived consequences and emotional response predict decreases in adherence. Specific beliefs relating to necessity and concerns surrounding immunosuppressants are not predictive of adherence, however, patients recognise the benefits of this treatment as outweighing the costs in managing and treating their condition. Whilst combined estimates of clinical adherence behaviour have advanced as a useful step to accurate measurement, the current study did not support this. The research has highlighted the continued role of illness perceptions and medication beliefs in further understanding health experiences and behaviour in an ESRD population, specifically adding to the dearth of research in this area for transplant recipients. The outcomes pave the way for considering whether illness perceptions in particular should be routinely assessed to signal patients who may

struggle to engage with treatment regimens, and who may benefit from exploring their illness perceptions further e.g. through psychological support, low intensity intervention or alike.

## Chapter 8: General Discussion

### 8.1 Introduction

The aim of this thesis was to present a programme of research that provides clinically useful insights into adherence in renal transplant recipients. It achieved this aim using a range of research methodologies including systematic review, quantitative data analysis, and qualitative methods to provide further depth of enquiry. Furthermore, the findings were drawn from multiple sources including clinical data collected as part of routine care, and engaging with both patients and health care professionals who work with this patient population. A brief summary of the main findings from each study chapter from this thesis are provided below:

#### *Systematic review (Study 1)*

Findings from the systematic review highlight that non-adherence remains a prevalent issue within the renal transplant population. A total of 60 studies were included in the review. Studies varied in how they measured adherence, including self-report, electronic monitoring, pharmacy refill, blood levels and collateral report, with some studies combining more than one measure in an attempt to increase reliability. The overall non-adherence prevalence ranged across studies from 0.06% to 89.2%, dependent on how adherence was measured and operationalised. The most commonly utilised measurement method to assess adherence behaviour was self-report. Meta-analysis of 38 studies revealed the pooled prevalence of self-reported non-adherence was 37.6%, however prevalence rates vary across measures used. Findings highlight a clear lack of consistency in how adherence is defined and measured across studies. Clear guidelines or consensus is needed for clinical practice to identify patients at risk for poorer outcomes. The review also found that younger age, greater transplant vintage, living related donor grafts, and symptoms such as side-effects and psychological distress, are useful targets for intervention in order to improve non-adherence rates.

### *Retrospective data analysis (Study 2)*

Non-adherence ranged from 25%-42% pre-transplant and 15.9%-22.7% post-transplant dependent on how it was operationalised. Across all measures of adherence used pre-transplant, non-adherence was less post-transplant, and in some cases, significantly so. However, although some patients do improve adherence to treatment post-transplant, a proportion of patients remain non-adherent. Poor phosphate control pre-transplant was associated with post-transplant clinic attendance. Patients who had missed one or more transplant clinic appointments had higher mean pre-transplant phosphate levels. In addition, non-adherent patients with high phosphate levels pre-transplant were significantly younger. Despite this, the findings did not indicate a strong direct relationship between pre and post-transplant adherence. The findings require confirmation and further research to assess whether pre-transplant adherence interventions may enhance post-transplant adherence and patient outcomes.

### *Qualitative interviews (Study 3)*

Post-transplant non-adherence remains a prevalent issue clinicians have to manage with their patients. Five main themes were identified on the understanding of non-adherence: “Barriers to adherence”, “Striving for normality”, “Mutuality in maximising patient adherence”, “Complexity in shining light on adherence in wait listing” and “Post-transplant normalization”. The findings demonstrate clinicians recognise and understand the barriers patients can face with adherence, and work to try and make treatment management easier, considering individual circumstances where possible. Improving patient understanding of medication taking and engagement was considered an effective way to promote adherence. Clinicians felt it was important to deliver this alongside providing continued patient education and implementing how to better use peer support. Clinicians felt patients viewed transplantation as an opportunity to return to what they perceived as a normal life and to avoid dialysis. However, as patients transplant function becomes stable over time, perceptions of wellness and a lack of immediate consequences following missed medication can lead to non-adherent behaviour. Agreement on how adherence is viewed as part of transplant eligibility was lacking, with clinicians managing pre-transplant non-adherence in different ways. The findings highlight the need

for agreement among the renal community about how non-adherence should be managed in the decision-making process for wait-listing.

