UNIVERSITY OF SOUTHAMPTON

PREVALENCE AND PSYCHOSOCIAL CORRELATES OF NON-ADHERENCE TO IMMUNOSUPPRESSANTS IN RENAL TRANSPLANT RECIPIENTS

Dr Janet Ann Butler MSc. MA. MB. BS. MRCP. MRCPsych.

Submitted for the degree of Doctor of Philosophy

University Mental Health Group,

Community Clinical Sciences Research Division,

Faculty of Medicine, Health and Biological Sciences,

March 2003

UNIVERSITY OF SOUTHAMPTON

PREVALENCE AND PSYCHOSOCIAL CORRELATES OF NON-ADHERENCE TO IMMUNOSUPPRESSANTS IN RENAL TRANSPLANT RECIPIENTS

Dr Janet Ann Butler MSc. MA. MB. BS. MRCP. MRCPsych.

Submitted for the degree of Doctor of Philosophy

University Mental Health Group,

Community Clinical Sciences Research Division,

Faculty of Medicine, Health and Biological Sciences,

This thesis is the result of work wholly done whilst I was registered in postgraduate candidature with the University of Southampton and is based on work done wholly by myself under the supervision of Professor Robert Peveler and Dr Paul Roderick

March 2003

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES
UNIVERSITY MENTAL HEALTH GROUP

Doctor of Philosophy

PREVALENCE AND PSYCHOSOCIAL CORRELATES OF NON-ADHERENCE TO IMMUNOSUPPRESSANTS IN RENAL TRANSPLANT RECIPIENTS

by Dr Janet Ann Butler

Existing studies suggest that non-adherence to immunosuppressants may be common and a significant cause of transplant loss in renal transplant recipients. Identification of potentially modifiable correlates of non-adherence should lead to design of an intervention capable of improving adherence. The main objectives of this study were firstly, to compare candidate measures of adherence (cyclosporin levels, self-report, clinician and interviewer ratings) used in all subjects with the 'gold standard' of electronic monitoring used in a random sample of 60 subjects to find the most valid and feasible method for use in clinical practice, and estimate the prevalence of non-adherence; secondly, to investigate the major variables associated with non-adherence with the aim of identifying potentially modifiable factors. Subjects were recruited to the cross-sectional survey in two waves from the population of adult renal transplant recipients in the Wessex Renal Unit 6 to 63 months post transplantation.

One hundred and seventy two subjects were invited to take part. Nineteen refused to take part and complete data were available for 145 subjects. The sample was representative of the eligible population. Other measures of adherence performed poorly when tested against electronic monitoring. Therefore main analyses were confined to the 58 subjects with data available from electronic monitoring of adherence to prednisolone. Two patterns of non-adherence were identified: missing medication and erratic timing of doses. Seven (12%) subjects missed at least 20% days prednisolone and 26 (45%) took their medication outside a 12 hour period 32% of the time. Multivariate analyses showed that the factors most strongly associated with non-adherence were having a transplant from a live donor, having less belief in the need for prednisolone specifically or for immunosuppressants as a group, being prescribed prednisolone on alternate days and functional limitations due to emotional factors. Depression occurred in 30% subjects but was not significantly associated with non-adherence.

The results show that a significant proportion of transplant recipients are non-adherent to immunosuppressants and that beliefs about medication are a promising target for an intervention designed to improve adherence. Clinicians need to be aware that subjects with transplants from live donors may be at greater risk of non-adherence and that patients may hold beliefs about immunosuppressants that differ from medical opinion and that impair adherence in manner that is logical to the patient.

Table of Contents

List of Tables

List of Figures

List of Appendices

Acknowledgements

I would like to thank the following people for their help during my study:-

My supervisors Professor Robert Peveler and Dr Paul Roderick from the Community Clinical Sciences research Division in the University of Southampton for their dedicated supervision, constructive criticism and encouragement

Dr Juan Mason from the Wessex Renal Unit in Portsmouth for allowing the study to include the unit's patients and for his help, interest and enthusiasm throughout the study

Professor Robert Horne from the Centre for Healthcare Research in the University of Brighton for his advice regarding the use and interpretation of the Beliefs about Medicines questionnaire and Illness Perception Questionnaire

Dr Peter Smith from the Department of Social Statistics in the University of Southampton for his ready availability and endless patience in providing statistical advice and teaching

Drs Venkat Ramen, Robert Lewis, Judith Stevens and Alison Hughes and Mr Sami Sadek, Mr Martin Wise and Miss Walters from the Wessex Renal Unit for their participation in the study

Mr Peter Smith from St Mary's hospital pharmacy for filling up the electronic monitoring bottles

All the patients who agreed to take part in the study

All the General practitioners who took part in the study

List of commonly used abbreviations in this thesis

%	percent
n	number of subjects
n/a	not applicable
ns	not significant ($p > 0.05$ or $p > 0.1$ as defined in the text)
IQR	inter-quartile range
SD	standard deviation
CI	confidence interval
r	Spearman's rank correlation coefficient
α	Cronbach's alpha
ESRD	end-stage renal disease
BMQ	Beliefs about Medicines Questionnaire
IPQ	Illness perception Questionnaire
CIS-R	Revised Clinical Interview Schedule
SF36	Medical Outcome Survey Short Form

1.0 Overview of the background literature

The provision of renal replacement therapy is an increasingly important issue for the National Health Service in view of the rising incidence of end-stage renal disease (Roderick et al. 1998). Transplantation is usually the treatment of choice but the supply of donor organs falls far short of that demanded (The Renal Association 2002). Graft survival is prolonged by continued immunosuppression using immunosuppressants. If a significant number of transplant recipients are non-adherent to their prescribed medicines, as occurs in other chronic diseases, improved adherence is a potential way to improve graft survival and thus decrease the mis-match between supply and demand for donor organs. Design of an intervention to improve adherence requires identification of potentially modifiable factors that influence adherence.

Existing studies already suggest that non-adherence is common in renal transplant recipients (e.g. Schweizer et al. 1990) but methodological problems limit the validity of their conclusions. Furthermore investigation of the correlates of non-adherence has tended to concentrate on socio-demographic and transplant-related factors that cannot be modified once transplantation has been performed.

Chapter two will introduce the clinical background to renal transplantation and review the evidence for the effectiveness of immunosuppression in prolonging graft survival. Chapter three will discuss methodological issues in adherence research needed to appraise existing studies. Factors thought to influence adherence in other chronic diseases and models used to understand the effect of health beliefs on adherence will be reviewed in chapter four. The introduction will conclude, in chapter five, with a detailed review of the existing literature relating to non-adherence in renal transplant recipients.

2.0 Background: end-stage renal disease

2.1 End-stage renal disease and renal replacement therapy

Over 500 people per million population in England and Wales are estimated to receive treatment for end-stage renal disease (ESRD, Ansell & Feest 1999). ESRD is present when the creatinine clearance is less than 10 ml/min (The Renal Association 2002) and is fatal unless the patient receives life-long renal replacement therapy with dialysis or transplantation.

There are two main forms of dialysis, haemodialysis and peritoneal dialysis. Patients on dialysis require multiple medications since dialysis does not correct the full range of biochemical abnormalities resulting from renal failure. They also have significant fluid and dietary restrictions to avoid fluid overload and the build up of metabolites between dialysis sessions. For a haemodialysis patient with no urine output, the daily fluid restriction is in the order of 500mls. With peritoneal dialysis patients can usually drink slightly more since they can remove some excess fluid each day.

Haemodialysis is an intermittent form of dialysis requiring circulation of the patient's blood through a dialysis machine. This allows diffusable exchange of metabolites and fluid and usually occurs three times a week for around four hours at a time. Patients can feel unwell during haemodialysis due to large fluid shifts in the body and they often complain of feeling very tired immediately after a dialysis session. Problems with haemodialysis arise when arterio-venous access becomes difficult, or when factors such as cardiovascular instability limit the amount of fluid that can be removed in one session.

Continuous ambulatory peritoneal dialysis (CAPD) is the commonest form of peritoneal dialysis and is performed by the patient. A 2-2.5 litre bag of dialysis fluid is drained in and out of the abdomen via a surgically implanted in-dwelling peritoneal catheter. Exchange of metabolites, electrolytes and fluid occurs across the peritoneum. Patients usually need to perform four exchanges a day, each taking around one hour. The main medical problems with CAPD are the risk of peritonitis, due to bacteria gaining entry to the abdomen via the catheter, and eventual peritoneal failure. Patients may also be distressed by associated factors such as abdominal distension.

Transplantation is regarded as the treatment of choice for ESRD (Royal College of Surgeons 1999) since it corrects more biochemical abnormalities and is more cost-effective than

dialysis (Brickman & Yount 1996). Transplants usually come from a cadaveric donor (cadaveric transplant) but may come from a living person who is currently usually a close blood relative of the recipient (live related transplant). The recipient's immune system recognises the transplant as 'foreign'. This leads to an immune response causing the graft to fail unless the response can be suppressed. To reduce the risk of rejection, immune markers (histocompatability antigens, HLA markers) on the donor organ are matched as closely as possible to those of the recipient and the recipient takes immunosuppressant medication.

2.2 The importance of reducing graft failure in relation to the demand for transplants

In the three year period 1996 to 1998, 5387 people received a renal transplant in the United Kingdom (UK Transplant 2001). However, in 1998, there were 4584 people on the 'active' waiting list (UK Transplant 2001), the median waiting time was 500 days and 13.5% patients waited more than five years (British Transplantation Society 1998). The waiting list is growing because the prevalence of treated ESRD is increasing (Roderick et al. 1998) due to improved survival of patients and an ageing population with increasing acceptance of the elderly onto renal replacement programmes. Thus there is an increasing demand for donor organs despite the supply of cadaveric organs already falling far short of that required to satisfy the current demand. This has led to recommendations to increase the rates of live donor transplants (Royal College of Surgeons 1999; The Renal Association 2002). In addition to the problem of initial organ procurement, the ability of supply to meet demand is limited by the rate of transplant failure.

2.3 Expected duration of renal transplant survival

The highest risk period for graft loss is in the first year (table 2.3). Recent standards (The Renal Association 2002) recommend that for any transplant unit, at least 85% of first and second cadaveric grafts, should function at the end of the first year and at least 66% should be functioning at five years. The comparable figures for live donor transplants are 90% and 73%.

Table 2.3: Kidney transplant survival for the period 1990 – 1998 in the United Kingdom (data provided by United Kingdom Transplant Support Service Authority, 2000)

Number of transplant	Percentage one year survival (95% confidence intervals)	Percentage five year survival (95% confidence intervals)
1st	87 (86 – 88)	76 (75 – 78)
2nd	87 (85 – 89)	76 (73 – 79)
3rd and subsequent	80 (75 – 86)	68 (61 – 760)

Graft loss occurs due to organ rejection or due to death of the patient from another cause despite a functioning graft. The latter is now the commonest cause of graft loss (Howard et al. 2002) and is most frequent in the elderly (British Transplantation Society 1998). Rejection can be classified in various ways but is often grouped according to the timing of rejection post-transplantation and the speed of the rejection process. Hyperacute rejection occurs immediately post-transplantation (British Transplantation Society 1998), acute rejection occurs over a short period of time and chronic rejection is a more insidious process occurring over several years. Acute rejection can be early, occurring within the first year of transplantation, or late, occurring after the first year.

2.4 Factors influencing renal transplant survival

Demographic factors, transplant-related factors and immunosuppressants have been shown to affect graft survival (table 2.4). Data from the eight year period 1990-1997 indicates significant increase in the relative risk of transplant failure to come from recipient age or diabetes, donor age and 'non-favourable' HLA matching (UK Transplant 2001). More recent transplants, have a lower risk of transplant failure compared to the baseline period of 1990-1992 (UK Transplant 2001). The effect of recipient age appears to be due to death with a functioning graft rather than increased rates of rejection (UK Transplant 2001). Since 1998 donor and recipient age and the degree of HLA matching have been incorporated into the National Allocation procedure in order to optimise overall graft survival. Time on the waiting list is considered for equity of allocation.

Table 2.4: Donor and recipient factors that increase renal transplant survival

Younger donor
Live donor
Donor without systemic diseases affecting the kidneys
Reduced time between organ procurement and transplantation
Better HLA match between donor organ and recipient
Younger recipient
First transplant (compared to re-grafts)
Absence of recipient diabetes

Immunosuppressants are thought to reduce rejection rates by reducing the risk of acute rejection episodes. Since acute rejection episodes increase the risk of chronic rejection, immunosuppressants may also reduce the risk of chronic rejection (Monaco et al. 1999). Many immunosuppressants, such as cyclosporin, have a dose-dependant effect but a narrow therapeutic index and there can be considerable inter- and intra-patient variability in plasma levels even at stable dosing. Therefore plasma levels are routinely monitored to guide dosing.

Not only have low trough levels of cyclosporin been related to increased risk of acute (Waiser et al. 2002) and chronic rejection (Kahan et al. 2000) and graft failure (Waiser et al. 2002) but variability of levels has also been linked to increased risk of acute rejection and graft failure (Waiser et al. 2002).

Once the organ is transplanted, demographic and transplant related factors cannot be altered. In contrast to this, immunosuppression is a factor influencing graft survival that can be altered. If immunosuppression is necessary for ongoing graft survival then non-adherence to the medication will be detrimental to graft function.

2.4.1 Evidence of the benefits of ongoing immunosuppression on transplant survival

There are three forms of evidence suggesting improved graft survival with ongoing immunosuppression:-

1) studies showing increased graft survival following the introduction of immunosuppressants,
2) studies of the consequences of withdrawal of agents,
3) studies indicating that non-adherence to immunosuppressants appears to increase the risk of graft failure.

2.4.1.1 Introduction of immunosuppressants

The first patients with renal transplants received immunosuppression with prednisolone. Then azathioprine was developed and added to the regime. Cyclosporin was introduced in the 1980s. Triple therapy with prednisolone, azathioprine and cyclosporin became the routine form of immunosuppression for renal transplantation and is still common today (British Transplantation Society 1998). Graft survival improved dramatically with these developments, particularly with the introduction of cyclosporin (Howard et al. 2002; Renal Transplant Audit 1992). For example in the United Kingdom, compared to the pre cyclosporin era (1981-1983), the relative risk one year graft failure fell to 0.64 immediately after the introduction of cyclosporin (1984-1986) and to 0.43 when cyclosporin was clearly established (1987-1989; United Kingdom Transplant Support Service Authority 1992). Since then however, developments in immunosuppression have resulted in smaller improvements in one year graft survival and have made little impact on longer term graft survival (Isaacs 2001). For example one year graft survival rose from 82% (95% confidence interval 80-84%) in 1990 to 86% (95% confidence interval 84-88%) in 1996 (UKTSSA 1996).

New immunosuppressants, such as mycophenolate mofetil, tacrolimus and rapamycin, are being introduced, and there is ongoing evaluation of the effect of these agents on graft survival (British Transplantation Society 1998). The overall level of maintenance immunosuppression is determined by clinicians from their perception of the risk of rejection due to factors such as type of donor organ, degree of HLA mis-match and history of acute rejection (Denton et al. 1999). Current guidelines (British Transplantation Society 1998) conclude that there is insufficient evidence to permit specific recommendations on optimal immunosuppressant regimes but each renal unit should have a written protocol for immunosuppression that is based on good research evidence.

Time series data showing an improvement in graft survival with the introduction of immunosuppressants needs to be interpreted with some caution since it is liable to confounding; many other factors, such as HLA matching and clinical care, have also changed over the same time period. A second form of evidence relating to the effectiveness of immunosuppression comes from studies looking at the consequences of withdrawing immunosuppressants.

2.4.1.2 Immunosuppressant withdrawal

All existing immunosuppressants have side effects that are risk factors for graft failure and patient mortality. For example cyclosporin causes nephrotoxicity and hypertension; tacrolimus is more likely to cause diabetes; azathioprine can cause bone marrow suppression and prednisolone can cause hypertension and diabetes (Denton et al. 1999). Immunosuppressants also cause side effects, such as hirsutism and weight gain, that are distressing to patients (Moons et al. 1998) even if they do not increase mortality. Concern about side effects that impair prognosis has prompted investigators to consider gradual withdrawal of agents in stable transplant recipients (Denton et al. 1999). Reduced immunosuppression is also likely to be supported by patients if it reduces distressing side effects.

Kasiske and colleagues (2000) conducted a meta-analysis of published randomised trials that attempted to withdraw either prednisolone or cyclosporin. Trials were identified from a systematic search of 'MEDLINE', conference abstracts and bibliographies. The dates of the 'MEDLINE' search were not specified but identified papers were published between 1983 and 1999. Conference abstracts published in specified journals between 1998 and 1999 and bibliographies of 'pertinent' journals were also searched. Although the 'pertinent' journals

were not specified the authors appear to have tried to find all published, randomised studies of prednisolone or cyclosporin withdrawal after renal transplantation. Identified trials were all published in English but other languages had not been excluded. Data regarding the selection of subjects, inclusion and exclusion criteria and time since transplantation at withdrawal were not provided. Studies were assessed for quality, reviewed by two independent reviewers and analysed on an intent to treat basis. If patients were reported more than once the authors extracted data from the publication with the longest follow-up. The number of excluded studies was not reported. The meta-analysis included nine studies of prednisolone withdrawal, thirteen studies of cyclosporin withdrawal, and three studies comparing cyclosporin withdrawal with prednisolone withdrawal (table 2.4.1.2).

Analysis of the studies of prednisolone withdrawal found that withdrawal of steroids increased the risk of both acute rejection ($p<0.001$) and graft loss ($p<0.012$) (table 2.4.1.2). Cyclosporin withdrawal did not lead to increased rates of graft loss ($p = 0.646$) but more acute rejection episodes were noted ($p < 0.001$). Analysis of studies comparing prednisolone withdrawal with cyclosporin withdrawal showed a non-significant trend for there to be a higher risk of graft loss in patients who were withdrawn from prednisolone ($p = 0.190$; table 2.4.1.2).

Table 2.4.1.2: Characteristics and results of studies in a meta-analysis of trials investigating the effect of immunosuppressant withdrawal on renal transplant survival

	cyclosporin withdrawal	**prednisolone withdrawal**	**cyclosporin versus prednisolone withdrawal**
Number of studies (number of studies including acute rejection episodes as an end-point)	13 (10)	9 (8)	3 (3)
Total number of subjects	1170	1984	259
Number of subjects per study	18 - 279	64 – 523	64 - 127
Date of publication	1983 - 1998	1987-1999	1990-1996
Mean (SD); total number of subjects in studies with graft failure as an outcome	96 (80); 1151	211 (186); 1899	86 (35); 259
Months of follow up of each study	12 - 96	12 – 60	36 - 49
Mean (SD) months of follow up of each study with graft failure as an outcome	45 (33)	28 (19)	44 (6)
Relative risk of graft loss after withdrawal (95% confidence intervals)	1.06 (0.82 - 1.29)	1.40 (1.09-1.70)	0.63 (0.08 - 1.16)
Increased proportion of patients with acute rejection after withdrawal (95% confidence intervals)	0.11 (0.07 - 0.15)	0.14 (0.10 - 0.17)	0.04 (-0.07 - 0.14)

Tests for heterogeneity were not shown but it was reported that there was heterogeneity in the studies of cyclosporin withdrawal. For acute rejection heterogeneity seemed to be mainly accounted for by sample size. This suggests the possibility of publication bias with publication being more likely for studies finding an increased risk of rejection. For graft failure, studies with shorter follow up seemed more likely to contribute to heterogeneity; they were more likely to report an increased risk of graft failure after cyclosporin withdrawal.

According to this meta-analysis prednisolone withdrawal increases the risk of both acute rejection and graft loss. Withdrawal of cyclosporin only appears to increase the risk of late acute rejection. However increased rejection episodes would be expected to increase the rates of graft failure and heterogeneity was demonstrated in studies of cyclosporin withdrawal. Trials of withdrawal of cyclosporin for purely financial reasons, irrespective of risk factors for graft failure, have found an increased risk of rejection episodes and graft failure (Jha et al. 2001).

The generalisability of conclusions from the meta-analysis are limited by the relatively small number of subjects studied and the lack of description of factors, other than duration of follow up, that may affect graft survival independently of immunosuppression. This is important since withdrawal trials tend to include only patients with stable renal function and an absence of other risk factors for graft loss.

2.4.1.3 Non-adherence to immunosuppressants

Combining the results of trials of withdrawal of agents with the evidence of increased graft survival following the introduction of triple therapy, withdrawal of cyclosporin (or a similar drug) or prednisolone appears to pose unacceptable risks of graft loss (Isaacs 2001). This suggests that adherence to immunosuppressant regimes is also required with non-adherence potentially increasing the risk of graft failure. Studies of the effects of non-adherence to immunosuppressants on renal graft survival have been carried out since 1988 (Didlake et al. 1988). The studies are fully reviewed in chapter five.

2.5 Summary of chapter two

Over 500 people per million population are estimated to receive renal replacement therapy for end-stage renal disease in the United Kingdom. Transplantation is usually the treatment of choice and around 2,700 transplants a year are performed in the United Kingdom. However the waiting list for cadaveric organs is increasing and in 1998 the median time on the waiting list was 500 days. The mismatch between supply and demand of organs is increased by rates of transplant failure. Immunosuppressants are thought to reduce the risk of transplant failure by reducing the chance of acute rejection episodes. Introduction of the immunosuppressant cyclosporin in the 1980s significantly reduced the rate of transplant failure. However improved survival has been less marked with new drug developments since then and currently 24% of first and second transplants fail within five years. There is medical debate about the amount of immunosuppression needed in the long term since postulated reductions in rejection need to be balanced against the long-term side effects such as an increased risk of cancer. Patients also report concerns with side effects such as weight gain and hirsutism. However recent meta-analyses suggest that graft survival reduces if immunosuppressants are withdrawn and the current consensus of medical opinion is that at least some immunosuppression needs to be continued throughout the duration of the transplant. For this to be efficacious, patients must take the medication as prescribed.

3.0 Background: methodological issues in adherence research

Since immunosuppressants appear to be needed to prolong renal transplant survival, it is important to be sure that patients take their medication as prescribed. However literature relating to taking medication is complicated by changing terminology and methodological difficulties for the research. This chapter will therefore first review the terminology used to describe taking medication as prescribed and explain why the term adherence has been chosen for this thesis. A review of relevant psychometric properties of measurement tools and aspects to study design will then lead onto a comparison of different methods used to measure adherence.

3.1 Terminology in adherence research and reasons for the choice of adherence in this thesis

The commonly used terms to describe taking medication as prescribed have been compliance, adherence and most recently concordance.

Compliance, the first term to be used, has been defined as 'the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice' (Haynes 1979). It is still thought to be the most widely used and understood term to describe how patients follow health-related advice (Laederach-Hofmann & Bunzel 2000). However the term compliance has become less favoured due to its implication that a patient is merely a passive follower of orders (Myers & Midence 1998). The term adherence was introduced to imply a more active and collaborative role for the patient and is said to place a greater emphasis on the patient's role in deciding whether to carry out a particular treatment (Myers & Midence 1998).

Compliance and adherence essentially refer to the same behaviour; the patient's taking of medication although adherence is currently thought to be a less judgmental term. Since both terms refer to the same behaviour, instruments designed to measure how a patient takes medication will be valid regardless of whether the term compliance or adherence is used.

The term concordance has been recommended in a report by the Royal Pharmceutical Society of Great Britain (1997). However concordance is not synonymous with compliance or adherence. Concordance is not tightly defined and refers to the process of negotiating treatment, rather than just the end result of actually taking treatment. For example the report

states that 'it is only the consultation and not the patient that is non-concordant' (Royal Pharmaceutical Society 1997). There are no currently available tools to measure concordance. Furthermore this study is addressing the beliefs and behaviour specific to the patient and, although recognised as important, other aspects of concordance, such as interactions between prescriber and patient, are not being measured.

3.1.1 Categories of adherence

Non-adherence is sometimes categorised according to presumed reasons for the behaviour. Intentional (or intelligent) non-adherence is said to reflect a conscious decision by the patient not to take their medication whereas unintentional (or unwitting) non-adherence occurs when the patient is not aware that they are not taking medicines correctly (Cochrane et al. 2000). Unintentional non-adherence includes forgetting medication and misunderstanding the prescribed regime. The terms intentional and unintentional are not used in this thesis since there are no measures that specifically test intentional versus unintentional non-adherence. Differentiation between the two categories requires the patient to disclose reasons for intentional non-adherence. Social desirability effects could therefore impair categorisation of non-adherence if patients use the more acceptable reason of forgetting tablets to account for any non-adherence.

Within transplant research, non-adherence is often categorized into 'clinical' and 'sub-clinical' according to whether a negative clinical outcome has occurred. The sub-divisions of 'major' and 'minor' clinical non-adherence have been used if there has been transplant failure or an episode of acute rejection respectively (Didlake et al. 1998).

3.1.2 Patterns of adherence

Many reports of non-adherence consider adherence as an all or none phenomenon, classifying subjects as adherent or non-adherent. Yet most departures from adherence appear partial, not total (Royal Pharmaceutical Society 1997) and include both intermittent and consecutively missed doses, the latter often being termed 'a drug holiday'. Furthermore adherence of the same individual varies over time (Cramer et al. 1990, Dew et al. 1996), with different medications (Hilbrands et al. 1995) and with different aspects of the treatment regime (Dew et al. 1996). The most frequent type of non-adherence appears to be delay in dosing (Waeber et al. 1999).

3.2 The importance of psychometric properties of measurement tools and study design when assessing adherence research

Adherence is difficult to measure and an understanding of these difficulties is needed to interpret the results of adherence research. The general psychometric properties of validity, reliability, sensitivity and specificity are defined in appendix B1. All need to be considered when assessing a measure of adherence (Farmer 1999) as does the possibility of bias in the study design.

One of the biggest problems for adherence research is that there is no perfect way of measuring the behaviour, no ideal 'gold standard' to judge criterion validity of new measures. Social desirability effects reduce the usual benefit of face validity in a measurement tool. If the subject is aware adherence is being studied and assumes that poor adherence would be looked upon unfavourably by the researchers or the clinical team they are less likely to report non-adherence. This is particularly likely to occur in transplant recipients since studies have shown patients fear not receiving another transplant if they admit to non-adherence (Sharpe 1999) and transplant staff admit to not listing patients for transplantation or not re-transplanting them once non-adherence is identified (Hathaway et al. 1999). Social desirability effects can be reduced by using a non-judgemental and non-threatening manner and assuring confidentiality of results from the clinical team (De Geest et al. 1995).

The Hawthorne effect is important in any behavioural research. If a subject is aware their adherence is being monitored they may pay more attention to it and so improve their adherence without necessarily trying to improve. The effect is reduced by minimising the subject's awareness of the aims of the study, for example by locating questions about adherence in a questionnaire amongst those asking about other issues so that adherence is less obviously the topic of interest.

Social desirability bias and the Hawthorne effect are likely to account for the finding that adherence is better in subjects who are aware that their adherence is being monitored compared to those who are not (Yeung et al 1994; Kruse & Weber 1990) and the finding that adherence improves just prior to an expected measurement of a clinical outcome, as occurs at a clinic visit (Cramer et al 1990; Mengden et al 1993).

Another problem is that non-response bias can affect recruitment. If less adherent subjects are less likely to take part in a study of adherence, this will reduce the estimate of the prevalence

of non-adherence and cause difficulties in identifying characteristics of non-adherent subjects compared to adherent ones.

3.3 Existing measures of adherence

Reviews of adherence research conclude that the quality of much work is poor due to shortcomings in the methodology, including the measurement of adherence (Nichol et al. 1999; Farmer 1999). Adherence can be measured 'directly', for example by biochemical assay of the drug, or 'indirectly' by self-report questionnaire. Direct measures are the only way to ensure a patient has actually swallowed prescribed medication. However no measure is perfect, making identification of a reference measure difficult (Farmer 1999). Measurement of adherence is also made difficult by problems defining adherence, particularly if non-adherence is partial or if a temporal component is considered.

Since there is no ideal measure of adherence, the use of several measures, to allow the strengths of one to compensate for the weaknesses of another, has been recommended in adherence research (Vitolins et al. 2000; Cluss & Epstein 1985; Nichol et al. 1999; De Geest & VanHaecke 1999). However guidelines for the use of combining measures have not been reported. Specific methods may be more applicable to certain situations, depending on the precision required and the intended application of the results (Farmer 1999). The following sections will review the strengths and weaknesses of different measures (table 3.3).

Table 3.3: Benefits and limitations of different methods of measuring adherence to medication

Method	Practicalities	Benefits	Problems
Direct observation	Impractical	Confirms drug ingestion	Hawthorne effect
Biochemical assay	Only possible for some drugs	Confirms drug was ingested, in routine use	Only indicates recent consumption, confounded by pharmacokinetic factors
Clinician rating	Easy	Already used clinically	Hard to standardize
Pill count	Cheap, not possible for liquid medication		Patient must remember container, needs accurate record of prescriptions and dispensing
Self-report	Easy, quick	Can allow disclosure of reasons for non-adherence	Social desirability bias
Electronic monitoring	Relatively expensive, needs to be available when medication is dispensed	Adherence over time can be seen, strong indication that a tablet was missed if an opening did not occur on the day it was prescribed	Bulky containers

3.3.1 Direct observation

Direct observation is not only impractical but is also likely to be affected significantly by the Hawthorne effect. Furthermore direct observation has been used as an intervention to enhance adherence, as occurs in multi-resistant tuberculosis therapy (Myers & Midence 1998).

3.3.2 Plasma assay of drug, metabolite or marker

Assay of the drug or a metabolite in urine or plasma is thought by some to be the best measure of adherence (Nicol et al. 1999). In clinical practice clinicians may use low levels of medication in biochemical assays to indicate non-adherence. However this is only possible for a limited number of drugs, there are many limitations to its validity and it is likely to be particularly insensitive to partial non-adherence. Biochemical assays are influenced by multiple factors, such as absorption, metabolism, excretion, dosing frequency, formulation of the tablets and drug interactions. Furthermore plasma assays cannot quantify adherence and usually only indicate recent drug consumption (Farmer 1999). The latter is important since adherence is reported to improve just prior to a clinic appointment (Cramer et al. 1990). This could cause plasma assays to result in falsely high estimates of adherence as demonstrated when urine analysis was compared to electronic monitoring (Fallab-Stubi et al. 1998).

3.3.3 Clinician rating

Clinicians are unlikely to assess adherence formally in most of their patients yet many report confidence in their ability to judge it (Hathaway et al. 1999). They are likely to base assessments on data from a range of clinical sources. A large survey of renal staff, predominantly from America, found 90%, 75% and 50% reported using the clinical interview, information in clinical notes and drug plasma levels respectively to estimate adherence (Hathaway et al. 1999). However clinician ratings have been difficult to standardise to produce reliable assessment tools. Different health professionals have been shown to differ significantly in their estimates of the prevalence of non-adherence for patients in the same clinic (Green et al. 1999). Furthermore, clinician ratings have been shown to be less sensitive in detecting non-adherence than other measures of adherence including electronic monitoring (Mason et al. 1995; Geletko et al. 1996) and pill counts (Geletko et al. 1996).

3.3.4 Pill count

Comparing the number of pills left in a bottle to the number that should have been taken according to the prescribed regime (pill count) is the method of assessing adherence that was favoured by many researchers until the advent of electronic monitoring (Farmer 1999). Since

then several studies have shown that electronic monitoring detects a greater degree of non-adherence (e.g. Choo et al. 1999; Waterhouse et al. 1993). Pill counts over-estimate adherence if the subject discards medication prior to a clinic visit as has been shown in studies of inhaled therapy for asthma (Rand et al 1992). Discarding medication prior to a clinic visit, due to social desirability bias, is particularly likely if the subject is aware that adherence is being monitored. Consistent with this hypothesis is the finding that adherence tends to be greater in subjects who are aware their adherence is being monitored (Kruse & Weber 1990). Pill counts will also be inaccurate unless there is accurate recording of changes to prescribed medication and an accurate record of the number of tablets dispensed. The latter can be difficult unless a single pharmacy is used by the patient. Even if they are accurate, pill counts cannot provide information on the pattern of non-adherence or the reasons behind it (Farmer 1999).

3.3.5 Self report

Self-report has the advantage of being an easy to use and cheap measure of adherence. Several studies have compared detection of adherence by electronic monitoring to self-report (e.g. George et al 2000; Waterhouse et al. 1993) and have shown that self-report over-estimates adherence. Self-report questionnaires have a high specificity but low sensitivity to detect non-adherence (George et al 2000). If a subject admits to non-adherence this can be relied upon (although the degree of non-adherence may be inaccurately reported), but if they say that they are adherent then the result may be less valid. Over-estimation of adherence may occur due to social desirability and response style biases and the limited reliability of memory. Similar processes limit self-disclosure at interview. To minimise such biases it is recommended that inquiry about non-adherence is made in a non-judgemental manner. Assessment by an independent researcher is thought to be more sensitive than disclosure to treating staff (De Geest et al. 1995) but is only useful in a research setting.

3.3.6 Electronic monitoring

In more recent years electronic monitoring, which only came into widespread use from the mid-1990s, has been recommended as the most valid measure of adherence (De Geest & Vanhaecke 1999; Burnier 2000; Schwed et al 1999; McGavock 1996; Farmer 1999). It is particularly useful in determining the extent of adherence over time (Farmer 1999). Electronic monitors of adherence rely on an electronic microchip in the top of a pill bottle, eye-dropper or across the back of a blister pack. The chip records the date and time that that the respective seal, such as between a bottle lid and the bottle, is broken. The assumption is that if this seal has been broken then the patient has taken the medicine.

One of the most widely used electronic monitors is the electronic Drug Exposure Monitor comprised of an electronic chip in a bottle lid (also known as the Medication Event Monitoring System, MEMS). A search of 'MEDLINE' for articles containing the abbreviation 'MEMS' or 'mems' revealed 15 articles where detection of adherence by electronic monitoring had been compared to other measures in a variety of patient groups. Electronic monitoring provided higher estimates of non-adherence than pill counts (e.g. Waterhouse et al. 1993; Namkoong et al. 1999; Lee et al. 1996; Mason et al. 1995; Choo et al. 1999; Schwed et al. 1999; Geletko et al. 1996; Mulleners et al. 1998), clinician rating (Mason et al. 1995; Geletko et al. 1996) and self report (George et al. 2000; Melbourne et al. 1999; Bachmann et al. 1999; Waterhouse et al. 1993; Mason et al. 1995; Chmelik & Doughty 1994; Svarstad et al. 1999; Geletko et al. 1996; Straka et al. 1997). The greater detection of adherence using electronic monitors occurred in all patient groups, including those with depression (George et al 2000), epilepsy (Cramer et al 1989), hypertension (Choo et al 1999), asthma (Chmelik & Doughty 1994) diabetes (Mason et al 1995) alcohol dependence (Namkoong et al 1999), tuberculosis (Fallab-Stubi et al. 1998), hypercholesterolaemia (Schneider et al 1999) migraine (Mulleners et al. 1998) and breast cancer (Waterhouse et al 1993).

Although electronic monitoring can be manipulated by the patient, a high motivation to deceive would be needed to continue to open the container in accordance with the prescription but not to take the medicine over a prolonged period of time. To circumvent the problem of social desirability bias, electronic monitors can be used without subjects being aware that the bottle monitors adherence. This leads to higher estimates of non-adherence, indicating greater sensitivity to detect non-adherence, than if subjects are aware that the device monitors their behaviour (Kruse & Weber 1990). However even when the purpose of the bottle has been disclosed in a research setting, significant non-adherence is still detected (Melbourne et al. 1999; Lee et al. 1996; Cramer et al. 1989; Svarstad et al. 1999; Straka et al. 1997). Furthermore adherence appears to decline with time (Cramer et al 1990), indicating that the effect of knowing adherence is being monitored may decline with duration of monitoring.

Despite its unique position in enabling a temporal description of adherence, electronic monitoring has the drawbacks that it cannot confirm ingestion of medication. If a bottle is opened in error, and no tablet is taken, this leads to an over-estimation of adherence if each opening is assumed to reflect a swallowed tablet. Similarly if there is a lack of openings for a period of time, the assumption that this reflects missed tablets leads to an under-estimation of adherence if the patient took their medication from another supply.

Discrepancies between openings and tablet ingestion were reported by 35% of subjects in a study of heart transplant recipients where adherence to immunosuppressants had been measured over a three-month period and subjects were aware of the purpose of the monitor (De Geest et al. 1998). Twenty-five percent of subjects had what the authors termed 'minor protocol violations' such as an opening of the bottle by a 'curious relative'; these openings were reported not to affect the overall results. However the authors reported that 10% of the sample had 'major protocol violations, such as taking out supplies of tablets for several days when going on holiday. When interviewed at the end of the study, 20% subjects reported altering their usual adherence behaviour during the monitored period. Forty-one percent also reported practical problems with the container being too large to use when travelling.

Therefore although electronic monitoring is now widely regarded as the most accurate measure of adherence, it is not a perfect measure if the pattern of openings fails to correspond to the patient taking a tablet each time the bottle was opened.

3.4 Clinical outcome is not a measure of adherence

Although adherence is only important in so far as it improves clinical outcomes, it is generally invalid to extrapolate back from clinical outcome to assess adherence. The effectiveness of treatment depends upon the efficacy of treatment as well as the degree of patient adherence (Cluss & Epstein 1985) and outcome is affected by other factors such as disease severity. Efficacy of a drug in any one individual will be influenced by factors such as its absorption, metabolism, dosing interval and formulation. If a drug has a long duration of action, and only isolated tablets are missed, poor adherence may not reduce the effectiveness of the medication (McGavock 1996). Furthermore in chronic disease requiring multi-faceted treatment regimes, there is unlikely to be a simple relationship between adherence to specific aspects of treatment and clinical outcome.

Rather than being a measure of adherence, clinical outcomes are useful to form a categorical definition of clinically significant non-adherence (De Geest & VanHaecke 1999) and to assess the predictive validity of adherence measures. The efficacious dose recommended following drug trials does not necessarily equate to the dose below which a patient would suffer clinical harm if non-adherent since the effect of erratic dosing, or partial adherence, is not measured in trials.

3.5 Summary of chapter three

Adherence describes a patient's following of medical advice such as the taking of prescribed medication. Some researchers have recently suggested the term concordance should be used but this term encompasses a broader range of factors, is not confined to the patient's beliefs and behaviour and is not yet commonly used in clinical practice. Furthermore, tools to measure concordance have not yet been developed. Non-adherence is usually partial and the pattern of non-adherence can change over time and be different with different elements of a treatment regime. In transplant research, non-adherence is often divided into clinical and sub-clinical non-adherence according to whether an adverse clinical outcome has already occurred. A major problem for adherence research is the difficulty in accurately measuring behaviour. Social desirability effects and non-response bias are particularly important to minimise. All measurement tools are prone to error. Although one study reported discrepancies between bottle opening and tablet ingestion in 35% of subjects, electronic monitoring is widely thought to be the best current measure of adherence. A major advantage is its unique ability to provide a continuous description of adherence over time. The detection of non-adherence is not an end in itself once detected, the reasons for non-adherence need to be identified to enable development of effective interventions to improve adherence.

4.0 Background: prevalence and correlates of non-adherence in chronic disease

This chapter will outline the prevalence and correlates of non-adherence in other chronic conditions before chapter five reviews in detail the smaller literature relating to renal transplant recipients. Theoretical frameworks, or models, to explain the effect of predictive variables on adherence are necessary to inform the design of generalisable interventions (Campbell et al. 2000). Existing models will be described at the end of this chapter. Many recent papers and reviews of factors influencing adherence suggest the importance of health beliefs as potentially modifiable influences on adherence (e.g. Horne 1998; Cochrane et al. 1999; Mc Gavock 1996). Therefore the development of models related to health beliefs will be reviewed in the most detail.

4.1 Prevalence and consequences of non-adherence

There is a large literature relating to adherence in chronic disease. Recent reviews tend to focus on specific diseases or specific correlates of non-adherence (e.g. Nagasawa et al. 1990). The most comprehensive review of the whole field was published by Sackett and Haynes (1976). They found non-adherence to prescribed medication to be common in all chronic diseases studied with the prevalence generally being around 50%. A more recent review also reports the same prevalence (Dunbar-Jacob et al. 2000). This frequency is concerning since some, but not all (Epstein & Cluss 1982), studies have found a link between adherence and clinical outcome. For example patients who failed to adhere to medication after a myocardial infarction were found to be 2.6 times more likely to die within 1 year of follow up than those adhering to treatment (Horwitz et al. 1990). However the relationship between adherence and outcome is complex; the relationship between adherence and better outcome was also found in subjects receiving placebo (Horwitz et al. 1990). Other studies have also reported improved outcomes in those who adhere to either placebo or active treatment (The Coronary Drug Project Research Group 1980; Horwitz & Horwitz 1993). This may be due to methodological limitations of studies or better adherence to other health behaviours that affect outcome in the adherent group.

Electronic monitoring, by its provision of a continuous record of adherence, is ideally placed to identify the relationship between clinical outcomes and degrees of adherence. In a study of adult heart transplant recipients 1 to 6 years post-transplantation, De Geest and colleagues (1998) divided subjects into excellent compliers, minor sub-clinical non-compliers and major sub-clinical non-compliers on the basis of cluster analysis at the end of the study (table 4.1).

These groups had decreasing degrees of adherence to the number and timing of prescribed doses (both $p < 0.001$). The levels of adherence were significantly related to the occurrence of future rejection episodes ($p = 0.01$) but data from only four subjects contributed to this analysis (table 4.1).