#### *Cross sectional questionnaire (Study 4)*

The findings showed no correlations between clinical data and MARS-5 self-reported adherence score. Illness perceptions may play a role in adherence to immunosuppressants among renal transplant recipients. Perceived personal control and treatment control were found to predict an increase in self-reported adherence. Perceived consequences and emotional response were found to predict decreases in self-reported adherence. Renal transplant recipients perceived the “benefits” of immunosuppressant medication to outweigh the “costs” in managing and treating their condition, however, specific beliefs relating to necessity and concerns surrounding immunosuppressants did not significantly predict self-reported adherence. The qualitative comments indicated a mixed view and experience of transplantation. Positive experiences reported included feelings of regained life, however, for some, symptom burden or side effects, for example, meant life after transplantation did not meet expectations. The findings highlight areas for potential intervention by considering whether illness perceptions in particular should be routinely assessed to signal patients who may struggle to engage with treatment regimens and who may benefit from exploring these further via intervention.

To summarise, the overall findings from this thesis as a whole make a contribution towards moving clinical practice and research forward. They include:

1. The value of mixed methodology as a method of enquiry;
2. The importance of multiple perspectives from both patients and providers (health care professionals);
3. The need for clear methods for defining and measuring adherence;
4. The complex relationship between pre and post-transplant adherence;
5. The importance of adherence in clinician’s decision making to wait-list patients for transplantation.

## 8.2 Overall findings

### 8.2.1 Value of mixed methodology

The mixed-method approach utilised within this programme of research provided a wide breadth of data and allowed exploration of patterns of behaviour as well as in depth understanding of experience. When both quantitative and qualitative methods are used within one study, these can be used to corroborate findings (Johnson et al., 2007). Mixed-methods research is becoming increasingly common and popular in health-related research (Protheroe et al., 2007) and can provide greater insight into specific issues. These are being utilised in exploratory work as well as alongside interventions and randomised controlled trials (Protheroe et al., 2007; O’Cathain et al., 2014). In these contexts, qualitative research, such as interviews, can be used to understand the benefits and limitations surrounding interventions, and whether they are successful or not. Utilising a range of methodologies is important in order to understand and evaluate complex issues (O’Cathain et al., 2007), such as non-adherence. In relation to this programme of research, a combination of approaches was considered appropriate to explore non-adherence in depth to provide a clear understanding of this topic area, including a systematic review, retrospective analysis of clinical data, questionnaires and qualitative interviews. A systematic review methodology provided a comprehensive way to identify and capture existing literature exploring non-adherence to immunosuppressants, providing an updated knowledge base of existing studies among adult renal transplant recipients. A retrospective data analysis of clinical data provided exploration of adherence behaviour using objective measures, without limitations of subjectivity, such as self-report. This provided a novel way of exploring patterns of behaviour between pre and post-transplant adherence. Qualitative interviews were appropriate and necessary for exploring the role of adherence in transplantation, as understood by clinicians and health care professionals. There is limited existing literature exploring the role of adherence behaviour pre-transplant when determining transplant eligibility, therefore rich and detailed responses were needed to understand this fully. Finally, questionnaire methodology allowed for wider scoping of behaviour patterns among renal transplant recipients in relation to adherence, clinical data and

psychological factors relating to how they perceive transplant and immunosuppressant medication and manage their treatment in relation to taking pills and timing. This provided a broad understanding of the topic area, highlighting areas for further exploration or development areas for intervention in future work.

### 8.2.2 Importance of multiple perspectives

The programme of research considered different perspectives on adherence behaviour among renal transplant recipients, by consulting both patients and clinicians/health care professionals. This was considered essential as it allowed for exploration of whether health care professionals understanding of non-adherence was similar to that of their patients' experiences. Establishing this match is important for ensuring medical professionals are able to support patients if they experience barriers that impact adherence in order to address and rectify issues and preserve graft function. Both patients and care-provider ultimately have a role to play within shaping outcomes and the extent to which they are "on the same page" is likely to be important. For example, a primary care study found that the level of concordance between patients and physicians about a presenting issue and how it should be managed predicted medication taking at follow-up (Kerse et al., 2004).

Additionally, different health care professionals were consulted as part of the qualitative interview study, including consultant nephrologists, transplant surgeons, registrars, specialist nurses and pharmacists. It could be considered that these health care professionals have different relationships with renal transplant recipients based on their interactions and roles. Nurses may have greater involvement with patients and be in contact with them more regularly regarding their health, well-being and medication, whereas consultant nephrologists and registrars may only see patients when they attend for their routine clinic visits or experience adverse events. It is possible that patients may share differing or alternative views and experiences with different health care professionals regarding treatment adherence or be more open with some staff compared to others. Understanding of patient's experiences and of barriers to adherence may have been different based on these encounters.