Table 4.1: Adherence to cyclosporin in heart transplant recipients (De Geest et al. 1998)

	All subjects (n=101)[1]	**Excellent compliers (n=84)**	**Minor sub-clinical noncompliers (n=7)**	**Major sub-clinical noncompliers (n=9)**
Median medication compliance[2] (IQR)	99.4 (98.1-100)	99.5 (98.8-100)	97.0 (96.7-100)	93.2 (91.7-93.8)
Median dosing compliance[3] (IQR)	98.8 (96.2-100)	98.9 (97.7-100)	95.0 (93.7-100)	87.9 (84.1-89.1)
Median dosing variability[4] (IQR)	1:38 (0:52-2:39)	1:30 (0:40-2:10)	2:50 (1:40-4:00)	4:30 (3:20-5:10)
Percentage of subjects coded as excellent compliers[5] by interview	52.0	59.5	0.0	25.0
Percentage of subjects coded as poor compliers[6] by interview	5.0	2.4	28.6	12.5
Number (%) subjects with an acute rejection episode after the monitored period	4 (4)	1 (1)	1 (14)	2 (22)

[1]Paper reports 101 subjects took part in the study but only categorises 100 subjects
[2]Percentage of bottle openings compared to the number of prescribed doses
[3]Percentage of days that the subject had opened the bottle twice as prescribed
[4]Standard deviation of inter-dose intervals (hours:minutes)
[5]Self-report of never skipping a dose of cyclosporin during the previous year and less than 1 hour deviation from dosing schedule
[6]Self-report of skipping more than 5 doses in the past year irrespective of the extent of deviations from the dosing schedule

4.2 Factors that influence adherence to treatment

Many factors that may influence adherence to medication have been investigated. These are sometimes grouped into categories according to their perceived origin (table 4.2); for example, patient, drug and health provider factors (Mc Gavock 1996). However the categories are overlapping and do not readily relate to possible interventions to improve adherence. Interventions to improve adherence need to be targeted to factors that can be modified. Factors that cannot be modified may indicate groups at high risk of non-adherence but, by definition, they cannot be changed to result in improvement of adherence. Therefore, for the purposes of this thesis, variables that have been studies in relation to adherence have been grouped into categories which can be linked to their chance of modification (figure 4.2).

Socio-demographic, disease-related factors and social support tend to be unmodifiable whereas medicine-related factors, knowledge, psychological symptoms and health beliefs are potentially modifiable.

Table 4.2: Groupings of variables related to adherence according to their perceived source

Patient factors
age, sex, education, cognitive function, knowledge, physical ability, self-efficacy, personality, mood, health beliefs
Drug factors
dose and frequency of prescription, side effects, visible benefit, consequences of not taking medication, formulation of medication
Health provider factors
advice given to patient, patient satisfaction with the consultation, health provider-patient relationship, precision of diagnosis and prescribing

The following sub-sections discuss the classic review by Sackett & Haynes (1976) and the more recent review, published after the start of this study, by Dunbar-Jacobs and colleagues (2000) and findings from other selected studies or expert opinion.

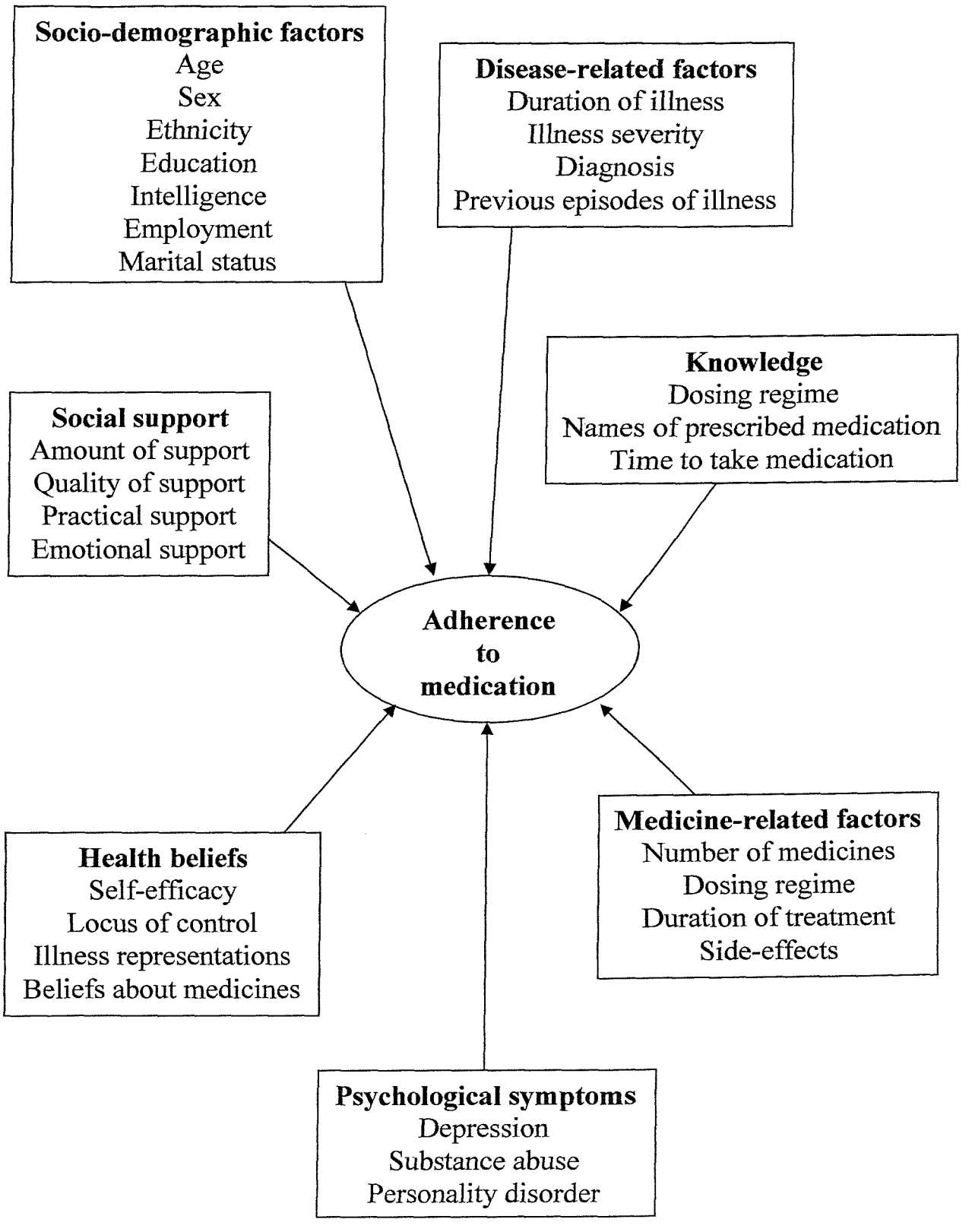
4.2.1 Socio-demographic factors

Studies showing that an individual's adherence can change over time and vary for different aspects of the treatment regime, indicate that stable socio-demographic factors are unlikely to be the sole determinants of adherence (Horne 1998). Nevertheless they may identify groups of patients at high risk of non-adherence. Horne (1998) reports that the early systematic review of 185 studies across a wide range of illnesses (Sackett & Haynes 1976) found no clear relationship to adherence for age, gender, educational attainment, intelligence, marital status, occupational status, income or ethnic background. However other correlates of adherence may vary according to socio-demographic groupings. For example, studies in transplant recipients report that women experience more side effects from immunosuppressants than men (Moons et al. 1998, Winsett et al. 2001).

4.2.2 Disease-related factors

Of the studies reviewed by Sackett and Haynes (1976) the majority found no association between adherence and disease-related factors such as severity, duration and previous episodes of illness. However the inclusion of such diverse patient groups may have obscured the effect of disease-related factors within specific patient groups.

Figure 4.2: Factors that may influence adherence in chronic disease



4.2.3 Treatment-related factors

The treatment-related factors of number of medications, number of side effects and duration of treatment were negatively correlated with adherence in at least half the studies reviewed by Sackett and Haynes (1976). A more recent review (McGavock 1996) also indicates that adherence deteriorates with increasing numbers of concurrent medications or side effects, increased duration of treatment and more frequent dosing. The findings from these two reviews suggest that adherence may be improved by minimising the number and frequency of prescribed tablets and ensuring a minimal number of side effects from treatment. However the potential for altering prescribing, and thus adherence, is likely to be limited.

4.2.4 Knowledge about the medication

Knowledge of what medication should be taken when is clearly necessary for adherence. However by itself it is not sufficient. Knowledge about disease and treatment has not been found to correlate with adherence in the majority of studies (Cluss & Epstein 1985). Inconsistency in the effect of knowledge on adherence is not surprising since neither knowledge nor adherence are simple concepts. For example assessment of knowledge requires identifying the actual advice given to patients, as well as what patients understand their treatment to be in terms of number and type of tablets, dosing frequency and action to take if they are late remembering a tablet. Furthermore, different aspects of knowledge may be more important than others and such knowledge may be more important in treatment of conditions, such as diabetes, that require particularly high degrees of patient involvement.

4.2.5 Social support

When measured, 'supportive' and 'stable' families were found to be important in predicting adherence in most studies reviewed by Sackett and Haynes (1976). The papers reviewed by Dunbar-Jacobs and colleagues (2000) gave conflicting results regarding the importance of social support. However, as for knowledge, social support is a multi-faceted concept and includes factors such as the number of supports, actual and perceived support and practical and emotional support. These different aspects of social support have not yet been widely studied in relation to adherence.

4.2.6 Psychological symptoms and psychiatric illness

Sackett and Haynes (1976) reported that patients with psychiatric diagnoses seemed to have poorer adherence than other patient groups. This has also been reported in other reviews, particularly for depression (e.g. Brickman and Yount 1996; Hand 1998). DiMatteo and

colleagues (2000) reviewed the literature published between 1968 and 1998 and found 13 articles correlating depression with adherence to treatments for physical illness. Only two studies used a diagnostic interview to diagnose depression but all studies used standardised measures, most commonly the Beck Depression Inventory. Meta-analysis showed the relative risk of non-compliance to be 1.74 (odds of non-adherence increased 3.03 fold, 95% confidence intervals 1.96 – 4.89) in depressed compared to non-depressed subjects. Sub-clinical levels of psychiatric symptoms have been reported to impair adherence (Shapiro et al. 1995, Dew et al. 1996) and clinical outcome (Dew et al. 1999) in heart transplant recipients. Depression may also affect other correlates of adherence. For example, depression has been reported to influence health-related beliefs (Salovey & Birnbaum 1989).

4.2.7 Health beliefs

Sackett and Haynes (1976) found correlations between health beliefs and adherence in at least half the studies that assessed patients' beliefs. Perceived seriousness of the disease, perceived susceptibility to the disease and perceived efficacy of treatment all showed positive correlations with adherence. Current models of health behaviour based upon illness perceptions and beliefs about medication offer potential theoretical frameworks to understand how multiple factors affect adherence.

4.3 Models to explain individual differences in adherence

There are a range of models to explain health behaviour. However those that have been used to predict behaviour change, and to be related to interventions to change behaviour, have tended to be either related to the Stages of Change Model or to models centring on health beliefs (social cognition models) (Rollnick et al. 1999). As for categories of variables that have been shown to relate to adherence, there is overlap in the components of models to explain health behaviour. The majority of research into predictors of adherence, has focused on models related to patients' beliefs and it is these models that form the basis for current recommendations relating to research and clinical practice targeted towards improving adherence (Mc Gavock 1996, Royal Pharmaceutical Society 1997).

Models to explain the relationship between beliefs and adherence have developed from focusing on individual components of the link, such as a cost-benefit analysis of treatment, to the more recent self-regulatory model (Leventhal et al. 1992) which integrates elements from earlier models and includes beliefs, emotions and appraisal of outcomes. This section will outline earlier models and then focus on the Self-Regulatory Model.

The main omission of these models related to health beliefs is the inability to account for practical problems that patients' may have taking medication, the ability of patients to solve such problems, self-efficacy beliefs and the accuracy and nature of advice given by healthcare providers to patients.

The Self-Regulatory Model was chosen to form the theoretical basis of the current study since it is the only model to include a feedback element which is needed to explain changes in adherence over time. Furthermore it incorporates the widest range of variables (demographic factors, social factors and individual factors such as personality and emotions are all proposed to contribute to the specific beliefs and emotions of the patient). It shows beliefs and emotions related to the illness as the final common pathway of all these other variables. The relative strengths of the Self-Regulatory Model compared to earlier models will be discussed.

4.3.1 Health Belief Model

According to the Health Belief Model (Becker 1974) health behaviour depends upon an individual's perceived seriousness of the illness, their perceived susceptibility to it and their assessment of the benefits of, and barriers to, treatment (Horne & Weinman 1998). The model yields associations between beliefs and adherence in some situations but this has not been the case for risk-reduction behaviours that are linked to more socially determined motivations (Blackwell 1989).

4.3.2 Locus of control

Locus of control models assert that the main determinant of an individual's health behaviour is their perception of control. The Health Locus of Control Model (Wallston et al. 1976) categorised this as internal or external. The Multidimensional Health Locus of Control Model (Wallston et al. 1978) broadened the earlier model after research showed that perceived control tended to lie in three, not two, areas; the third area was chance. The areas of internal or external control and chance correspond to individuals' beliefs that events are under their own control, under the control of others or down to chance or fate. Although the model has been shown to predict health behaviours in some studies, the relationship between general measures of health locus of control and health behaviours in specific illnesses is weak (Horne & Weinman 1994). For some illnesses such as diabetes (Bradley 1994), disease specific measures of locus of control have been developed, but this is not yet the case for renal disease or transplantation.

4.3.3 Theory of Reasoned Action

According to the Theory of Reasoned Action (Ajzen & Fishbein 1980) an individual's behaviour is best predicted by preceding intentions (Horne & Weinman 1994). Intentions are thought to result from the patient's beliefs regarding other people's views of the behaviour (e.g. 'my partner wants me to follow the recommendations') and their own attitudes towards the behaviour (e.g. 'following the doctors recommendations for using insulin will keep my diabetes under control') (Horne and Weinman 1998). However, like the Health Belief Model, the Theory of Reasoned Action has not been widely used to predict adherence in chronic illness (Horne & Weinman 1994).

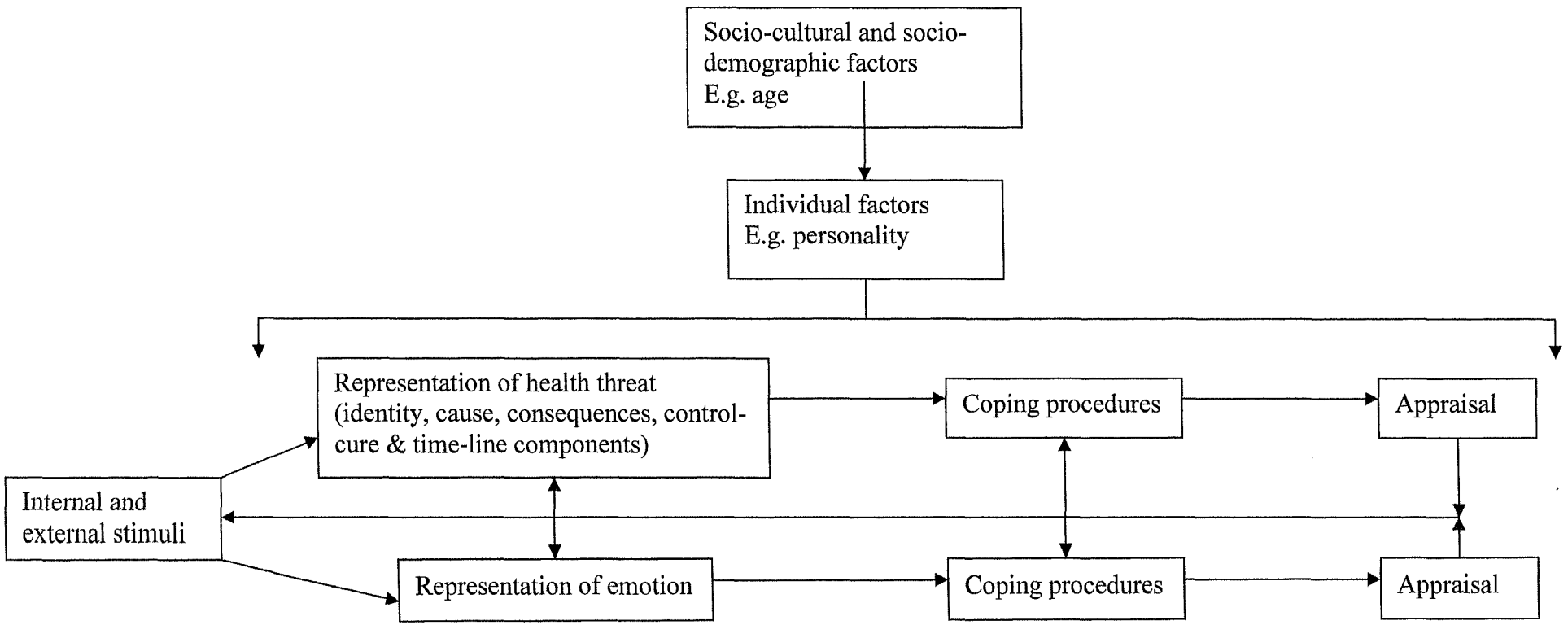
4.3.4 Self-Regulatory Model

The Self-Regulatory Model (Leventhal et al. 1992, figure 4.3.4) was developed from the framework of an earlier 'parallel-processing' model (Leventhal 1970) to explain how people respond to health threats, or illness. A stimulus, usually a symptom, is postulated to trigger the formation of a representation (understanding) of both the threat (the illness) and associated emotions. From this the individual develops coping procedures (ways of responding to the health threat and associated emotions) and then the outcome is appraised. This appraisal is fed back into the representations and selection of coping procedures. The two cognitive and emotional pathways proceeded in parallel and all stages interact with each other.

The parallel-processing model was elaborated into the Self-Regulatory Model by including the components needed to form the illness representation (figure 4.3.4). Research into lay theories of illness indicated that illness representations are composed of five themes (Scharloo & Kaptein 1997):-

- identity: the individual's label or symptoms that make up the illness
- time-line: perceived course of the illness as acute, chronic or cyclical
- consequences: physical, social, emotional and economic outcomes of the illness
- causes: what the individual thinks led to the illness
- cure and/or control: the individual's belief in the potential for amelioration of their condition

Figure 4.3.4: The Self-Regulatory Model



Earlier cognitive models of health behaviour have tended to rely on one aspect of cognition (Leventhal et al. 1992) such as perception of risks (health belief model), treatability (locus of control models) or ability to take successful action (self-efficacy models). All these are considered within the Self-Regulatory Model which integrates social, environmental and individual factors with cognition and affect (Leventhal et al. 1992). The other main factor differentiating the Self-Regulatory Model from earlier models is the inclusion of an appraisal stage. Appraisal of new information and current behaviour can either maintain or modify the specific beliefs which form the components of illness and emotional representations. Individuals are thought to attempt to maintain a coherent model, that is all elements should make sense in relation to each other. The result of this is that an individual may maintain false beliefs that are self-fulfilling due to biased 'testing' (Leventhal et al. 1992).

Leventhal and colleagues (1992) illustrate how the Self-Regulatory Model can be used to understand behaviour with an example of a person with hypertension. If the person thinks all illnesses have symptoms and is told that they have the illness 'hypertension', the individual may develop the belief that they can tell when their blood pressure is raised only if they experienced a symptom such as a headache. Their illness representation for hypertension then includes a headache as part of the identity construct. Belief that hypertension is serious and treatable with medication may trigger development of a coping procedure when the individual experiences a headache. They may 'cope' by checking their blood pressure and on discovering that their blood pressure is raised, taking anti-hypertensive medication. Their belief that a headache is a sign of their blood pressure being raised would be maintained because they do not check their blood pressure when they do not have a headache. This example illustrates the integration of beliefs regarding risk, treatability and self-efficacy in the Self-Regulatory Model; the person has the belief that hypertension is risky and thus needs treatment, that medication is an effective treatment and that they are able to measure their own blood pressure and take the correct medication. However in contrast to models concentrating on one element, such as perception of risk in the Health Belief Model, only the Self-Regulatory Model can be used to explain why the person took medication only when symptomatic (Leventhal et al 1992)

A recent systematic review of articles assessing illness perceptions in patients with chronic physical conditions (Scharloo & Kaptein 1997) concluded that illness perceptions (especially perceived consequences and perceived control) are important factors affecting adherence. However there are many shortcomings in the literature: the most frequently investigated

group of patients were those with chronic pain syndromes, non-validated semi-structured interviews were the main method of collecting information about beliefs, few studies investigated all five dimensions of illness representation and few took account of illness severity.

Standardised measurement of illness perceptions and assessment of their link with adherence, as predicted by the Self-Regulatory Model, has been aided by the development of the Illness Perception Questionnaire (Weinman et al. 1996; section 8.4.2). For example, considering the causal component, a study of patients who were recovering from a myocardial infarction (Petrie and Weinman 1997) found that subjects who believed a faulty lifestyle caused their infarction were more likely to have followed advice to improve their diet and increase their exercise at a six month follow up compared to those without such beliefs. Different illnesses have been distinguished by a different relationship between the components of illness representation and subsequent behaviour (adherence). For example amongst patients with a strong illness identity, those on haemodialysis tended to adhere less to medication whereas those with diabetes or asthma tended to adhere more (Petrie and Weinman 1997). However the Illness Perception Questionnaire only examines components of the illness representation. It does not test other aspects of the self-regulatory model such as the influence of the emotional representation.

The Self-Regulatory Model can be used to explain how individual, social and environmental factors may affect a patient's belief system and thus alter their behaviour. To maintain coherence of their system, people develop models that are consistent with their own personality and social network (Leventhal et al. 1992). This may explain how social influences can affect the patient's illness representations (Leventhal et al. 1992). For example patients with chronic fatigue syndrome tend to make somatic attributions for symptoms (and are thus more likely to form an illness representation when they experience symptoms) and relatives of patients with chronic fatigue syndrome have also been shown to make somatic attributions for symptoms in their relative despite making normalising explanations for their own symptoms (Butler et al. 2001). In this manner, the patient's social network may, inadvertently, strengthen a false belief system that all symptoms are due to active illness.

The appraisal stage in the Self-Regulatory Model has parallels to the collaborative hypothesis testing and appraisal of outcomes that is the basis for treatments in cognitive-behavioural therapy. The drive to maintain coherence of the model predicts that belief change will result

from altered appraisal. The example of the person with hypertension given above can be used to show how therapeutic interventions could, via the appraisal stage, alter illness behaviour by altering the component beliefs within the illness representation. If the person was asked to take their blood pressure when they were symptom free and found that their blood pressure was raised without them having a headache, their belief system could not make sense, it would not be coherent. The Self-Regulatory Model would predict that the person may then modify their belief that hypertension will always be manifest by symptoms. However cognitive-behavioural therapy has not yet been described as an intervention for non-adherence.

In line with the Self-Regulatory Model, it is recommended that future research into the effects of health beliefs on adherence takes into account contextual and personal (e.g. treatment history and age) variables and employs medical, psychological and behavioural indices of outcome (Scharloo & Kaptein 1997).

4.3.4.1 Self-Regulatory Model and beliefs about medicines

A recent report from the Royal Pharmaceutical Society of Great Britain (1997) identified the role of medication beliefs in treatment adherence as a priority for future research. Horne (1997) suggested that including an assessment of beliefs about medication may enhance the explanatory power of the Self-Regulatory Model in relation to medication adherence. He argued that decisions about taking medication are likely to be informed by beliefs about the medicines as well as beliefs about the illness. This led to the design of the Beliefs about Medicines Questionnaire (Horne et al. 1999, see section 8.4.1). This has been used to show that beliefs about specific medication relate to adherence with that medication in patients under the care of asthma and cardiac clinics and renal haemodialysis and oncology units (Horne & Weinman 1999).

4.4 Summary of chapter four

Non-adherence to medication is reported to occur in around 50% patients with chronic illness and is associated with adverse clinical outcomes. Despite the severe consequences of graft loss, non-adherence to immunosuppressants has been demonstrated in heart transplant recipients and the level of non-adherence has been shown to relate to the risk of future rejection episodes. Research to date has failed to find consistent correlates of adherence across different illness groups with the possible exceptions of age, medication-related factors and depression. The latter is particularly important since effective treatments already exist for depression. Identification of potentially modifiable correlates of non-adherence and the presence of theoretical models to understand the process of non-adherence would facilitate design of interventions to improve adherence and thereby reduce the risk of adverse clinical outcomes. The development of the Self-Regulatory Model of health behaviour offers the potential to understand how environmental and individual factors influence adherence. Health beliefs, in the form of beliefs about the illness (illness representation) are central to the Self-Regulatory Model and recent studies suggest that illness perceptions are important predictors of adherence. Inclusion of beliefs about medication may enhance the explanatory power of the Self-Regulatory Model in relation to medication adherence. However much of the work to date that links illness and medication beliefs to adherence has come from the group of researchers who developed the questionnaires used to measure beliefs in studies of adherence. The work needs to be replicated by other groups and other aspects of the Self-Regulatory Model, including emotional factors, need to be investigated.

5.0 Background: adherence to immunosuppressants in renal transplant recipients

Research into non-adherence with medication in transplant recipients developed after Didlake and colleagues (1988) found non-adherence to be the third leading cause of graft failure. Many studies now suggest that non-adherence with immunosuppressants in adult renal transplant recipients is common and a major cause of transplant failure, particularly after the first year of transplantation (Schweizer et al. 1990, De Geest et al. 1995, Nevins et al. 2001). This has led to calls for interventions to reduce non-adherence, assuming that this will prolong graft survival and thus preserve the scarce supply of donor organs (De Geest et al. 1995). However much of the existing literature has significant methodological limitations and the prevalence of non-adherence has not been determined in a United Kingdom population. Furthermore modifiable variables to target have not been consistently identified and the size of expected benefits from an intervention are not known since estimates of the prevalence of non-adherence, and the degree of impact on graft survival, vary widely between studies.

This chapter will discuss why non-adherence following renal transplantation is an important area to address. It will then systematically review the current literature relating to the prevalence and correlates of non-adherence following renal transplantation and discuss some of the methodological problems with previous research.

5.1 The importance of reducing non-adherence in relation to the demand for transplantation

The possibility that non-adherence to immunosuppression is a major factor limiting graft survival raises the possibility of improving transplant outcomes, and therefore organ availability, by improving adherence. Using figures from the literature, the cost savings from such an intervention can be estimated.

Using figures for the three year period 1996-1998, 1796 renal transplants are performed each year and, for primary transplants, the three year survival is 75% (UK transplant 2001). Thus 449 transplants would be expected to fail by the end of three years. A patient returning to dialysis costs an extra £23,000 (Hendry, personal communication 1999). If 15% of graft failures occur due to non-adherence (based on figures from published studies, see table 5.2.3), 67 transplants and over £1.5 million could potentially be saved over the first three years of transplantation by improved adherence to immunosuppression. It is therefore essential to obtain an accurate estimate of the scale of non-adherence in renal transplant

recipients and confirm its deleterious effect on graft survival. Modifiable predictors of non-adherence in this population need to be identified so that interventions to improve adherence, and hence graft survival, can be developed.

5.2 Systematic review of the existing literature relating to the prevalence and impact of non-adherence to immunosuppression in renal transplant recipients

The electronic databases 'MEDLINE' and 'EMBASE' were searched from January 1980 - January 2002 using the thesaurus terms 'patient compliance', 'treatment refusal', 'kidney transplantation' and 'immunosuppressive agents' and the free text terms 'compliance' and 'non-compliance' (figure 5.2). No limits were set on the search. Articles were included if they reported the number of non-adherent subjects, or the number of graft failures assessed as being due to non-adherence and reported on adult renal transplant recipients irrespective of donor source, number of transplants or the degree of graft function at the time of the study. Three articles fulfilled these criteria but were excluded: one provided purely descriptive data (Feldman et al. 1999), one was a follow-up study of subjects in a previous study of chronic rejection (Papajcik et al. 1999) and one was a sub-group analysis from a study attempting to use cyclosporin as the sole immunosuppressant (Touchard et al. 1997). Articles were excluded if they reported on less than 5 subjects, more than 10% sample were children or received a kidney-pancreas transplant or the article was a review. Articles not in English were not excluded but due to lack of translation facilities, the review relied on data presented in the English abstract (Orifino et al. 1994, Fernandez-Lucas et al. 1998). One article was excluded since the reference was incorrect and could not be traced. Duplicate publications from the same cohort were pooled for analysis. A further search for relevant articles using the same inclusion and exclusion criteria was made by searching reference lists of relevant articles, examining the contents pages of 'Transplantation', 'Transplantation Proceedings', 'Nephrology Dialysis and Transplantation', 'Kidney International', 'Clinical Transplantation', 'American Journal of Kidney diseases', British Journal of Renal Medicine' and 'Dialysis and Transplantation' from January 2000 to January 2002 and obtaining the conference abstracts from the 'First European Symposium on Non-compliance in Organ Transplant Recipients' and 'The First International Symposium on Transplant Recipient Compliance (Transplantation Proceedings volume 31 Number 4A 1999)'.

The type of study design is an important factor determining how much weight can be given to the results of the study when used to answer a research question; for example, randomized controlled trials are thought to be the best form of evidence to answer an analytic question.

Therefore identified studies were analysed in groups according to their design. Table 5.2 shows the study designs that could be used to address the questions in this review.

Table 5.2a: Study designs relevant to the systematic review

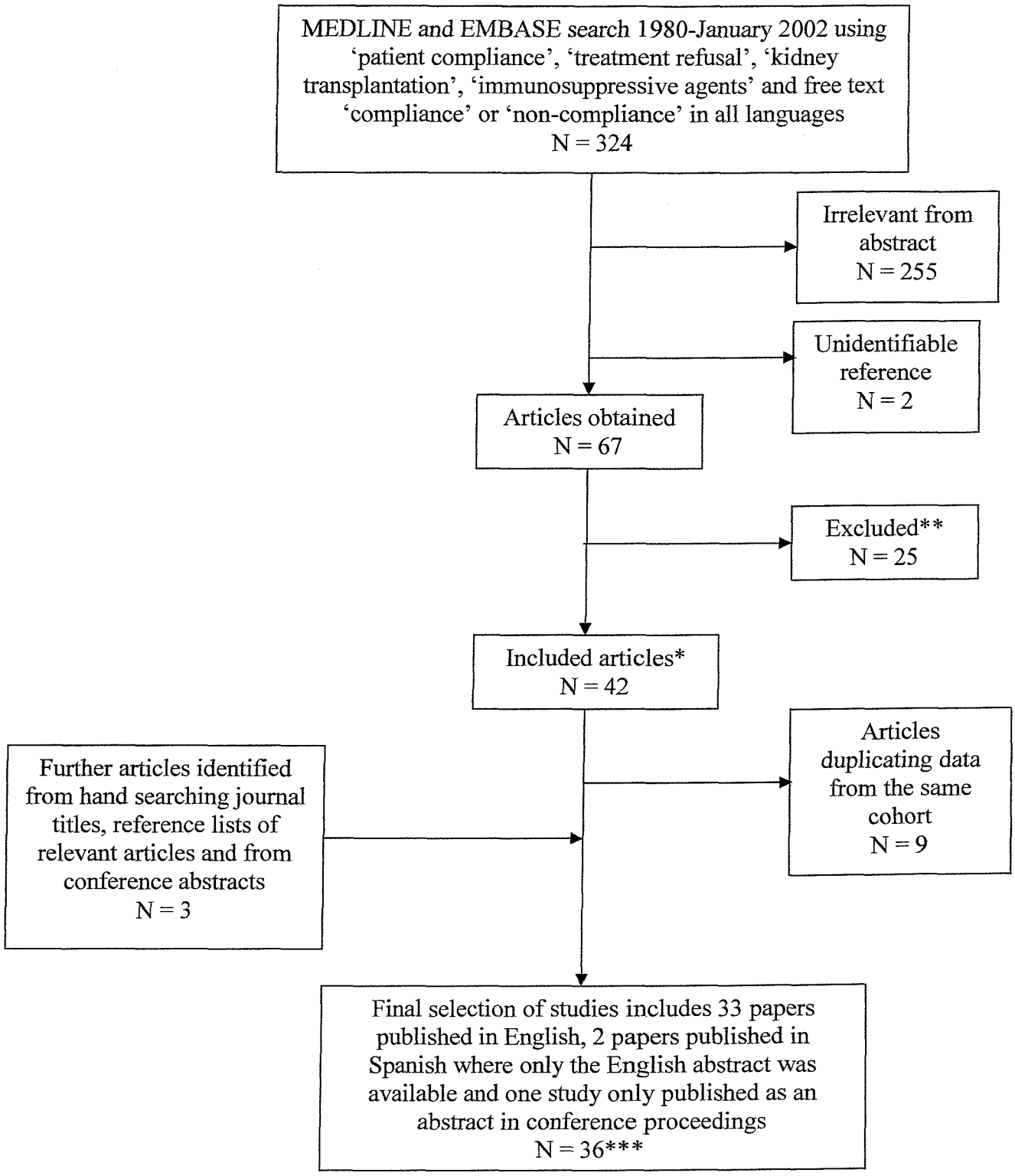
Question addressed by the review	**Hierarchy of trial design ('best' design first)**
what is the frequency of non-adherence in renal transplant recipients?	cross-sectional (to detect the prevalence) prospective cohort (to detect the cumulative incidence) retrospective cohort (to detect the cumulative incidence)
what is the impact of non-adherence on graft survival?	randomized controlled trial of an intervention to improve adherence with graft survival as the main outcome prospective cohort retrospective cohort case control case series

The search identified 38 studies, in 36 papers, investigating the frequency of non-adherence or the association of adherence and graft survival in a population of predominantly adult renal transplant recipients (tables 5.2b, c and d). The studies were grouped as follows.

- **cross-sectional studies (n = 15):** studies of patients with functioning grafts. These assessed the prevalence of non-adherence in a clinic population (table 5.2d, page 68).
- **cohort studies (n = 11):** studies that included a cohort of patients transplanted over a defined time period, regardless of current graft function. These assessed the proportion of subjects who had ever been non-adherent over a variable time period since transplantation. The studies also assessed the impact of non-adherence on graft survival by comparing the proportion of subjects who had been classified as non-adherent according to whether their transplant had failed or was still functioning at the time of the study (table 5.2c, page 67).
- **case series (n = 12):** studies that recruited from a defined cohort but only included subjects whose transplants had failed. These assessed the proportion of graft failures that had been preceded by non-adherence (table 5.2b, page 66).

The 38 selected studies had been carried out in a variety of countries but came predominantly from the United States.

Figure 5.2: Identification of articles relating to the frequency and impact of non-adherence



* included articles: sample size greater than 5, kidney transplant recipients, results report the number of subjects with non-adherence in the whole sample or in a defined sub-set of the sample,

** excluded articles: more than 10% sample under 18 years old or without a single kidney transplant, review articles, 1 study with 'infant en-bloc kidney transplants'

***36 papers described 38 studies

One paper (Didlake et al. 1998) reported two designs, a retrospective cohort study and a cross-sectional survey. One paper (Schweizer et al. 1990) reported two consecutive cohort studies. These were not pooled for analysis since the paper reports a change in unit protocol regarding the selection of transplant candidates as a result of the data found in the first study. One paper (Michelon et al. 1999) reported three consecutive case series. The data from each case series is presented but the analysis is performed on the entire sample and is thus analysed as if the study was one large case series. One study (Nevins et al. 2001) measured adherence prospectively over a 6 month period but reported results for all subjects regardless of current graft function. Thus it was included with the other cohort studies, although all other cohort studies were retrospective.

The case series included subjects transplanted between 1969 and 1999. Cohort studies included subjects predominately transplanted in the 1980s or early 1990s (range 1976-1997). The period of transplantation was only reported in 3 of the 15 cross sectional studies; in these subjects were transplanted from 1980 to 1998. In the majority of studies primary cadaveric transplants predominated. Only one study (Isaacs et al. 1999) included solely transplants from live donors. A median of 61% (range 43-85%) subjects were male. Although the majority of studies provided some details of the study sample, less than half described all features of gender distribution, age, percentage of re-grafts plus the percentage of cadaveric grafts in the sample or the distribution of time post-transplantation. More detailed description of the sample occurred in cross-sectional studies compared to cohort studies or case series.

Most studies gave a poor description of the time post-transplantation. This is an important omission since duration of transplantation may confound estimates of the prevalence of non-adherence. If non-adherence increases the risk of graft failure, the longer subjects have been transplanted, the greater the chance of survivor bias. This would result in the sample containing less non-adherent subjects, thereby leading to a falsely low estimate of the prevalence of non-adherence. Conversely if non-adherence increases with time since transplantation, as has been suggested in several studies (Didlake et al. 1988; Kalil et al. 1992; Sketris et al. 1994; Siegal & Greenstein 1997; Greenstein & Siegal 1998), then the prevalence of non-adherence would increase with a longer average time since transplantation. If non-adherence both increases with time since transplantation and also increases the risk of graft loss then the influence of time post transplantation will be even more difficult to assess.

5.2.1 Definition and measurement of adherence

The method of measuring adherence was not reported in 7 case series and one cohort study. Electronic monitoring became a commonly used measure in adherence research in the mid-1980s and is now regarded by many as the best measure. However it was used in only one study of the prevalence of non-adherence (Nevins et al. 2001) and one descriptive study (Feldman et al. 1999). Even studies published since 1995, when electronic monitoring was readily available, have tended to rely on self-report. This is more of a problem since no study described its self-report measure in detail and studies have used different measures.

Non-adherence was precisely defined in only 2 of the 26 cohort studies and case series. Definitions were based on the percentage of days without medication as assessed by electronic monitoring (Nevins et al. 2001) or by the number of cyclosporin levels below 30 ng/ml (Kiley et al. 1993). Nine of the remaining studies attempted a definition but these were non-standardised statements such as 'identified as overtly non-compliant' (Kalil et al. 1992), 'a definite history' of non-adherence (Lai et al. 1992) or 'graft loss thought to be due' to non-adherence (Didlake et al. 1998). Non-adherence was better defined in the cross-sectional studies. Eight studies defined a response, in terms of quantity and frequency of missed medication, assessed by questionnaire (Sketris et al. 1994; Siegel & Greenstein 1997; Greenstein & Siegel 1998; Raiz et al. 1999), interview (De Geest et al. 1995; Teixeira de Barros & Cabrita 2000), pill counts (Hilbrands et al. 1995) or pharmacy refill data (Chisholm et al. 2000).

Studies that have quantified non-adherence in terms of dosing have usually used missing, forgetting or altering a dose at least once a month (Didlake et al. 1998; Sketris et al. 1994; Siegel & Greenstein 1997; Greenstein & Siegel 1998; Raiz et al. 1999; Teixeira de Barros & Cabrita 2000) or taking medication 2 or 2.5 hours late at least once a month (Sketris et al. 1994; Teixeira de Barros & Cabrita 2000) as their criterion. The two studies defining non-adherence in terms of the percentage of missed doses have used 10% (Nevins et al. 2001; Hilbrands et al. 1995) or 20% (Chisholm et al. 2000) missed doses to define non-adherence. Assuming daily dosing and 30 days in a month, these percentages correspond to missing 3 or 6 doses per month respectively.

Ideally the definition of non-adherence would be the level of missed medication that increases the risk of a clinically significant outcome such as a rejection episode or graft failure. This level is likely to vary between recipients according to other factors influencing

transplant survival yet even an average level is not known. However no existing studies of adherence following renal transplantation report any attempt to reach a clinically important definition and few report whether non-adherence was defined prior to data collection.

There is only one prospective study of clinical outcome following assessment of adherence in renal transplant recipients (Nevins et al 2001). This found that subjects who miss at least two doses more of azathioprine in the second month compared to the first month of transplantation have a relative risk of graft failure of 2.5 compared to subjects whose adherence remains stable. However this was a post hoc analysis, the investigators did not report the absolute level of adherence that determines risk and have so far only reported adherence data for the first six months post transplantation. In heart transplant recipients missing 3% or more doses of cyclosporin or varying the dosing regime by more than 3 hours has been found to significantly increase the risk of late acute rejection (De Geest et al. 1998).

Two large surveys of transplant teams have asked clinicians to estimate the degree of non-adherence to immunosuppressants that increases clinical risk. In a European survey of 28 transplant centres, 20 (71%) of which transplanted adult renal recipients, 93% clinicians agreed that missing immunosuppressants 'occasionally' or 'frequently' or discontinuing them was significant (on a 5-point scale of never, seldom, occasionally or frequently missing, or discontinuing, Pruna & Fornairon 2000). In a study of predominantly American transplant centres, 149 (49%) of which transplanted adult renal recipients, clinicians estimated that a median (range) of missed doses increasing the risk was 10 (0-100)% and that taking medication a median of two hours early or late (range 0-48 hours) increased the clinical risk (Hathaway et al. 1999).

Thus the degree of non-adherence that increases clinical risk is not known in relation to immunosuppressants following renal transplantation and there appears to be little consensus of an appropriate value amongst teams involved in transplantation. This is likely to have contributed to the range of definitions and varied measurement approaches used in existing studies. However although a clinically important definition of non-adherence is not known, in general, existing studies have also not attempted to use reproducible definitions.

5.2.2 Frequency of non-adherence to immunosuppressants

The reviewed cross-sectional studies found a median prevalence of non-adherence of 22.4% subjects (IQR 17.7-25.9%). The cohort studies found that a median of 15.0% (IQR 4.8-20.0%) subjects had been non-adherent between transplantation and the time of the study (table 5.2.2).

Two studies using electronic monitoring report a continuous description of non-adherence. Feldman and colleagues (1999) report a two-month pilot study assessing adherence with cyclosporin and azathioprine in 25 subjects whose time post-transplantation was not specified. Subjects missed a median of 3.8% (range 0-24.3%) doses of cyclosporin and 3.6% (range 0-67.3%) doses of azathioprine. Thirty-six percent of subjects missed four or more consecutive doses and 16% missed at least 10 consecutive doses. Nevins and colleagues (2001) report non-adherence with azathioprine in the first six months after transplantation. Over the six-month period, 20% subjects missed at least 10% days medication and nearly 18% missed four or more doses a month.

The different assessment methods, definitions and incomplete description of the sample make it difficult to see relationships between these factors and results of studies. When assessed in cross-sectional studies using self-report with the same definition of missing, forgetting or altering a dose of medication at least once a month, the prevalence of non-adherence was similar, ranging from 17-26% (Didlake et al. 1998; Sketris et al. 1994; Siegel & Greenstein 1997; Greenstein & Siegel 1998; Raiz et al. 1999; Teixeira de Barros & Cabrita 2000).

The prevalence of non-adherence was greater in the cross-sectional studies compared to the proportion of subjects who had ever been non-adherent in the cohort studies. This suggests that either the increase of non-adherence with time post-transplantation has a larger effect than the rate of graft loss due to non-adherence or that documentation in clinical notes, the main measure of adherence in the transplant cohort studies, is a particularly insensitive measure. Furthermore the cross-sectional studies tended to rely on self-report, likely to be biased by reluctance of patients to admit to non-adherence and the limits of their memory. This may mean that the true prevalence of non-adherence is higher than found in this review.