A direct comparison between patient and health care professionals' perspectives via one study was not provided as part of this programme of research, however, this would be useful in future research within this patient population. Previous literature using focus groups of patient and clinician perspectives explored what patients want to know about their medications, finding a disparity in understanding of how much information patients should receive in relation medication (Nair et al., 2002). The authors indicated that patients want more information relating to medication side-effects, however the use of evidence-based information sheets was considered beneficial. Clinicians and pharmacists highlight concerns over detailed discussion surrounding side-effects due to risks of leading to non-adherence (Nair et al., 2002). Although this research was not conducted within the renal transplant population, it highlights the importance of exploring expectations across these multiple perspectives considering and comparing views from patients and health care providers relating to medication taking.

This programme of research did provide an understanding via a qualitative interview study of how health care professionals understand and manage patients exhibiting signs of non-adherence, and barriers they consider may impact medication taking. Findings from the quantitative studies (retrospective and questionnaire study) using patient related data highlighted patterns of adherence behaviour and predictors of non-adherence, providing supplementary information to add to health care professional's knowledge base. This consolidation of findings takes into consideration both patients and health care providers perspectives in relation to non-adherence, and further supports the need for interventions and for identifying patients that should be targeted for intervention to improve adherence rates.

### 8.2.3 Measurement methods for adherence

This thesis clearly highlights a lack of consistency in measurement methods used in the literature when exploring adherence to immunosuppressant medication. As highlighted in the systematic review, researchers exploring adherence use different forms of measurement, for example, self-report, electronic monitoring, collateral report, blood assay and pharmacy refill, leading to different levels of

non-adherence reported as a result. The systematic review found an overall non-adherence prevalence rate ranging from 0.06% to 89.2%, dependent on how adherence was measured and operationalised. This is a similar or wider range than previous reviews, which found prevalence rates ranging from 2% to 67% (Denhaerynck et al., 2005) and 1.6% to 96% (Belaiche et al., 2017). This may be due to the increase in number of studies included in the systematic review compared with previous reviews and therefore a wider range of measurement methods and definitions utilised.

Additionally, studies that have aimed to capture adherence behaviour via self-report have used a variation of different self-report measures (including validated and unvalidated measures). These may include differing items/questions to assess adherence which define and score adherence using different cut-off points for categorising non-adherent behaviour. This results in a lack of ability to understand and compare reported non-adherence rates across the published literature. The systematic review found across studies using self-report measures non-adherence prevalence rates ranged from 7.4% to 89.2%, with an overall pooled estimate of 37.6%. Previous reviews have reported prevalence rates over studies including self-report measures, with one review reporting a weighted mean prevalence of 27.7% (Denhaerynck et al., 2005) and a median of 22% (Butler et al., 2004). Again, the overall prevalence rate in this review may be higher due to an increase in number of studies included and a greater variation in self-report measures used.

Although electronic monitoring is considered the most reliable and efficient way of measuring adherence behaviour to immunosuppressant medication, due to the expense associated with this measurement method it is used less frequently (Kreys, 2016). As a result, studies often rely on alternative, and more cost-effective methods, such as self-report. Due to the limitations that come with using self-reported measures, such as potential under-reporting of adherence rates from patients (DiMatteo, 2004; Kreys, 2016), researchers have attempted to use a combination of measurement methods to assess adherence. Most commonly, researchers combine self-report alongside blood assay and collateral report from physicians (e.g. Schafer-Keller et al., 2008). Although a composite score can be more reliable, again there are challenges in comparing these across studies due to differences

in assessment and definition of non-adherence used via these other methods, and how these are combined to create the composite score.

Future developments in the measurement of adherence behaviour should include encouraging researchers to use validated reliable self-report measures. This would provide better consistency of self-report measures that can be utilised to yield reliable non-adherence rates and allow for comparisons to be made across studies. Additionally, clearer definitions and cut-off points when categorising adherent and non-adherent patients via clinical data is also needed to provide clear target ranges for researchers to classify patients. This would also allow for comparisons to be made across studies using clinical data such as immunosuppressant blood levels and clinic attendance to assess adherence in this patient population. Some studies have used target blood ranges (e.g. Schafer-Keller et al., 2008; Gelb et al., 2010; Griva et al., 2012; Huckler et al., 2019), however, this is often defined based on existing literature or clinical guidance. Clear guidance on how to assess adherence via clinical data e.g. target ranges (with consideration for differing patient factors such as transplant vintage) would be useful to provide clarity for researchers on how to use this measurement method. This is also necessary for defining adherence via other methods, including electronic monitoring, pharmacy refill and physician ratings.