5.2.3 Impact of non-adherence on graft survival

The case series of subjects with failed grafts, show a median of 14.4% (IQR 5.1-21.7) graft failures were preceded by non-adherence (table 5.2.3a and b). If subjects who died with a

functioning graft are excluded, non-adherence accounts for a greater proportion of graft failures (table 5.2.3b). The cohort studies found a greater proportion of subjects with failed grafts who had also been classified as non-adherent was higher in studies including all subjects transplanted within a defined time period (transplant cohort studies; median 36.4%, IQR 13.8-65.2%; table 5.2.3b and c).

Table 5.2.3a: Summary of the impact of non-adherence in renal transplant recipients

Type of studies (defined on page 50)	**Median percentage of graft losses preceded by non-adherence (IQR)**	**Median relative risk of graft failure in non-adherent compared to adherent subjects (IQR)**
Case series	15.8[1] (9.1-23.1)	n/a
Cohort studies	36.4 (13.8-65.2)	3.2[2] (2.7-4.0)

[1]excluding death with function if data is available (14.4, 5.1-21.7 if this is not excluded)
[2]excluding outlying study with relative risk of 20.5 (median 3.4 if this is included).

Two cohort studies had particularly high proportions of graft loss in non-adherent subjects. Their methods of measuring adherence may account for the higher proportions. In the first study (Kiley et al. 1993) non-adherence was defined as 'unexpectedly low trough cyclosporin levels' of under 30ng/ml suggesting either that this is a much more sensitive measure to detect non-adherence than notes review or that trough cyclosporin levels lack specificity. In the second study (Schweizer et al. 1990, study B) the assessment of adherence, which relied on clinician rating, was likely to have been biased because the unit that had altered its practice regarding non-adherence following the results of an earlier study of adherence undertaken in the unit.

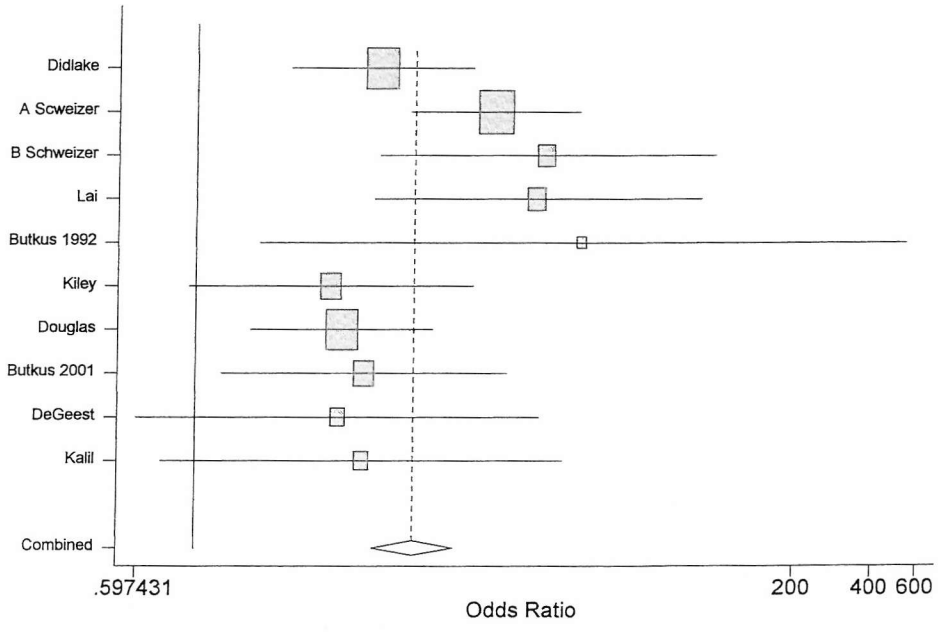
The study by Michelon and colleagues (1999) shows an increasing proportion of graft losses attributed to non-adherence over three consecutive time periods. This suggests that the impact of non-adherence is increasing over time. The authors also report a greater proportion of graft failures are attributed to non-adherence after the first six months of transplantation compared to the early post-transplant period. This supports the hypothesis that non-adherence is a relatively more important cause of graft loss after the initial post-transplantation period. However the study by Nevins and colleagues (2001) reports that the risk of graft failure is still increased by non-adherence in this early period. Subjects whose adherence declined in the first six months post transplantation were 2.5 times more likely to experience transplant loss compared to those with stable adherence. Most studies have included death with function as a cause of transplant failure. Where data is given, if death with a function is excluded, non-

adherence appears to contribute to an increased proportion of graft failures, thus supporting the hypothesis that it is that lack of immunosuppression to the kidney that is crucial.

Despite the variation in the absolute frequency of non-adherence, studies tend to be fairly consistent in their estimates of the relative risk of non-adherence on graft failure. This had a median of 3.4 (IQR 2.7-4.4) in non-adherent subjects compared to adherent ones.

Relative risk is significantly affected by the frequency of the outcome (graft failure). Meta-analysis using odds ratios overcomes this difficulty and forest plots (estimates plus 95% confidence intervals) are used to represent the results graphically. Woolf's method for estimating the pooled (combined) odds ratios (OR) was estimated from meta-analysis of results from the reviewed transplant cohort studies using STATA v7.0. In figure 5.2.3 the solid vertical line represents no difference within strata (odds ratio = 1 corresponding to no effect of non-adherence on graft survival), whilst the dashed vertical line represents the pooled estimate. This meta-analysis of the cohort studies (excluding the study by Nevins and colleagues, see figure 5.2.3) shows the odds of failure in the non-adherent group to be 7-fold greater in non-adherent compared to adherent subjects (Fixed effects combined odds ratio = 7.1, 95% confidence intervals 4.4 to 11.7, $p<0.001$; figure 5.2.3). There was no significant heterogeneity ($p = 0.100$).

Figure 5.2.3: Meta-analysis of the cohort studies reporting of the effect of non-adherence on graft survival[1]



[1]Nevins et al (2001) is not included in the meta-analysis since the study did not report graft survival in adherent versus non-adherent subjects, the study reported graft survival according to the change in adherence between months one and two of the study

5.3 Systematic review of the existing literature relating to potential predictors of non-adherence to immunosuppression in renal transplant recipients

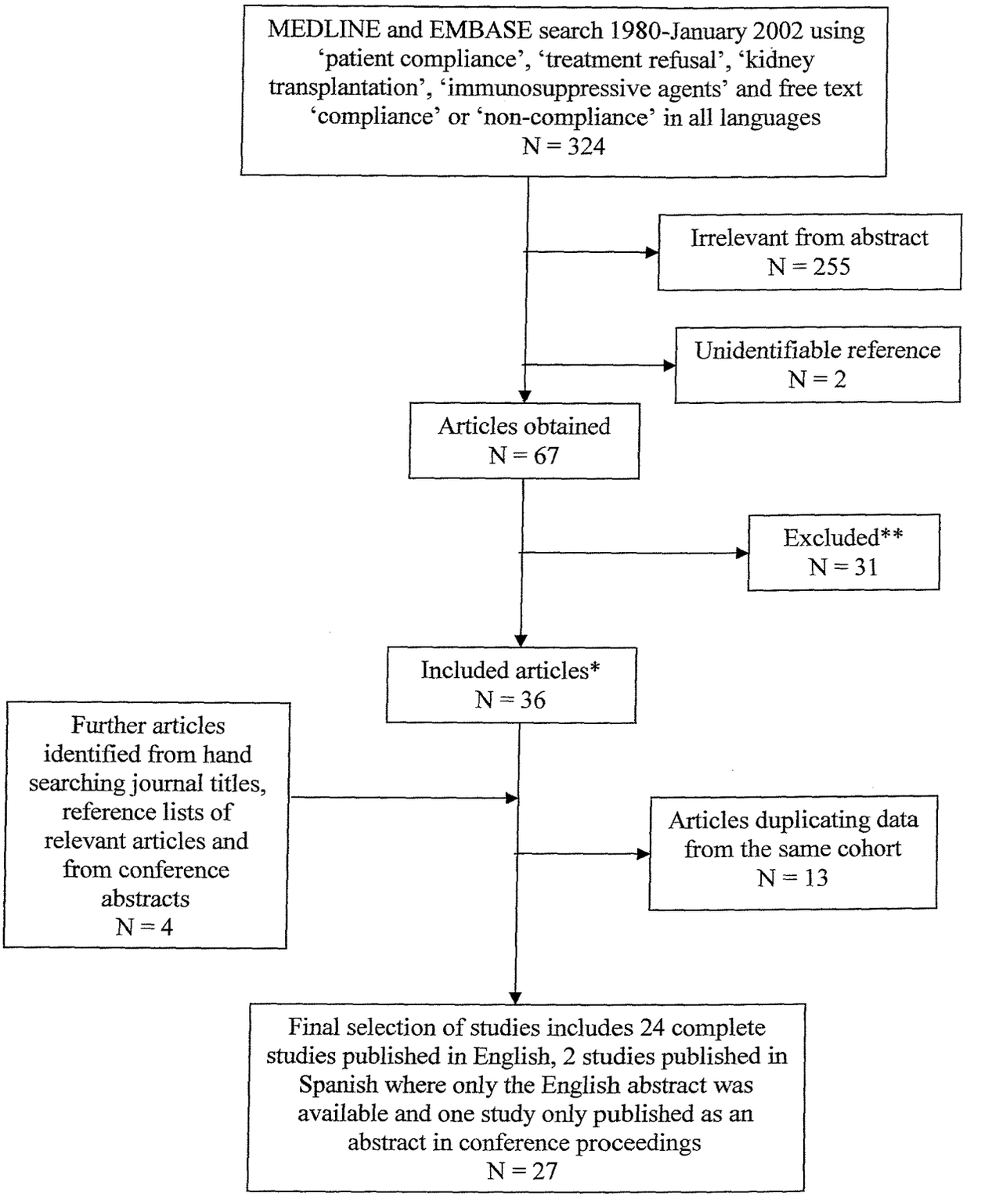
A systematic review of the literature, using the same methodology as reported in section 5.2, was used to identify existing studies reporting potential predictors of non-adherence. This identified 27 relevant studies (figure 5.3), one of which was a matched case control study not included in studies of the frequency of non-adherence (Rodriguez et al.1991).

Although many factors have been studied in relation to adherence to immunosuppression in renal transplant recipients (table 5.3a, page 72), the majority of studies have confined themselves to variables that cannot be modified after transplantation (table 5.3b).

Table 5.3b: Groups of factors that have been related to adherence (from table 5.3a)

Type of factor	Number of reports of a significant relationship with adherence	Number of reports of a non-significant relationship with adherence
Socio-demographic	40	38
Medical	1	1
Transplant-related	9	16
Medicine-related	6	3
Symptom-related	2	2
Psychological	12	6
Health beliefs	7	1

Figure 5.3: Identification of articles relating to correlates of non-adherence



* included articles: sample size greater than 5, kidney transplant recipients, results report the number of subjects with non-adherence in the whole sample or in a defined sub-set of the sample,

** excluded articles: more than 10% sample under 18 years old or without a single kidney transplant, review articles, 1 study with 'infant en-bloc kidney transplants'

5.3.1 Socio-demographic factors

The most consistent finding of a socio-demographic correlate to non-adherence is younger age (table 5.3a). However some studies have not found age to be significant (Dunn et al 1990; Kiley et al. 1993; De Geest et al. 1995; Hilbrands et al. 1995; Papajcik et al. 1999; Rodriguez et al 1991). There are inconsistent findings with respect to sex with slightly more studies finding males (Dunn et al 1990; Hong et al. 1992; Kiley et al. 1993; Siegal & Greenstein 1997) rather than females (Didlake et al. 1988; Frazier et al. 1994; Hilbrands et al. 1995) to have an increased likelihood of non-adherence. One of the latter studies found female sex to be important only for the immunosuppressant prednisolone (Hilbrands et al. 1995).

Few studies have looked at the influence of marital status but from those that have, all but one (Rodriguez et al. 1991) found a higher prevalence of non-adherence in those who live alone or who are unmarried (Frazier et al. 1994; De Geest et al. 1995; Fernandez-Lucas et al. 1999; Teixeira de Barros & Cabrita 2000). The evidence for the role of ethnicity in determining non-adherence is conflicting and one study found that the apparent effect of ethnicity was explained by socio-economic status (Schweizer et al. 1990). Other socio-demographic factors such as employment and educational level have been investigated in a few studies but again the conclusions are conflicting.

Therefore it appears that with the possible exceptions of younger age and living alone, demographic factors do not strongly predict non-adherence in renal transplant recipients. Definite conclusions about the influence of these factors are limited by the differences in study methodology. Furthermore although such factors might allow identification of individuals at high risk of non-adherence they cannot be altered once the transplant is in place. However they may affect modifiable factors. Recent studies have started to investigate this, for example a combination of gender and ethnicity has been found to relate to medication-related beliefs and the experience of side effects (Greenstein & Siegel 1998).

5.3.2 Transplant-related factors

Most studies investigating the frequency of non-adherence in patients with transplants from cadaveric and living donors have not found the type of transplant to be a significant influence on adherence (Gaston et al. 1999; Michelon et al. 1999; Didlake et al. 1988; Schweizer et al. 1990; Lai et al. 1992; Frazier et al. 1994; Sketris et al. 1994; Papajcik et al. 1999; Rodriguez et al. 1991). However the two studies that did find a relationship (Hong et al. 1992;

Greenstein & Siegal 1998) both found a higher frequency of non-adherence in those who had received a live-related transplant. All studies reporting an effect of time since transplantation have found non-adherence to increase with time (Didlake et al. 1988; Kalil et al. 1992; Sketris et al. 1994; Siegal & Greenstein 1997; Greenstein & Siegal 1998). However all but one have been retrospective or cross-sectional in design.

The suggestion that non-adherence is commoner with longer times since transplantation is particularly important since the article describing the increasing frequency of non-adherence in one transplant unit over time (Schweizer et al. 1990). A greater percentage of graft losses were attributed to non-adherence for grafts that functioned for more than six months compared to all grafts. This effect became progressively larger over each time period so suggests that the relative influence of non-adherence on graft survival is increasing with time.

However like socio-demographic factors, transplant-related factors cannot be altered once the transplant is in place. Potentially modifiable factors are therefore important to identify. Few studies to date have investigated the influence of such factors on non-adherence in renal transplant recipients. Studies have used different measurement tools and investigated different aspects of knowledge, psychological factors or health beliefs.

5.3.3 Side effects of immunosuppressants

Immunosuppressant side effects are common in transplant recipients (Moons et al. 1998) and are thought by clinicians to be an important determinant of non-adherence (Hathaway et al. 1999; Pruna & Fornairon 2000). All 3 studies of the influence of side effects on adherence in renal transplant recipients found the presence of side effects to be positively correlated with non-adherence (Sketris et al. 1994; Siegel & Greenstein 1997; Teixeira de Barros & Cabrita 2000). However the most frequent symptoms are not necessarily the most distressing (Teixeira de Barros & Cabrita 1999; De Geest et al. 1995).

5.3.4 Treatment-related knowledge

Knowledge of treatment and disease related factors, however defined, have only been investigated in three studies. Two failed to find a significant effect (Fernandez-Lucas et al. 1999; Teixeira de Barros & Cabrita 1999) and the other only found a positive relationship for one of several measures of knowledge (De Geest et al. 1995).

5.3.5 Psychological symptoms and psychiatric illness

Psychiatric illness is thought to be a major determinant of non-adherence by staff (Hathaway et al. 1999) with depression being particularly important (Bunzel & Laederach-Hofmann 2000). However the evidence concerning this is conflicting. Some studies demonstrate a positive relationship between depression and non-adherence (Kiley et al. 1993; Frazier et al 1994) but others show an inverse relationship (Hilbrands et al 1995) or a non-significant effect (Didlake et al 1988). However depression is important in view of its possible contribution to graft loss (Kiley et al. 1993) and impairment of quality of life.

5.3.6 Health beliefs

Studies assessing health beliefs have found a correlation with non-adherence. Beliefs relating to the need for medication (Greenstein & Siegel 1998), duration of action of immunosuppressants (Greenstein & Siegel 1999) barriers to taking medication (Kiley et al 1993), the role of chance in health outcomes (Raiz et al 1999, Frazier et al 1994) and side effects (Siegal & Greenstein 1998) have been correlated with non-adherence. However the studies have not used the same instruments to measure beliefs and all have looked at different types of belief. This makes it difficult to draw generalisable conclusions from the literature.

5.3.7 Combinations of predictors identified using multivariate analysis

Several studies have used multivariate modelling to identify correlates of non-adherence (table 5.3.7). The description of the procedure and results of modelling were poor. Only one study reported that they had used logistic regression (De Geest et al. 1995) although the others implied a binary dependant variable and only one study reported the odds ratios and significance values for variables within the model (Greenstein & Siegel 1998). No study reported any tests of the assumptions of the model. Furthermore all studies investigated a different pool of potential independent variables so would be unlikely to reach the same conclusions. However despite these limitations, all models included potentially modifiable factors. The model by Greenstein & Siegel (1998; table 5.3.7) was reported to have a good ability to predict non-adherent subjects when adherence was reassessed 18 months later (Greenstein & Siegel 2000).

Table 5.3.7: Groups of variables related to self-reported adherence identified using multivariate models

Study	Frazier et al. 1994 (n=246)	De Geest et al. 1995 (n=150)	Raiz et al. 1995 (n=309)	Greenstein & Seigel 1998 (n=1402)
Variables	Gender	Gender	Age	Age
	Marital status	Marital status	Pain	Employment*
	'Stress'	Self-efficacy	Locus of control	Duration of transplant*
		Self-care agency	Feeling 'bothered' by the transplant	Belief in the need for immunosuppressants*
		Knowledge about administration of medicines	SF36 social functioning scale	Belief in the timely administration of immunosuppressants
		Knowledge about the signs of infection		Belief in the duration of action of immunosuppressants*
		Situational-operational knowledge (ability to solve problems)		

* importance varied according to the type of transplant

5.4 Summary of chapter five

Studies of non-adherence in adult renal transplant recipients published between 1980 and 2002 were reviewed. The 13 cross-sectional studies indicate a median of 22 (IQR 18-26)% subjects fail to take immunosuppressants as prescribed. This is a particularly important issue to address in view of the 7-fold increase in the odds of graft failure in non-adherent compared to adherent subjects. Predictors of non-adherence need to be identified to reduce non-adherence. The 27 studies assessing the correlates of non-adherence have tended to produce conflicting results, partly due to inconsistencies in variables studied. Younger age, living alone, side effects of medication and depressive illness are the variables that have been most commonly related to increased non-adherence in cross-sectional or retrospective studies. Only 4 studies have investigated the influence of health beliefs but all found a positive association. An 18-month follow up of the cohort in one study, published after the start of the current study, shows that beliefs about the need for, and duration of action of, immunosuppressants are predictive of future non-adherence.