As electronic monitoring is often too expensive for researchers to utilise, clearer guidelines on how to implement other more cost-effective measurement methods should be considered. Additionally, guidelines on composite scores including which measurement methods should be combined to provide the most reliable adherence rates and how to combine outcomes from each measure to create a total measure should be considered. This would provide a clearer and more streamlined way to measure adherence that could then be more easily compared across published literature. Taking a more strategic approach to how transplant researchers and clinicians explore and report adherence is one suggestion that could unite efforts and provide a bank of more comparable data for the future.

#### 8.2.4 Comparing pre and post-transplant adherence

The thesis included one of the few existing studies exploring the relationship between pre and post-transplant adherence (Hucker et al., 2019). It is important to consider how adherence behaviour may transfer from one treatment modality to another. This study used clinical data as an objective measure of adherence behaviour. Although it may be considered that a non-adherent dialysis patient will become a non-adherent transplant patient, the findings highlight that a strong direct relationship in these behaviours is unlikely. The prevalence of non-adherence was greater pre-transplant by some but not all of the measures utilised. This may suggest that adherence with treatment post-transplant is more manageable than to treatment pre-transplant which involves adherence to HD, associated medications and fluid and diet restrictions. Additionally, side-effects, symptom burden and impact on quality of life may also be reduced (Jansz et al., 2018). These findings are important for clinicians when considering whether non-adherent HD patients are eligible for transplantation. However, the study was limited by a small sample size and further research is needed to support these findings. Additionally, pre-transplant and post-transplant definitions of adherence were determined based on previous literature (Leggat et al., 1998; Saran et al., 2003; Hecking et al., 2004; Schafer-Keller et al., 2008; Wileman et al., 2011; Methven et al., 2017) and clinical experience. A clear agreed way of defining adherence using clinical data would be beneficial for future research.

Previous studies have shown a relationship between adherent behaviour prior to transplantation and graft loss or mortality (Douglas et al., 1996) reporting 61% of the patients identified as non-adherent pre-transplant experienced graft loss or death. Studies exploring this behaviour pattern in other organ transplant types (heart, liver, lung) found pre-transplant non-adherence with medication taking, higher education and low conscientiousness were predictors of non-adherence to immunosuppressants at one-year post-transplant (Dobbels et al., 2009). In addition, low social support with medication taking and pre-transplant medication adherence have been associated with non-adherence and late acute rejection respectively (Di Matteo et al., 2004). Findings across other organ transplant types highlight the need to attend to pre-transplant behavioural patterns in predicting potential post-transplant outcomes. Further research is needed within the renal transplant population comparing pre and post-

transplant adherence in order to identify a reliable pattern of behaviour to interpret and consider in clinical practice. Alternatively, drawing on the findings of the qualitative study within this thesis, it might be plausible that patients try to “escape HD” with a promise of a better life, which at least in the short term might impact on better adherence post-transplant. Whether this changes over time would require a higher-powered study considering adherence behaviour over a longer duration, and ideally in a longitudinal rather than retrospective design. This would allow for using mixed-methods to track the changes in life circumstances, beliefs and attitudes that impact on adherence over-time. For example, whilst Taber et al., (2017) found that missing appointments was related to graft outcomes in kidney transplantation, a lack of qualitative follow-up with patients means that reasons for missing appointments are unknown and this restricts the design of suitable interventions to address behavioural confounds.

#### 8.2.5 Importance of adherence in decision making to wait-list for transplantation

Findings from the qualitative interview study highlight a lack of consistency in the role of adherence behaviour when determining transplant eligibility. Whilst there are clear guidelines on the medical and surgical assessment required to assess fitness for the transplant operation (Dudley & Harden, 2011), compatibility tests and psychosocial assessments in relation to coping with the physical and emotional transplant aspects, the role of adherence and how non-adherent behaviour should be considered as part of this process is unclear. Where some health care professionals consider all patients should be given the opportunity of a transplant as their behaviour may change post-operation, others consider demonstration of improved adherent behaviour pre-transplant, whether that be to dialysis or to transplant work-up appointments, is important prior to activation on the transplant waiting list. Ironically, those who did not consider adherence in the decision-making process felt that this would lead to inconsistency due to subjectivity but clearly this is already happening in routine care. The research might suggest benefit in opening a dialogue on this issue in transplant care teams.

In addition to considering the importance of pre-transplant behaviour as part of the transplant work-up assessment, patients additionally need to be well informed and prepared for when transplantation may

take place. Available kidneys can turn up at any time with no warning, which could result in patients not necessarily being fully prepared. It is essential that patients have the best opportunity to be well, and therefore require the knowledge and ability to enact behaviours in order to ensure this. Greater resources or education sessions available to patients could be increased during the transplant work-up period, given that care teams are providing the best service possible within the time and resource constraints that many NHS services contend with. This could ensure the best usage of resources, not only in terms of patient outcomes but additionally in terms of cost-effectiveness for health services, such as the NHS, due to the higher cost burden of dialysis treatments compared with immunosuppressant medication required for transplant recipients (Jindal et al., 2003). Currently, there are more patients on the waiting list for kidneys than organs available for transplantation. It is clear from the literature that non-adherence to immunosuppressants can lead to graft rejection and graft loss (Loghman-Adham, 2003; Butler et al., 2004). If clinicians want the best outcomes for patients in terms of graft function and survival, consistent agreement on adherence is needed for transplantation.

The law change in England from Spring 2020 to an opt-out system aims to improve organ donation rates and reduce the number of patients on the waiting list. Adults will be considered as consenting to donating their organs unless they have recorded to opt-out or fall into a category meaning they are not eligible to donate (Department of Health and Social Care, 2019). This change in law could lead to an increased availability of kidney organs available for transplantation, however success is dependent on patients' families supporting the decisions of their deceased relatives regarding organ donation (Noyes et al., 2019). Although this could lead to a positive development in improving kidney organ availability, it is important to ensure that assessment of suitability is still maintained and respected by patients and clinicians. Clinicians will need to ensure that although an increased number of organs may become available, patients are still suitable for transplantation and likely to utilise and benefit from the organ in terms of graft function and survival. This point becomes even more important given that qualitative enquiry revealed that clinicians were less worried about adherence when a live related organ was being used. It is plausible that an increase in organs could bring about the same wider spread attitude. Additionally, in relation to patients who have experienced graft loss, careful

consideration should remain when determining eligibility for re-activation on the transplant waiting list considering why the graft failed, as transplant outcomes and graft function have been shown to deteriorate with increasing number of re-transplantations (Ahmed et al., 2008; British Transplantation Society, 2014). Finally, patients will need to ensure that although waiting times for a suitable organ may reduce, they are prepared to adhere to treatment requirements and do their best to ensure graft longevity and survival.

### 8.3 Clinical implications and future research

The findings from this thesis have useful clinical implications that could guide future research and clinical practice. The need for clear operationalised definitions of non-adherence for the commonly used measurement methods is demonstrated. This should include how to measure and categorise patients as adherent and non-adherent, and is important for improving the quality and reliability of research being conducted in this field, allowing for comparisons to be made across studies. This is not a novel finding per se, but given that the field has not yet moved towards consistency in operationalizing non-adherence (Belaiche et al., 2017), an important contribution to highlight. Additionally, as self-report remains the most commonly used form of measurement method, researchers should be encouraged to use validated and reliable measures in order to provide accurate non-adherence rates in their studies. Research and clinical practice could benefit from experts in the field of adherence providing agreement and guidance on how and what should be used to measure adherence behaviour to improve accuracy of reported findings.

The findings from this thesis demonstrate there are challenges in identifying accurate ways of measuring adherence using clinical data. Mean tacrolimus levels of a range of tacrolimus blood test result values, for example, may not be reliable, as there are multiple factors that could influence results. Additionally, findings suggest a strong relationship between pre and post-transplant adherence is unlikely. A longitudinal study is needed to further explore the relationship between pre and post-transplant adherence, following patient behaviour through the transplantation journey. Although further research is needed on the use of clinical data as markers of adherence and the reliability of

using this to identify adherent and non-adherent patients, the initial findings from this thesis are useful and should be considered in clinical practice.