Table 5.2b: Description of case series looking at the causes of graft failure in adult renal transplant recipients

First author, year & country of study	Inclusion criteria	Time since transplant (months)	Description of sample	Definition of non-adherence	Method to detect non-adherence
1. Jeffery, 1988, Canada	tx November 1969-July 1988, primary tx	Not given	Number of males not given; 91% were over 20 years; 81% cadaveric; 100% primary tx[a]	Not given	Not given
2. Dunn, 1990, USA	tx January 1981-December 1986; tx functioned at least 24 months	Minimum 24	67% male; mean (SD) age 34 (15) years; 74% cadaveric tx; 74% primary tx	Not given	Not given
3. Moosa, 1992, South Africa	tx January 1976-December 1989, primary cadaveric tx,	Not given	60% male; Mean age not given; 100% cadaveric tx; 100% primary tx[a]	Not given	Not given
4. Hong, 1992, USA	tx March 1983-January 1989; tx functioned at least 12 months	Range 12-60	65% male; mean age not given; 80% cadaveric tx; Number of tx not given	Patient's report of missing immunosuppressants or missing 2 consecutive out-patient appointments	Clinical notes
5. Bergman, 1992, USA	tx May 1984-January 1991, tx functioned at least 6 months	Mean 55 Range 12-84	Not given	Not given	Clinical notes
6. Kim, 1994, Korea	tx February 1984-January 1993, primary live-related tx	Not given	Not given	Not given	Patient dtabase
7. Matas, 1994, USA	tx January 1986-December 1991; primary tx; tx functioned at least 12 months	Minimum 12	Number of males and mean age not given; 43% cadaveric tx; 100% primary tx	Not given	Not given
8. Shoskes, 1997, USA	tx January 1984 – December 1991, tx failure within 3 years	Range 0-36	Number of males and mean age not given; 82% cadaveric tx; 87% primary tx[a]	Not given	Not given
9. Isaacs, 1999,USA	Tx January 1988-December 1994, live-related donor	Range 6-96	100% live related tx; Number of males or primary tx and mean age not given	Not given	Clinical registry
10. Michelon, 1999, Brazil	tx May 1977-December 1991	Not given	No data given	' When the patient discontinued immunosuppressants'	Not given
	Above plus tx functioned at least 6 months	Minimum 6	No data given		
	tx January 1992-April 1995	Not given	No data given	When back on dialysis the patient or their 1st degree relative said regular intake of immunosuppressants was 'not the rule'	Report of patient or relative to clinical team after transplant failure
	Above plus tx functioned at least 6 months	Minimum 6	No data given		
	tx May 1995-June 1998	Not given	No data given	When back on dialysis the patient or their 1st degree relative said regular intake of immunosuppressants was 'not the rule' or if it was strongly suspected by staff	Report of patient or relative to clinical team after transplant failure or staff suspicion
	Above plus tx functioned at least 6 months	Minimum 6	For May 1977-June 1998:- 56% male; mean age not given; 40% cadaveric tx; 92% primary tx		
11. Moon, 2001, South Korea	Tx April 1979-May 1989, primary tx, HLA identical sibling donor	Mean 134	85% male; Mean age 34 years; 100% live-related tx; 100% primary tx	Not given	Not given
12. Birkeland, 2001, Denmark	tx 1996-1999, primary or second tx, discharged with functioning tx, adult	Median 30	65% male; Median age 44 years (7 under 15 years); 67% cadaveric tx; 83% primary tx[a]	Not given	Not given

tx = transplant or transplantation

[a]demographic details relate to the whole population of transplant recipients from which the sample of graft failures are identified

10. data from this sample also published in Bittar et al. 1992 and Garcia et al. 1997

Table 5.2c: Description of cohort studies reporting the frequency of non-adherence in adult renal transplant recipients

First author, year & country of study	Inclusion criteria	Sample size[a]	Time since transplant (months)	Description of sample	Definition of non-adherence	Method to assess non-adherence
13. Didlake, 1988,USA	tx August 1980-December 1986,	531	Not given	67% male; mean age 34±14years; 74% cadaveric tx; 83% primary tx	Graft loss ('major non-NA') or acute rejection episode ('minor NA') thought to be due to NA	Self report at two interviews after graft failure ('major NA') or rejection ('minor NA'),
14. Schweizer, 1990,USA	tx 1971-1984; graft functioned at least 3 months, not failed due to 'technical loss' (study A)	260	Minimum 3	66% male; mean age 32 years; 62% cadaveric; 96% primary tx	'Indication in clinical notes ' that patient had not taken medicines as directed (eg: by patient or relatives disclosure or staff suspicions when a rejection episode was readily reversed)	Clinical notes
	tx 1984-1987; graft functioned at least 3 months, not failed due to 'technical loss' (study B)	196	Minimum 3	63% male; mean age 34 years; 80% cadaveric tx; Number of primary tx not given		
15. Lai, 1992, Taiwan	tx July 1981-August 1991	228	Not given	71% male; mean age not given; 64% cadaveric tx; Number of primary tx not given	'Definite history' of discontinuation or reduction of prescribed immunosuppression	'Careful history-taking'
16. Butkus, 1992, USA	tx January 1985-April 1991, primary cadaveric tx, on cyclosporin, tx functioned at least 12months	100	Mean (SD) 40(17) Minimum 12	61% male; mean age not given; 100% cadaveric tx; 100% primary tx	2 consecutive unmeasurable cyclosporin levels or self-discharge from hospital or missing 3 consecutive out-patient appointments	Clinical notes
17. Kalil, 1992, USA	tx January 1976-August 1982; tx functioned at least 12 months	202	Minimum 12	43% male; mean age not given; 94% cadaveric tx; 87% primary tx	'Identified by physicians and nurses as overtly non-compliant'	Clinical notes
18. Kiley, 1993,USA	tx January 1985-December 1987, patient still alive	105	Minimum 18	64% male; mean (SD) age 42(11) years; Number of cadaveric and primary tx not given	'Repeated' CyA levels < 30ng/ml with no other explanation for low levels	Clinical notes
19. Orifino, 1994, Spain[c]	tx functioned at least 3 months	394	Minimum 3	Not given	'great transgression' or 'incomplete adherence'	'Anonymous self-report'
20. Douglas, 1996,USA	tx January 1986- December 1988; tx functioned without rejection for at least 3 months; over 18 years	126	Minimum 3	60% male; mean (SD) age 41(12) years; Number and type of tx not given	Single mention of 'non-adherence' to medication or clinic appointments in clinical notes	Clinical notes
21. Butkus, 2001, USA	Tx September 1992-July 1997, sociodemographic data collected pre-transplant, at least 1 year follow up by April 1999	128	Minimum 12	59% male; mean age, number and type of transplants not given	Not given	Not given
22. Nevins, 2001, USA	Tx March 1993-October 1995, discharged with functioning graft, on azathioprine tablets	134	Maximum 6 months after hospital discharge	From 180 subjects initially agreeing to the study:- 57% male; mean (SD) age 42(14) years; 45% cadaveric tx; Number of tx not given	monthly *compliance rate of 90% or less*[d], missed 2 more doses in the second month than in the first month (*'declining compliance'*)	Electronic monitoring for the first 6 months of transplantation

tx = transplant or transplantation

[a]population from which the sample was drawn was not given for three studies (Schweizer et al. 1990, Butkus et al. 1992 & Orifino et al. 1994) but complete recruitment was implied, complete recruitment occurred in 3 studies (Didlake et al. 1998, Lai et al. 1992 & Kalil et al. 1992), the other studies failed to recruit 2% (Douglas et al. 1996), 40% (Kiley et al. 1993), 65% (Nevins et al. 2001) & 72% (Butkus et al. 2001) subjects

[b]study B was started after the results of study A were available and the unit had implemented policies to try to reduce non-adherence by not transplanting those with non-adherence to medications or on dialysis)

[c]data extracted only from the abstract (published in Spanish)

[d]*'monthly compliance rate'* was the percentage of days with an opening of the monitor compared to the number of days azathioprine was prescribed (excluding days when the subject was hospitalized or the monitor was unavailable)

14. data from this sample also published in Rovelli et al. 1989a and 1989b

Table 5.2d: Description of cross sectional studies reporting the prevalence of non-adherence in adult renal transplant recipients

First author, year & country of study	Inclusion criteria	Sample size (number eligable)	Duration post-transplant (months)	Description of sample	Definition of non-adherence	Measures of non-adherence
13. Didlake, 1988,USA	tx August 1980-December 1986; under 'active' follow up	185 (295)	Not given	No details given	'Subclinical NA' if self report of ever miss CyA or prednisolone in last month	self report questionnaire ('subclinical NA')
22. Frazier, 1994,USA	tx June 1987-October 1990	241 (500)	Mean (SD) 21(12) Range 3-46	58% male; Mean (SD) age 42(14) years; 59% cadaveric tx; 85% primary tx	Reported frequency of missing tablets at least 'some of the time' or 'occasionally or often'	Self report questionnaire (11 items rated on 5point scale very-never),
24. Sketris, 1994, Canada	'under active follow up'; on cyclosporin	361 (495)	61% of sample were over 36	60% male; Mean (SD) age 46(13) yrs; 71% cadaveric tx; Number of primary tx not given	More than once a week took an altered dose or took tablets 2hrs away from usual time or more than once a month chose not to take a dose	Self report questionnaire (6 items)
25. De Geest, 1995, Belgium	tx functioned at least 12 months; on cyclosporin, over 18 years old; speaks Dutch; literate	148 (150)	Median 55 Range 12-228	84% male; Mean (SD) age 46(12) years; Number of cadaveric and primary tx not given	Decision by researchers after subject reported missing several doses per month or having drug holidays in the last 12 months	Self report at interview to researcher and subsequent decision by researchers
26. Hilbrands, 1995, Holland	In a drug trial; primary or second cadavric tx, over 3 months post tx, no history of alcohol abuse or psychiatric history, good Dutch	113 (Not given)	Minimum 3	100% cadaveric; Number of males and primary tx and mean age not given	10% more or less tablets in the pill bottle than expected for at least 20% monitored 12 months	Monthly pill count in presence of the subject
27. Siegal, 1997, USA	on CyA; over 18 years old; functioning tx	519 (865)	Mean (SD) 38 (28) Range 1-270	56% male; Mean (SD) age 45(13) years 70% cadaveric tx; 85% primary tx	Self-report of 'forgetting', 'deciding not to take' or 'altering' a dose of medication in last 4 weeks	Self report questionnaire
28. Greenstein, 1998,USA	on CyA; over 18 years old; functioning tx	1402 (2500)	Mean (SAD) 38 (20)	49% male; Mean (SD) age 47 (13).years; 76% cadaveric tx; 88% primary tx	Self-report of ever missing a dose of immunosuppressants in the last 4 weeks	Self report questionnaire
29. Fernandez-Lucas, 1998, Spain[a]	Not given	1353 (not given)	Not given	Not given	Not given	Self report questionnaire
30. Raiz, 1999,USA	tx functioned at least 12 months; over 18 years old; primary tx	Not clear (712)	Mean 53	53% male; Mean age 50yrs; 75% cadaveric tx; 100% primary tx	In the last month self-report of, at least once, not taking tablets as prescribed or forgetting them	Self report questionnaire
31. Green, 1999,UK[b]	Not given	29 (not given)	Not given	No details given	Thought to be non-adherent by renal staff	Self report at interview with clinic nurse; opinion of nephrologist
32. Teixeira de Barros, 2000, Portugal	tx 1995-1997	113 (not given)	Not given	70% male; Mean age 44 years; Number of cadaveric and primary tx not given	In at least 2 interviews, the subject admitted missing one tablet or being 2.5 hours late taking their immunosuppressants in the last month	Self report at interview
33. Chisholm, 2000, USA	tx Febuary 1997- May 1998; over 18 years old; primary tx; had free medication for first year	18 (not given)	Range 0 - 12	83% male; Mean (SD) age 48(9) years; 67% cadaveric tx; 100% primary tx	Less than 80% of prescribed doses being refilled by pharmacy in at least one of the first 12 months post transplantation	Pharmacy refills
34. Sharma, 2000, India	Not given	152 (152)	Not given	No details given	'Confirmation' by relatives in patients with tx dysfunction and 'suspected' non-adherence	Clinical notes and interviews with patients and their relatives
35. Valentine, 2000,UK	Consecutive attenders to annual tx review clinic	83 (not given)	Range 12-300	60% male; Age range 21-72 years; Number of cadaveric or primary tx not given	Ever miss a tablet	Self report at structured interview with clinic nurse
36. Rodriguez, 1991, Peurto Rico	Not given	24 (not given)	Not given	63% male; mean age 29 years; 50% cadaveric tx; number of primary tx not given	'Poor attendance' to clinic or blood tests, delayed notifying staff of problems, poor adherence to diet or weight gain, poor adherence to medicine	Discussions amongst transplant staff

tx = transplant or transplantation; [a]data extracted from only the abstract only (published in Spanish); [b]conference abstract only

27. data from from this study also published in Siegel 1993

28. data from this study also published in Greenstein et al. 1997, Greenstein & Siegel 1998, Siegel & Greenstein 1999, Greenstein & Siegel 1999, Siegel et al. 1999

36.a study only of the correlates of non-adherence, not a study of the frequency of non-adherence

Table 5.2.2: Results of cross-sectional studies reporting the prevalence of non-adherence

First author, year of study	Minimum duration of function of transplants	Prevalence of NA	
		Number assessed as non-adherent / total number of transplants	%
Didlake, 1988	Functioning	36/192[1]	18.7
Frazier, 1994	At least 3 months	108/241 'at least some of the time' 11/241 'occasionally or very often'	44.8 4.5
Sketris, 1994	Not given	119/361	18.0
De Geest, 1995	At least 12 months	33/148	22.3
Hilbrands, 1995	At least 3 months	26/113 for cyclosporin 26/113 for prednisolone 15/113 for azathioprine	23.0 23.0 13.0
Siegel, 1997	At least 1 month	96/519	18.5
Greenstein, 1998	Not given	314/1402	22.4
Fernandez-Lucas, 1998	Not given	19/1353	1.4
Raiz , 1999	At least 12 months	Denominator not clear	25.9 'sometimes forget' 32.5 'not take as prescribed'
Green, 1999	Not given	1/29 by nephrologist 7/29 by nurse	3.5 24.1
Teixeira de Barros, 2000	Not given	18/113	16.8
Chisholm, 2000	At least 12 months	12/18	66.7
Sharma,. 2000	Not given	19/152	12.5
Valentine, 2000	Not given	22/83	26.0
Median (%)			18.6[2]

[1]although the papers reports that 185 subjects competed the study questionnaire, they give results for 192 subjects (156 adherent, 24 non-adherent 1-2 times a month and 12 non-adherent 3 or more times a month)

[2]using the 'at least sometimes' results for Frazier et al. 1994, the results for cyclosporin for Hilbrands et al. 1995, the 'sometimes forget' result for Raiz et al. 1999 and the estimate by the nurse for Green 1999.

Table 5.2.3b: Results of case series assessing the percentage of graft failures due to non-adherence

First author, year of study	Minimum duration of function prior to transplant failure	Graft failure including all causes of graft failure		Graft failure excluding death with function	
		Number of transplant failures in subjects with non-adherence / Total number of transplant failures	%	Number of transplant failures in subjects with non-adherence / Total number of transplant failures	%
Jeffery, 1988	Not given	3/138	2.2	3/107	2.8
Dunn, 1990	Functioned at least 24 months	16/58	27.6	16/45	35.6
Moosa, 1992	Not given	5/123	4.1	5/85	5.9
Hong, 1992	Functioned at least 12 months	11/83	13.2	11/71	15.5
Bergman, 1992	Functioned at least 6 months	17/59	28.8	15/32	46.9
Kim, 1994	Not given	6/112	5.4	6/59	10.2
Matas, 1994	Functioned at least 12 months	8/75	10.7	8/47	17.0
Shoskes, 1997	Not given (maximum function was 36 months)	11/92	12.0	11/76	14.4
Gaston, 1999	Functioned at least 6 months	64/185	34.6		
Issacs, 1999	Not given	84/2031	4.1		
Michelon, 1999	From day 0 (tx May 1977-December 1991) Functioned 6 months	11/135 11/71	8.1 15.5		
	From day 0 (tx January 1992-April 1995) Functioned at least 6 months	13/102 13/68	12.7 19.1		
	From day 0 (tx May 1995-June 1998) Functioned at least 6 months	24/148 23/117	16.2 19.7		
Moon et al. 2001	Not given	4/25	16.0		
Birkeland 2001	Functioned 'at hospital discharge'	3/10	33.3		
Median (%)			15.5[1]		16.0[2]

[1]using the values given for transplants that functioned at least six months in the study by Michelon et al 1999 for transplants performed between 1992-1998
[2]excluding death with function if data available

Table 5.2.3c: Results of cohort studies reporting the frequency of non-adherence and the impact of non-adherence on transplant failure

First author, year of study	Minimum duration of function of transplants	Cumulative incidence of non-adherence		Graft failure			
		Number assessed as non-adherent / total number of transplants	%	Number of transplant failures in non-adherent group/ Total number of transplant failures (%)	Number of transplant failures in non-adherent group / Number assessed as non-adherent (%)	Number of transplant failures in adherent group / Number assessed as adherent (%)	Relative risk of transplant failure in non-adherent group (incidence in non-adherent group/incidence in comparison group)
Didlake, 1988	Not given	25/531	4.7	15/126 (12.0)	15/25 (60.0)	111/506 (21.9)	2.7
Schweizer, 1990	Functioned at least 3 months (study A)	47/260	18.0	36/74(48.6)	36/50 (72.0)	38/213 (17.8)	4.1
	Functioned at least 3 months, baseline for study B	30/196	15.0	8/10 (80.0)	8/30 (26.7)	2/152* (1.3)	20.5
Lai, 1992	Not given	11/228	4.8	9/42 (24.1)	9/11 (81.8)	33/217 (15.2)	5,4
Butkus, 1992	Functioned at least 12 months	10/100	10.0	10/46 (21.7)	10/10 (100.0)	36/90 (40.0)	2,5
Kalil, 1992	Functioned at least 12 months	4/202	2.0	3/42 (7.1)	3/4 (75.0)	39/198 (19.7)	3.8
Kiley, 1993	Not given	56/105	53.3	11/14 (78.6)	11/56 (19.6)	3/49 (6.1)	3.2
Orifino, 1994	Functioned at least 3 months	16/394 'great transgressions' 59/394'incomplete adherence'	4.0 15.0	Not given[3]	Not given	Not given	N/a
De Geest 1995[1]	Functioning at least 12 months	n/a	n/a	2/4 (50.0)	2/33 (6.1)	2/115 (1.7)	3.6
Douglas, 1996	Functioned at least 3 months	60/126	47.6	26/37 (70.3)	26/60 (43.5)	11/66 (16.5)	2.6
Butkus, 2001	Not given	10/128	7.8	5/26 (19.2)	5/10 (50.0)	21/118 (17.8)	2.8
Nevins, 2001	Functioned at hospital discharge after transplantation	27/134 with a compliance rate of 90% or less	20.0	Not given[4]	Not given	Not given	N/a
Median (%)			15.0[2]	36.4			3.2[5]

[1] only included subjects with functioning transplants (see table 3) so calculated the prevalence of non-adherence but used data to estimate actuarial graft survival in non-adherent and adherent subjects

Schweizer, 1990 (unit stopped transplanting subjects who were non-adherent on dialysis after study A)

[2]using 'incomplete adherence' figure of 15.0 for Orifino et al. 1994

[3]raw data not given but reports 'a close correlation' between non-adherence and graft failure

[4]*report rejection rates in the best to the worst adherence quartiles were 0, 12, 18 and 29% respectively and graft loss was significantly increased in patients in the worst compared to the best adherence quartiles (raw data not given)*

[5]excluding risk increase of 20.5 from study B of Schweizer et al. 1990 since this appears to be an outlying value, maybe with a study biased by the results of study A having altered practice or having altered the estimation of non-adherence by transplant staff (median risk increase of 3.4 if this study is included)

Table 5.3a: Correlates of non-adherence to immunosuppressants in renal transplant recipients (from studies in tables 5.2)

Type of variables	Specific variables	Number of studies finding increase in non-adherence (direction of significance)	Number of non-significant studies	Significant studies[1]	Non-significant studies [1]
Socio-demographic	age	11 (all younger)	5	13a,14,15,10,23,24,27,28,29,30	13b,2,36,18,25,8
	sex	6 (3 male, 3 female)	10	13b,2,18,23,27,34	14,36,15,24,25,28,29,10,30
	ethnicity	5 (4 'non-white', 1 'white')	6	13a,13b,18,27,9	14,3,16,23,8,32
	lack of partner	4	1	23,25,29,32	36
	educational level	4 (2 lack college education, 2 had college education)	4	15,28,24,34	13,36,18,26
	pre-transplant non-adherence	3	2	13b,36,20	13a,21
	employment	2 (1 unemployed, 1 'white collar' job)	4	18,28	13,23,26,32
	live far from the renal unit	1	0	34	
	low income	1	1	14	36
	pre-emptive transplant	1	2	13c	13d,23
	social support	0	1		23
	not pay for medication	0	1		33
Medical	diabetic	1	0	28	
	abnormal liver function	0	1		14
Transplant related	more rejection episodes	7	0	13c,15,24,25,26,20,22	
	longer time since transplantation	5	3	24,28,29,10,33	15,23,25
	number of transplants	3 (2 primary transplant, 1 re-graft)	3	2,23,8	13e,26,28
	live transplant donor	1	7	28	13b,14,36,15,23,24,10
	degree of mis-match	0	1		15
	duration of prior dialysis	0	1		36
Medicines related	more side effects	3	0	13,14,24,28	
	more medicines	2	0	18,24	
	less knowledge about medicines or transplant	1	2	32	25,29
	higher dose of prednisolone	0	1		24
Symptoms related	more symptoms	1	1	32	25
	more distress from symptoms	1	1	32	25
Psychological factors	depression	4 (3 more depression, 1 less depression)	0	36,18,22,26	
	more pain	1	0	30	
	more anxiety	1	0	23	
	'severe mental disease'	1	0	23	
	avoidant coping style	1	0	23	
	less 'self-care'	1	0	25	
	more family problems	1	0	36	
	more behaviour problems	1	0	36	
	past history of substance mis-use	1	2	26	13,13
	past psychiatric history	0	4		13,13,13,13
Health beliefs	locus of control not internal	2	0	23,30	
	feel more 'bothered' by transplant	1	0	30	
	more perceived barriers to treatment	1	0	18	
	less belief that it is okay to delay medicines	1	0	28	
	more belief that medicines are active for over 24 hours	1	0	28	
	lower belief in importance of medicines	1	1	28	29

[1]ID numbers from tables 5.2a,b and c; For Didlake et al. 1998: 13a is 'major NA' versus all other subjects, 13b is 'minor NA' versus all others, 13c is 'major NA' and 13d is 'minor NA' versus matched controls 13e is 'major NA' versus 'minor NA'

6.0 Justification for, and design of, the current study

6.1 Justification for the current study

Research investigating adherence in renal transplant recipients to date has been limited by inconsistent, and sometimes a complete lack of, definitions of non-adherence. Furthermore definitions have not been related to clinically significant events. The method of measuring adherence has also been inconsistent. Many studies have relied on self-report, a method acknowledged to lack sensitivity. Few studies report the duration of transplantation for subjects in their sample. This is an important omission in view of a suggested link between adherence and time since transplantation. The current study was designed using a clearly defined population and accounts for non-responders and drop-outs. The study is the first to use electronic monitoring to obtain the prevalence of non-adherence in renal transplant recipients 6 months post-transplantation and is the first to describe the prevalence within a United Kingdom population. Attempts have been made to identify a clinically significant level of non-adherence. Non-adherence has been clearly defined using electronic monitoring and other measures have been validated against this.