The thesis also highlights areas that could be targeted for intervention in order to try and improve adherence rates. Patient education sessions could be utilised to promote self-management and empower treatment autonomy, providing more in-depth information to better educate patients about their medicines and the importance of taking these to prolong graft survival. Additionally, placing emphasis on this prior to transplantation will ensure patients are better prepared for managing expectations for life post-transplant. The questionnaire study revealed that patients with greater perceptions of personal control over their kidney transplant were more adherent, therefore instilling autonomy in patients prior to transplantation could better prepare them for adjusting and managing treatment post-transplant. Patients may also benefit from reminder/refresher education sessions every few years to try and prevent adherence from decreasing as transplant vintage increases. Longitudinal follow-up is needed to see how and at which point adherence changes as time progresses post-transplantation.

Research has highlighted the importance of patient education sessions when making decisions about kidney transplantation (Wilson et al., 2012) considering patient factors and best practices such as individually tailoring education, culturally competent and making it understandable for those with low health literacy (Skelton et al., 2015). Providing peer support for patients could also be beneficial for promoting adherence and consciously or not, the clinicians contributing to this thesis made efforts to add to patient social capital through peer support. Experienced patients with greater transplant vintage are able to provide useful advice based on their treatment journey to patients both with ESRD preparing for transplantation and those more recently transplanted, to promote the importance for taking immunosuppressant medication and following treatment regimens. Broader formalised support in this way should be considered and implemented in clinical practice. Peer support may be particularly effective in young patients as they transition from paediatric to adult care services

(Harden & Sherston, 2013). As well as face-to-face, today's digital world offers a better way to do this online, which could also benefit younger people.

Factors associated with non-adherence have also been highlighted. Targeting those at risk with adherence promotion messages may help encourage and improve adherence. Interventions could be simple reminders during appointments or via telephone, providing information or encouraging engagement with a face-to-face intervention, such as patient education. These could be easily implemented and should be considered in clinical practice among renal care teams. Additionally, providing support for patients experiencing side-effects of medication or psychological distress could also lead to improvements in adherence rates. The questionnaire study highlighted that patients experiencing physical or mental challenges may be at greater risk for non-adherence. Exploring and monitoring these issues regularly with patients could reveal individuals who would benefit from support. The quantitative patient studies provide an insight into non-adherence among this patient population, however, further research using qualitative methods, such as interviews or focus groups, could provide greater in-depth understanding of patient treatment experiences. A qualitative methodology would also allow for further exploration of factors associated with non-adherence providing greater insight into how to support patients with barriers they are experiencing to medication taking. Further research of this nature is needed with patients to explore these issues.

Future research is also needed to develop guidance for clinicians and health care professionals surrounding the role of non-adherence in patient eligibility for transplantation alongside the medical and psychological assessments. Findings from the qualitative study indicate there is a lack of consistency in how non-adherent patients are assessed and managed pre-transplant, with some differences in how pre-transplant non-adherence is viewed dependent on prospective donor type. Further work is needed to develop these findings. Patients are often treated on a case by case basis by a multidisciplinary team; however, it might be that encouraging patients to demonstrate adherent behaviour to either dialysis or transplant work-up appointments for a particular period of time may be beneficial for encouraging behaviour change and support improved behaviour post-transplant. These

preliminary findings should be considered in clinical practice to ensure staff agreement and consistency in how patients exhibiting pre-transplant non-adherence are managed when determining eligibility for transplantation.

#### 8.4 Strengths and limitations

Some of the key strengths of the thesis have already been signposted. Specifically, the mixed methods nature and individual study contributions to the field. Another major strength is the multidisciplinary team that were involved in planning the programme which has arguably yielded many avenues to pursue further. The thesis has and could continue to impact the field of study. The thesis set out to inform clinical practice and has achieved this in a pragmatic way. The body of research generated, and avenues to take forward are a testament not only to mixed methods, but multidisciplinary research teams with different approaches towards answering the same question. A major strength of the research is therefore not only what it has contributed to the field of study, but where it can be taken in the future.

Despite the strengths of this work, it is acknowledged that there were some limitations. The majority of the data was collected from one NHS trust which should be considered when interpreting and generalising to the wider renal transplant population. Further, a cross-sectional study was utilised to explore the relationship between self-reported adherence and clinical parameters, including psychological factors such as medication beliefs and illness perceptions. A longitudinal design would have been beneficial to explore adherence behaviour over time, particularly considering that the risk of non-adherence increases with transplant vintage (Chisolm-Burns et al., 2008; Griva et al., 2012; Burkhalter et al., 2014; Hamedan & Aliha, 2014). However, due to the timeframe available to complete a patient related study, a cross-sectional questionnaire study was deemed most appropriate. Additionally, no qualitative interviews were conducted with patients. It may have been useful to conduct a more in-depth understanding of patient experiences and perspectives on the topic; however, it was not pragmatic in the time frame alongside the other studies within this programme of research.