Regarding the correlates of non-adherence, existing work has tended to focus on demographic and transplant-related factors that cannot be altered after transplantation. This has not led to the development of interventions to improve adherence. The current study concentrated on standardised assessment of health beliefs and mental state, both of which are potentially amenable to modification.

6.2 Objectives of the study

The main objectives of this exploratory study were to:-

1) compare candidate measures of adherence with the 'gold-standard' of electronic monitoring to find the most valid and feasible method to use in clinical practice.
2) use the identified measure of adherence to estimate the prevalence of non-adherence to immunosuppressants in renal transplant recipients at least six months post transplantation.
3) investigate major variables contributing to variation in adherence with the aim of identifying potentially modifiable factors strongly associated with non-adherence to immunosuppressants. Such factors could inform the design of an intervention to improve adherence that could be tested in a subsequent randomised controlled trial.

6.3 Overview of the study design

The study was a cross-sectional survey of 153 renal transplant recipients. Subjects were randomly selected from the population of patients 6 – 63 months post-transplantation in a regional transplant unit. Recruitment occurred in two waves in an attempt to keep the distribution of time since transplantation the same as that in the original population. Adherence to immunosuppressants was assessed in all subjects using self-report and clinician and interviewer ratings. In addition, a randomly selected sub-sample received electronic monitors. Data from the monitors was used as the 'gold-standard' measure of adherence in the current study. Data on factors potentially associated with adherence was collected by questionnaire, interview and notes review. The questionnaires included standardized measures of beliefs about immunosuppressant medication and the renal transplant (Beliefs About Medicines Questionnaire and Illness Perception Questionnaire).

7.0 Method: Procedure

7.1 Ethical approval

Ethical approval was granted from the South & West Multi-centre Research Ethics Committee and relevant Local Research Ethics Committees.

7.2 Description of the renal unit containing the study population

Subjects were recruited from the population of transplant recipients within the Wessex renal transplant unit (table 7.2), a medium sized unit within the United Kingdom. At the time of the study, the unit served an estimated population of 1.9 million residing in Hampshire, Wiltshire, West Sussex, the Isle of Wight and the Channel Islands. The area included urban and rural locations with a predominantly Caucasian population. The hospital dialysis programme served 249 patients. The continuous ambulatory peritoneal dialysis programme served 118 patients. At the time of the study the unit performed about 50 transplants each year but prior to reorganisation of regional boundaries in 1997, when the area served was larger, around 90 transplants a year were performed. At the time of the study, three transplant surgeons and four full-time and one part-time nephrologist were employed. Transplant recipients were typically followed up by surgeons for three months post-transplantation and then nephrologists took over their care. Medication was reviewed and adjustments made in the out-patient clinic but, due to financial constraints, prescribing remained the responsibility of the patient's General Practitioner.

Table 7.2: Characteristics of the unit's transplant population compared to the rest of the United Kingdom in 1998

	Portsmouth Unit adults only	**United Kingdom adults and children**
Number of kidney transplants	51	1613
Number (%) of cadaveric kidney only transplants	41 (80)	1369 (85)
Number (%) of live kidney transplants	10 (20)	244 (15)
% of recipients aged over 50 years	Not known	564 (35)
Number (%) of male recipients	31 (61)	Not available
Number (%) first grafts	44 (86)	1339 (83)
Number (%) adults with favourable matches (000, 100, 010 or 110 mis-match)	Not available	732 (52)
Number on waiting list	112	5693

7.3 Inclusion and exclusion criteria

All patients over the age of 18 years with a functioning renal transplant who received their current transplant 6-63 months prior to recruitment were eligible.

Exclusion criteria included:-

1) currently residing in the Channel Islands or outside the region served by the unit.
2) inability to give informed consent due to language or cognitive difficulties

The two subjects living on the Channel Islands were excluded due to practical difficulties in visiting them. Language was assessed by the researcher during telephone contact with the subject and cognitive impairment was indicated by a relative. Inability to read the questionnaires was not an exclusion criterion – in such cases the questionnaire was read out by a relative or by the researcher. To minimise contamination by a relative's view the researcher offered to read out the questionnaires if she was made aware of the difficulty prior to completion of the questionnaires.

7.4 Estimate of the confidence in the results given the expected sample size

The maximum number of subjects the researcher could recruit in the time available was estimated to be 170. Assuming a refusal rate of 10%, the study would include 153 subjects. With a true 'unknown prevalence' of 15% (based on previous studies) and a sample size of 153, the prevalence of non-adherence could be estimated to within ± 5.7 percentage points assuming that the prevalence of non-adherence in the sample is close to 15%. The most conservative estimate of precision comes with a population prevalence of 50%. If the true unknown prevalence was 50%, in a sample of 153, the true prevalence of non-adherence could be estimated to within ± 8.0 percentage points.

Using a 2-sided 5% t-test, a sample of 153 subjects, with 15% in one group (23 non-adherent subjects) and 85% in another group (130 adherent subjects), would allow identification of a standard deviation of 0.56 between scores on each scale of the Beliefs about Medicines Questionnaire with 80% power. If the scale scores were skewed, assuming a 95% efficiency of the t-test, a standard deviation of 0.60 could be detected. If the sample size was restricted to the 58 subjects with adherence measured by electronic monitoring, a standard deviation of 0.90 could be detected.

7.5 Identification of the sample

Recruitment was estimated to take 18 months. Subjects' duration of transplantation would increase during recruitment compared to when they were identified at the start of the study. For example, a subject 12 months post-transplantation at the time of identification, would be 30 months post-transplantation after 18 months of recruitment. Previous studies suggest time since transplantation affects adherence (table 5.3a). To obtain an accurate estimate of the prevalence of non-adherence in the population it was therefore important to keep the distribution of time since transplantation of the sample as similar as possible to that of the overall population. To minimise the differences in the time since transplantation between identification and recruitment, subjects were recruited in two waves following identification from the population at two census dates (months one and eleven of the study, figure 7.5).

A random numbers table was used to order all patients fulfilling inclusion criteria prior to the first census date of 1.1.00. The first 70 of these subjects were interviewed in the first wave of recruitment. Subjects assessed in the second wave of recruitment were identified from the eligible population on the second census date of 1.11.00. If a subject failed to meet inclusion criteria or was discovered to have an exclusion criterion at recruitment, they were replaced with the next subject from the randomly ordered list of the population.

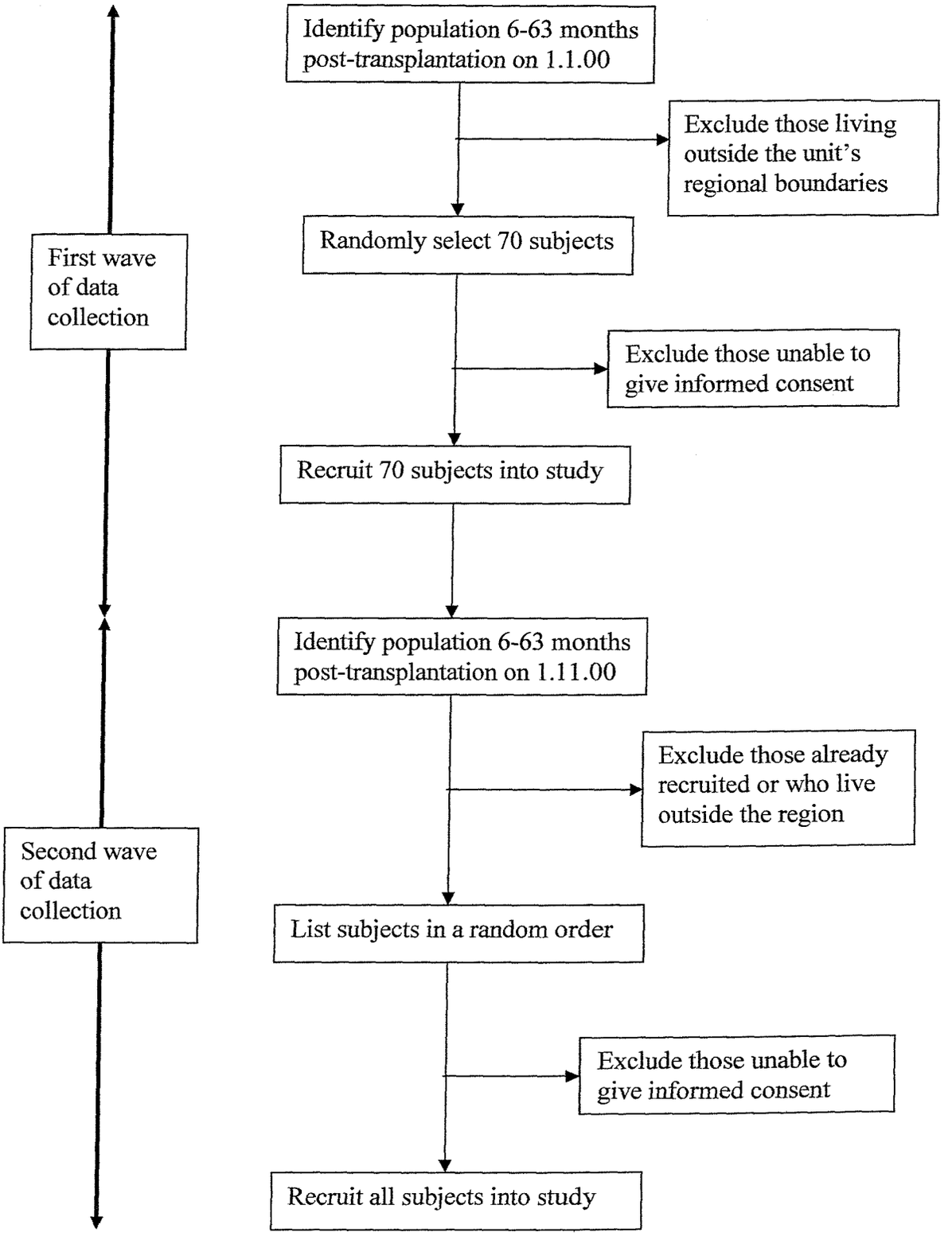
7.5.1 Identification of sub-sample to receive electronic monitoring

Due to financial constraints, not all subjects could receive the gold-standard measure of adherence (electronic monitoring). A random numbers table was used to select a sub-sample of 60 to receive electronic monitors. Stratification by year of transplant was used to attempt to keep the distribution of time since transplantation the same as in the unit's population. Thirty-one and 29 monitors were allocated in the first and second waves of recruitment respectively. If a subject was allocated to electronic monitoring but either refused this or was no longer receiving prednisolone, the monitor was offered to the next subject in the randomly ordered list.

7.6 Recruitment of subjects

A study information sheet and written consent form was posted to all eligible subjects. Non-responders received one written reminder and a telephone call to check if they required further information.

Figure 7.5: Identification and recruitment of subjects



7.7 Procedure for collecting data

Questionnaires were posted to subjects with a stamped addressed envelope (figure 7.7). Each subject was requested to complete the questionnaires with their own answers, not those of a relative or friend. The subject's General Practitioner was notified that they were taking part in the study and was asked +to return a record of the subject's current prescription. If this was not returned within two months, the researcher telephoned the practice staff.

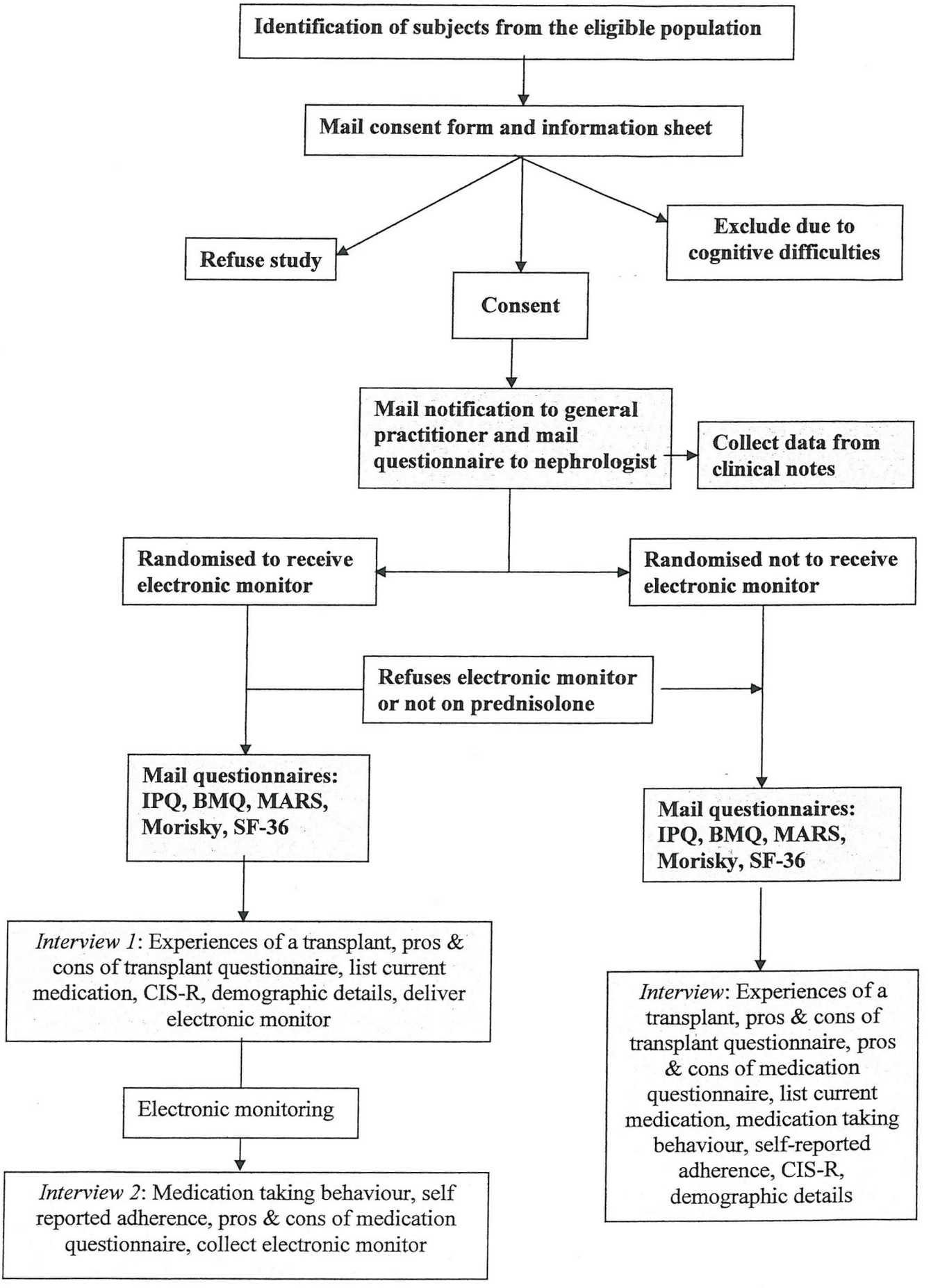
Interviews were conducted in the subject's home unless they requested to be seen in the renal unit. The interview started with an open question about the subject's experiences of a transplant (appendices A8 and A9). Following this, a semi-structured schedule was followed asking about pros and cons of the immunosuppressants and transplant, medical history and current medication. Then subjects completed the questionnaires relating to pros and cons of their transplant and medication. The subject was asked how they took their medicine at the most convenient point in the interview, usually after completing the forms listing pros and cons of a transplant. Finally the revised Clinical Interview Schedule was administered and demographic details were collected.

7.7.1 Procedure for delivering the electronic monitors

Electronic monitors were filled with six weeks' supply of the subject's prescription for prednisolone. If a subject had a dose requiring two strengths of tablet, a six week supply of the 5mg tablet was dispensed into the container and the subject was asked to take the 2.5mg tablet from their own supply. During conversations with the first 10 subjects receiving electronic monitors, it became apparent that some subjects worried that their medication would be altered by the monitor and thus refused electronic monitoring. Therefore each subject was given the opportunity to fill an empty container with prednisolone that they had in store at home. The dose of prednisolone was checked when telephoning the subject to arrange the interview. General Practitioners were telephoned to confirm the prescription. The purpose of the monitor was explained but the General Practitioner was told that the subject was not aware that the bottle monitored non-adherence.

Subjects were asked to take their prednisolone as usual, using the bottle supplied by the researchers. If asked, the researcher said that part of the study involved testing this new bottle. The interview was split into two parts (figure 7.7) occurring at delivery and collection of the monitor. Discussion of adherence occurred in the second interview to try to avoid biasing the subject's behaviour before it was measured.

Figure 7.7: Procedure



8.0 Method: Measures

Data were collected from clinical notes, questionnaires and research interviews. Four categories of variables were collected for each subject: adherence, medical, demographic and psychosocial (table 8.0).

Table 8.0: Collected variables

Adherence	Medical	Demographic	Psychosocial
Immunosuppressants Antihypertensives	Number of transplants Type of donor Duration of transplant Number of rejection episodes HLA match Duration of dialysis Donor diabetes or hypertension Duration of past transplants Disease severity Past medical details Functional health status Height & weight	Age Gender Marital status Employment status of self & partner Social class Ethnicity Level of education	Illness beliefs Medication beliefs Psychological illness Expectation of transplant

8.1 Measures of adherence to medication

Adherence to immunosuppressant medication was assessed in all subjects using:-

1) biochemical assay
2) self-report questionnaires
3) self-report at interview
4) clinician rating
5) interviewer rating

In a sub-sample of 60 subjects, adherence was also measured using electronic monitoring.

Electronic monitoring is thought to be the best reference measure of adherence (De Geest & Vanhaecke 1999; Burnier 2000; Schwed et al 1999; McGavock 1996; Farmer 1999) but would be relatively expensive to use in routine practice. Plasma monitoring of cyclosporin levels and a global impression are widely used to indicate non-adherence (Pruna & Fornairon 2000). A short, self-report measure would be cheap to introduce. An interviewer rating and self-report in the interview were also obtained.

8.1.1 Biochemical assay

Detection of cyclosporin in plasma confirms ingestion of the drug. The six cyclosporin levels prior to the interview assessment of adherence were documented from the routine levels taken in clinic. The range, the difference between the lowest and highest levels in the series, was thought to be a better indicator of poor adherence than a single low level by clinicians in the unit. The lowest level was also recorded since others report the use of this (Pruna & Fornairon 2000). Levels recorded as inaccurate in the notes were excluded since it was assumed that clinicians would not base estimates of adherence on levels they considered not to be true trough levels.

8.1.2 Self-report

Self-reported adherence to immunosuppressants was assessed at interview and using the Morisky questionnaire (Morisky et al. 1986) and Medication Adherence Rating Scale (MARS, Horne 1999, personal communication). The former is a four item categorical measure (appendix A3) requiring all items to be rated as either 'yes' or 'no'. It has an internal reliability (α) of 0.61 and, when used to assess adherence to anti-hypertensive medication, has a predictive validity in terms of predicting blood pressure at 5 years (positive predictive value 75%, negative predictive value 47%, Morisky et al. 1986).

Since adherence is likely to be dimensional rather than categorical, the MARS questionnaire was used. This includes five items, each rated from '1 = always' to '5 = never'. For the current study, one item was added asking about delay in taking medication because patients are often told to take their cyclosporin twelve hours apart (appendix A3). The MARS was not used as the sole self-report measure because, at the time of starting the project, validation data was not published. Pilot data indicates the questionnaire to have good internal reliability ($\alpha = 0.83$; Horne 1999, personal communication) and to correlate with the Morisky questionnaire in subjects with hypertension, non-insulin dependent diabetes and those on warfarin treatment (correlations of 0.62, 0.47 and 0.50 in respectively; all $p < 0.001$) although in patients with asthma the correlation was only 0.23 ($p < 0.05$).

8.1.3 Clinician rating

Nephrologists were asked to rate on a 5-point scale how often they thought subjects were late taking their immunosuppressants, how often they missed them completely and how often they missed clinic appointments. The scales were simple measures designed for this study that had not previously been validated. (appendix A10).

8.1.4 Interviewer rating

After discussing how subjects took their immunosuppressants, the interviewer rated her own assessment of patients' adherence to the timing and dosage of the medication on the same scales as used by clinicians (Appendices A8 and A9).

8.1.5 Electronic monitoring

Each electronic monitor was a lid and a 60ml opaque plastic bottle filled with a six week supply of prednisolone. Within the lid was a microchip containing a device capable of recording the date and time of each opening of the container. A printout of data was obtained after downloading of information from the lids by the manufacturer, Aardex.

The initial plan was to monitor adherence to cyclosporin, the main immunosuppressant used in the renal unit. However this was not feasible as cyclosporin capsules were too large to fit into the monitors, so adherence to prednisolone was monitored instead. Of the three studies reporting prevalence of non-adherence to different immunosuppressants, two report an identical (Hilbrands et al. 1995) or similar (Feldman et al. 1999) frequency of non-adherence to cyclosporin and prednisolone and one reports a higher frequency of non-adherence to cyclosporin (Siegel & Greenstein 1997). This suggests that adherence to prednisolone is not worse than adherence to cyclosporin thus estimates of non-adherence to cyclosporin are unlikely to be overestimated if based on assessments of adherence to prednisolone. Cyclosporin is prescribed twice daily and prednisolone is prescribed daily or on alternate days. However it was assumed that subjects would take all their morning medications together, so the time of taking prednisolone would be the same as that for cyclosporin.