The self-report measures utilised for the questionnaire study were brief versions or shorter measures. This was due to the nature of the data collection method necessary for the study. Patients were asked to complete the questionnaires during the post-transplant clinic whilst waiting for their appointment, therefore questionnaire length needed to consider this to ensure patients would not be discouraged from completing it if they felt it was too long to complete during this time. It is possible that due to the short nature of the measures utilised, behaviour/beliefs may not have been fully captured. However, patient burden is a key consideration to avoid questionnaire fatigue. Additionally, the MARS-5 (Horne & Weinman, 2002) had poor internal reliability in the study. It is possible that in the context of the patient sample explored, patients understood the questions relating to different types of adherence with differing consequences for non-adherent behaviour. However, this scale has been validated in a number of long-term conditions, and other previous studies using the MARS-5 within a renal population have found good internal reliability of the scale (Butler et al., 2004; Griva et al., 2012; Wileman et al., 2015).

Finally, definitions for non-adherence utilised in the retrospective study were based on previous literature and clinician experience. There is limited existing research indicating how non-adherence should be defined clinically pre and post-transplant, therefore it is possible that the measures used to define non-adherence were not the most reliable and valid. There may be other parameters which may be more relevant. This highlights the need to identify clinically relevant definitions that accurately measure non-adherence rates to ensure reliable reporting in future research. Additionally, the study only explored adherence patterns between HD and post-transplantation. We did not explore patterns between patients on other RRT modalities, such as PD and home HD, and post-transplantation. This would be useful to identify if similar patterns are observed among patients who experienced other RRT modalities prior to transplantation. The sample size was small as this was a specific patient population using data from one NHS trust, including only patients with an active transplant who had been attending the post-transplant clinic for one year. It is possible findings may have been underpowered. However, data was collected for as many patients that met the inclusion criteria as possible and these limitations are considered in relation to the interpretation of the findings.

## 8.5 Conclusions

The findings from this programme of research support previous literature in confirming that non-adherence to immunosuppressants and the wider treatment regimen remains a prevalent issue for renal transplant patients. It is clear that there is a lack of consistency in how adherence is measured and defined in the literature, which needs to be addressed in future research to ensure reliability of reported non-adherence prevalence rates. Patients at risk for non-adherence should be targeted for intervention pre-transplant where possible in order to improve post-transplant behaviour. To enable this to happen, further research is needed to confirm the relationship between adherence behaviour pre and post-transplantation and verify pre-transplant risk factors. Finally, consistent agreement is needed on how non-adherence should feature in decision making on eligibility for transplantation in order to ensure that organs are given the best chance of long-term survival and that patients being listed have equality in contributing factors.

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## Appendices

[Appendix A: East and North Hertfordshire NHS Trust approval for retrospective data retrieval](#)

[Appendix B: East and North Hertfordshire NHS Trust letter of support for qualitative interview study](#)

[Appendix C: Royal Free London NHS Trust placement agreement for qualitative interview study](#)

[Appendix D: University of Hertfordshire ethical approval for conducting interviews with clinicians](#)

[Appendix E: University of Hertfordshire ethical approval extension for conducting interviews with clinicians](#)

[Appendix F: Qualitative interview study participant information sheet – Lister Hospital](#)

[Appendix G: Qualitative interview study participant information sheet – Royal Free Hospital](#)

[Appendix H: Qualitative interview study participant consent form](#)

[Appendix I: Qualitative interview study topic guide](#)

[Appendix J: Qualitative interview study debrief](#)

[Appendix K: NHS research ethics committee and HRA approval to conduct research with renal transplant patients using questionnaires](#)

[Appendix L: University of Hertfordshire full sponsorship approval to conduct research with renal transplant recipients using questionnaires](#)

[Appendix M: Patient questionnaire study information letter to patients](#)

[Appendix N: Patient questionnaire study participant information sheet](#)

[Appendix O: Patient questionnaire study participant consent form](#)

Appendix P: Copy of questionnaire administered to patients

Appendix Q: Patient questionnaire study debrief