8.1.6 Interpretation of data from electronic monitors to obtain measures of adherence

Assessment of adherence using electronic monitors relies on the assumption that a tablet was taken when the bottle was opened. If an opening did not occur the subject definitely did not take prednisolone from the electronic monitor (although they could have taken it from an alternative supply). When extra openings occurred, it was not possible to differentiate between openings made in error and extra dosing.

Two assumptions, that gave a conservative estimate of non-adherence, were made about the relationship between bottle opening and prednisolone ingestion:-

1) Days where an expected opening did not occur (missed days) were counted as missed doses. If two openings occurred on one day, it was assumed that one occurred in error and the dose used to identify the timing of dose ingestion was the opening closest to that subject's usual time of opening the bottle.
2) The number of monitored days were assumed to be those days lying between the first and last openings of the bottle. If the subject told the researcher that they had not used the container for a specified period, such as if they were admitted to hospital, this time was excluded. If several days without an opening occurred between delivery of the bottle and the first opening, subjects were assumed not to have started to use the bottle immediately. Gaps occurring between the first and last openings were interpreted as missed doses.

Three continuous measures of non-adherence were calculated from electronic monitoring data as shown below.

$$\textbf{Percentage missed doses} = \frac{\text{Number of days without an opening}}{\text{Number of days where prednisolone was prescribed}} \times 100$$

Longest delay in dosing

a) for daily dosing = Maximum number of hours between 2 openings – 24 hours
b) for alternate day dosing = Maximum number of hours between 2 openings – 48 hours

Variability of dose timing

a) for daily dosing = standard deviation of inter-dose intervals under 48 hours
b) for alternate day dosing = standard deviation of inter-dose intervals under 72 hours

8.2 Identifying the level of non-adherence used to define a subject as non-adherent

8.2.1 Expert consensus

Although electronic monitors provide continuously distributed data, the clinically important issue is the level of non-adherence that results in an increased risk of graft failure. This level is not known in relation to immunosuppressants and renal transplant failure. The half-life of cyclosporin could provide some information about the rate of decline of plasma levels if consecutive doses were missed. However pharmacokinetics vary between individuals and it is not known how plasma levels relate to clinical efficacy if the drug is taken erratically.

In an attempt to estimate a clinically important number of missed doses to define non-adherence, renal staff were surveyed to try to identify an 'expert consensus'. The five nephrologists and three surgeons in the renal unit were asked to anonymously estimate the number of consecutive and sporadic doses of immunosuppressants that they thought an average patient 6-63 months post-transplant could miss without damaging their transplant. Unfortunately there was little agreement between staff (table 8.2.1).

Table 8.2.1: Clinicians' estimates of the number of missed tablets that affect clinical outcome

		All clinicians (n = 7)	**Nephrologists (n = 4)**	**Transplant surgeons (n = 3)**
Number of sporadic doses that could be missed in one year without transplant damage	median (IQR)	24 (4-100)	65 (26-175)	4 (1-12)
	range	1 - 200	24 - 200	1 - 12
Number of sporadic doses that could be missed in one week without transplant damage	median (IQR)	2 (2-4)	3 (1-5)	1 (1-2)
	range	1 - 5	1 - 5	1 - 2
Number of consecutive doses that could be missed without transplant damage	median (IQR)	2 (2-4)	4 (2-12)	2 (0-2)
	range	0 - 14	2 - 14	0 - 2

8.2.2 Choice of a categorical definition of non-adherence instead of using a continuous measure

To investigate factors associated with non-adherence, either a categorical definition of non-adherence was needed or adherence had to be treated as a continuous variable. The lack of previous studies and the poor consensus from the survey of staff meant that a categorical definition of non-adherence had not be found for a level known, or thought, to relate to an increased risk of transplant rejection. However a continuous distribution of adherence was not hypothesised to be useful when used to look for correlates of clinically significant non-adherence. The distribution of adherence was expected to be highly skewed in the current study, as has occurred in previous studies of adherence in renal transplant recipients (e.g. Greenstein & Siegal 1998). Thus if a continuous measure was used, most of the variation in adherence associated with other variables would be related to minor changes in adherence. Therefore to detect factors associated with higher degrees of non-adherence, a categorical definition was hypothesised to be needed.

After inspecting the distribution of adherence in the current study, to confirm a highly skewed distribution, a conservative level of missing 20% or more days medication was chosen to categorise subjects into those who were non-adherent compared to those who were adherent according to missed medication.

Although cyclosporin is usually prescribed twice daily with each dose to be taken twelve hours apart, there is no good research evidence to identify the degree of timing variation likely to lead to increased risk of graft failure. In one study, clinicians' median estimate of dosing variation likely to increase the risk of rejection was two hours (Hathaway et al 1999).

In the current study, a standard deviation of inter-dose intervals of two hours would have classified 39 (67%) subjects as non-adherent. This value is much larger than levels of non-adherence quoted in the literature and is much larger than the 7 (12%) subjects in this study classed as non-adherent according to the measure of missing at least 20% days medication (section 11.8). Thus this cut-off seemed too low to define non-adherence. Therefore a standard deviation of six hours or more (corresponding to taking the medication outside a twelve hour time period 32% of the time) was used to indicate non-adherence to dose timing.

8.3 Measures of medical factors

Most disease factors (table 8.0) were assessed from clinical notes. Co-morbidity was assessed at interview using severity section items to be included on the national renal transplant database (UKT, personal communication). Functional health status was assessed using the Short Form 36 from the Medical Outcomes Survey Short Form (SF36, Ware & Sherbourne 1992). Subjects were reminded that the questionnaire asked about their health overall, not just their transplant.

8.3.1 Medical Outcome Survey Short Form (SF36)

The SF36 (Ware & Sherbourne 1992) is a widely used self-report measure for adults of physical and emotional health. It was designed from the Medical Outcomes Survey, a large American multi-centre primary care study of health status. It has been adapted for British use by minor alterations to the wording of some items. The questionnaire contains 36 items (appendix A5) that relate to 8 health concepts forming 8 scales (physical functioning, social functioning, role limitations due to poor physical or mental health, pain, general mental health, vitality and an overall rating of health). Items are coded so that a high score indicates better health status (less disability). Scale scores are obtained by summing relevant items. To

aid comparison of the severity of disability on different scales, scores are transformed linearly to percentages as shown in the equation below. Higher scores indicate less disability (better health).

$$\text{Transformation: Score (0-100)} = \frac{\text{(actual score - lowest possible score)}}{\text{(highest possible score - lowest possible score)}} \times 100$$

The scales have good internal reliability (α is above 0.79 on all scales and above 0.85 on all but two scales; Jenkinson et al. 1993). The SF36 also has good construct validity as indicated by the pattern of responses on the SF36 distinguishing physical and emotional illness (McHorney et al. 1993).

The SF36 was chosen for this study since it is short and acceptable to patients, it distinguishes subjects with a wide range of disability, provides a multi dimensional measure of health status, has been shown to be sensitive to changes in health status over time and has normative data for a British population (Jenkinson et al. 1993). Scores have also been described in renal transplant populations (Fujisawa et al. 2000; Manu et al. 2001).

8.4 Measures of socio-demographic variables

Age and sex of subjects were recorded from clinical notes. Marital status, employment of the subject and their partner, self-reported ethnicity, years of full-time education and highest level of academic attainment were recorded during the interview (appendices A8 and A9). Social class was calculated from the patient's occupation using the Standard Occupational Classification (Office of Population Censuses and Surveys 1991).

8.5 Measures of psychosocial variables

Questionnaires used to measure psychosocial factors are listed in table 8.5.

Table 8.5: Questionnaires used to measure psychosocial variables

Psychosocial variable	**Questionnaire**
Medication beliefs	Beliefs About Medicines Questionnaire Medicine Pros & Cons Questionnaire
Illness beliefs	Illness Perception Questionnaire Transplant Pros & Cons Questionnaire
Social support	Short version of the Significant Others Scale
Psychological illness	Revised Clinical Interview Schedule

8.5.1 Beliefs about Medicines Questionnaire (BMQ)

Medication beliefs were assessed using the Beliefs about Medicines Questionnaire (BMQ, Horne et al. 1999). Subjects rate their degree of agreement with 18 statements about medicines on five point scales (table 8.4.1; appendix A2). The first eight items relate to common beliefs about medicines in general (general BMQ items) and the next ten relate to beliefs about a specific medicine that is named by the researcher (specific BMQ items). The general items comprise two four item scales assessing beliefs that medicines in general cause harm (harm scale) and are overused by doctors (overuse scale). The specific items comprise two five-item scales that assess beliefs about the necessity for (necessity scale), and concerns with (concern scale), the specified medicine.

To develop the BMQ, statements about medicines were identified from a literature review of lay beliefs about medicines and from interviews with patients with renal or cardiac disease (Horne et al. 1999). The questionnaire's psychometric properties were tested in patients with predominantly chronic medical conditions, including those with end-stage renal disease. Items in all scales had a test-retest reliability of between 0.60 and 0.78 and an internal consistency (α) of between 0.51 and 0.86 (Horne et al. 1999).

Table 8.5.1: Items on the Beliefs about Medicines Questionnaire

Section	Scale	Items in the scale
General	Overuse	Doctors use too many medicines Doctors place too much trust on medicines If doctors had more time with patients they would prescribe fewer medicines Natural remedies are safer than medicines
	Harm	Medicines do more harm than good People who take medicines should stop their treatment for a while every now and then Most medicines are addictive All medicines are poisons
Specific	Necessity	My health at present depends on my medicines My life would be impossible without my medicines Without my medicines I would be very ill My health in the future depends on my medicines My medicines protect me from becoming worse
	Concerns	Having to take medicines worries me I sometimes worry about long term effects of my medicines I sometimes worry about becoming too dependent on my medicines My medicines are a mystery to me My medicines disrupt my life

The BMQ was chosen for this study since it was developed in patients with a wide range of chronic illnesses including end-stage renal disease. Furthermore the specific section allows for assessment of beliefs about a specified medication and scores have been shown to correlate to self-reported adherence to medication in other disease areas (Horne et al. 1999).

For this study the necessity scale item 'my medicines protect me from becoming worse' was changed to 'my medicines protect me from my transplant failing'. The term 'anti-rejection medicines' was used in the specific section of the BMQ. These medicines were grouped together rather than giving separate questions relating to each anti-rejection medicine since pilot work indicated that patients saw all their anti-rejection medicines as similar. Also repeated questions about different medicines were thought likely to be tiring for subjects who may then answer items in the same way, regardless of differential beliefs. To enable direct comparison with electronic monitoring of adherence, subjects receiving electronic monitors were also given BMQ specific items relating specifically to prednisolone. An unpublished study of adherence in renal transplant recipients using the BMQ was obtained to look at rewording of items for a transplant population (Stabler 1999, personal communication) and items for the study were checked by one of the developers of the original questionnaires (RH) to minimise the risk of an inadvertent change in meaning of an item.

8.5.2 Illness Perception Questionnaire (IPQ)

Illness beliefs were measured using the Illness Perception Questionnaire (IPQ, Weinman et al. 1996). This 38 item self-report measure is derived from Leventhal's Self-Regulatory Model of how people understand illness. It contains five scales reflecting general themes of beliefs that people have about their illness (table 8.4.2; appendix A1). The identity sub-scale is a checklist of twelve symptoms. Items from the causal (10 items), time-line (3 items), consequences (7 items) and control/cure (6 items) scales are rated on five point scales ranging from '1 = strongly agree' to '5 = strongly disagree'. The internal consistency of the scales are good (α ranges from 0.73 to 0.82; Weinman et al. 1996).

The IPQ was chosen for this study since it was developed and validated in patients with a wide range of chronic conditions, including end-stage renal disease. The questionnaire was designed to allow addition of items thought to be relevant in the population being studied and it allows for altering 'my illness' to a specified condition. A renal version replacing 'my illness' with 'my renal disease' was reworded for this study so that it applied to a transplant population (appendix A1). A previous, unpublished study (Stabler 1999, personal

communication) using the IPQ in a study of adherence in renal transplant recipients was obtained to look at rewording of items. Finally the reworded items were checked by one of the developers of the original questionnaires (RH) to minimise the risk of an inadvertent change in meaning of an item. Also, as recommended (by RH), the item 'my transplant has had major consequences on my life' was changed to 'my transplant has had major negative consequences on my life'.

Table 8.5.2: Scales on the Illness Perception Questionnaire

Scale	**Type of beliefs assessed by the scale**	**Scale items**
Identity	symptoms of the illness	Pain, Nausea, Breathlessness, Weight loss, Fatigue, Stiff joints, Sore eyes, Headaches, Upset stomach, Sleep difficulties, Dizziness and Loss of strength
Cause	causes of the illness	A germ or virus caused my illness Diet played a major role in causing my illness Pollution of the environment caused my illness My illness is hereditary – it runs in my family It was by chance that I developed my illness Stress was a major factor causing my illness My illness is largely due to my own behaviour Other people played a large role in causing my illness My illness was caused by poor medical care My state of mind played a large part in causing my illness
Time-line	how long the illness will last	My illness will last a short time My illness is likely to be permanent rather than temporary My illness will last for a long time
Consequences	severity and possible negative effects of the illness	My illness is a serious condition My illness has had major consequences on my life My illness has become easier to live with My illness has not had much effect on my life My illness has strongly affected the way others see me My illness has serious economic and financial consequences My illness has strongly affected the way I see myself as a person
Control-cure	treatability of the illness	My illness will improve with time There is a lot which I can do to control my symptoms There is very little that can be done to improve my illness My treatment will be effective in curing my illness Recovery from my illness is largely a matter of chance or fate What I do can determine whether my illness gets better or worse

8.5.3 Additions to the Beliefs about Medicines and Illness Perception Questionnaires

Ongoing testing of the BMQ and IPQ suggests that additional constructs are used by people when thinking about their illness and medication. (Horne 1999, personal communication). A benefit scale in the general section of the BMQ and an emotions scale in the IPQ were added for this study from new versions of the questionnaires (table 8.4.3; appendix A1). Items thought to particularly relate to transplants were also added. At the suggestion of one of the developers of the original questionnaires (RH) two items were added to the concerns scale of the BMQ and three items were added to the consequences scale of the IPQ.

Early in the main study, in contrast to the pilot study, several subjects' comments reflected different beliefs regarding their anti-rejection medicines as a whole and prednisolone specifically. The reference measure of adherence (electronic monitoring) only recorded adherence to prednisolone so subjects were given a BMQ specific section relating to prednisolone alone as well as to anti-rejection medicines as a group.

Table 8.5.3: Items added to the IPQ and BMQ

Questionnaire	Section and/or Scale	Added items
BMQ	General, Benefit	Medicines help people live better lives In the future medicines will be developed to cure most diseases In most cases the benefits of medicines outweigh the risks Medicines help many people to live longer
	Specific, Concerns	I sometimes worry about changes in my appearance caused by my anti-rejection medicines I have experienced unpleasant side effects due to my anti-rejection medicines I have been given enough information about how to take my anti-rejection medicines
IPQ	Emotions	Symptoms related to my transplant are distressing to me I get depressed when I think about my transplant My transplant makes me feel angry When I think about my transplant I get upset My transplant does not worry me Having a transplant makes me feel anxious I worry a lot about my transplant My transplant makes me feel afraid
	Consequences	My transplant causes difficulties for those around me My transplant has a negative impact on me My transplant is not a problem for me

8.5.4 Development of Pros and Cons Questionnaires for a Renal Transplant and Immunosuppressants

In pilot interviews, the researcher asked renal transplant recipients about problems with, and benefits from, their transplant and immunosuppressants. Nephrologists were asked about problems and benefits they thought patients had. For the pros of a transplant questionnaire, all the stated benefits of a transplant were put together to create a form asking subjects how much better each item was for them compared to when they had been on dialysis (appendix A6). Subjects who had not been dialysed were asked to rate these items compared to what they thought dialysis would have been like. All the problems of a transplant were put together to create a form asking subjects how worried or concerned they were about each item.

For the pros and cons of immunosuppressants questionnaire disadvantages of anti-rejection medication given by subjects were added to side effects of prednisolone, cyclosporin and azathioprine in the British National Formulary (1999) to create a form asking subjects how worried they were about each side effect (appendix A7). Reasons for taking immunosuppressants given by pilot subjects were listed to create a pros of immunosuppressants section.

Each item was rated on a four point scale from '1 = not at all' to '4 = always'. Subjects were asked to mark a not applicable response if they had not experienced the item in relation to their transplant or medication. The total score on each scale indicated an overall experience of the benefits and problems associated with a renal transplant or immunosuppressants.

8.5.5 Revised Clinical Interview Schedule (CIS-R)

The revised Clinical Interview Schedule (CIS-R, Lewis et al. 1992) was used to assess psychiatric symptoms. Separate sections cover somatic symptoms, fatigue, concentration and memory, sleep, irritability, worry about physical health, worry, anxiety, phobias, panic, compulsions and obsessions and there are two sections covering depression. If a subject responds positively to mandatory 'probe' questions starting each section, then further specified questions are asked to ascertain the nature and severity of the symptom. An overall score between 0 and 57 indicates the degree of psychological distress in the preceding seven days. The current study used a score of 12 or more to define a case as is recommended in the general population. In the worry about physical health section subjects were not asked whether they thought they had a serious illness. This does not affect scoring and is recommended if subjects being studied have a significant physical illness. A standardised

algorithm (Meltzer et al. 1995) is available convert responses to diagnoses according to the 10th International Classification of Diseases (1992).

The CIS-R has good inter-item ($\alpha = 0.82$) and test-retest (correlation 0.90) reliability (Lewis et al. 1992). The total score has been shown to be valid compared to psychiatrists' impressions of illness severity (correlation 0.77). Although designed for use by trained lay interviewers, results are not significantly different whether the interviewer is a psychiatrist or a lay person (correlation 0.70). In the current study, the interview was administered by the researcher who is a psychiatrist and who was trained in administration of the CIS-R.

The CIS-R was used in the current study since it was developed in a British primary care population of a similar age (mean 39 years) to that predicted for subjects in this study and with levels of psychiatric disorder similar to that found in medical out-patient populations (Lewis et al. 1992). It removes the need for clinical judgements about a diagnosis, is briefer than other standardised interviews and allows both dimensional and categorical descriptions of mental illness. Disadvantages of the CIS-R for this study relate to the population from which reliability data were derived (Lewis et al. 1992). The study had a response rate of only 10%, included a relatively large proportion of subjects (7%) who had previously seen a psychiatrist and was undertaken in a deprived inner city area unlike the majority of the catchment area of the Wessex renal unit.

A limitation of the CIS-R is that it does not assess symptoms of eating disorders. Strict dietary control on dialysis is followed by changing dietary advice and treatment with prednisolone after transplantation. Patients are initially instructed to eat a high calorific diet and are later asked to return to 'a healthy diet'. These demands of transplantation and the recognised problem of obesity following transplantation led to the addition of bulimia items from the Schedule of Clinical Assessment in Neuropsychiatry (SCAN) to the end of the CIS-R to elicit concerns about eating in this study.

8.5.6 Short version of the Significant Others Scale

Social support was measured using the eight item short version of the Significant Others Scale (Power et al. 1988). This assesses received (actual) and desired (ideal) levels of emotional and practical support. Items are rated on a seven point scale from '1 = never' to '7 = always' and summed to give a measure of both emotional and practical support and the discrepancy of what is received to what would be desired (appendix A4).

Previous studies relating social support to immunosuppressant adherence (Kiley et al 1993; Frazier et al. 1994; Rogers 1987; Dew et al. 1996) have used different measures of social support. Thus there is no measure that is consistent across previous research. The main variables assessed in this study were health and medication beliefs therefore, to avoid overburdening the subjects and thereby risking non-completion, a brief measure of social support was used. However the questionnaire has not previously been used in renal disease or transplant recipients.

8.6 Pilot work

Measures were piloted in four subjects; two transplanted within the last six months and two transplanted more than 63 months previously. The wording of questionnaires, consent form and information sheet were tested to ensure that subjects understood them. Pilot interviews were used to familiarise the researcher with the interview and identify items for the pros and cons of a transplant and immunosuppressants questionnaires (section 8.4.4). Pilot work also allowed testing of the procedures used in the main study.

8.7 Additions to measures during the first wave of recruitment

During the first wave of interviews subjects often said that they viewed their immunosuppressants as more important than their other long-term medicines. It was hypothesised that perceived importance may affect adherence. Therefore subjects were asked to estimate the importance of their anti-rejection medicine in keeping their transplant working and to estimate the number of doses that could be missed before the transplant was damaged. To test whether the same subject could hold different beliefs about different medications, all subjects were asked the same questions and given the self-reported adherence questionnaires relating to their anti-hypertensive medication. If a subject was not on anti-hypertensives, they were asked the questions in relation to their prophylactic antibiotics or other long-term medication.

Also during the first wave of interviews, it was noted that many subjects did not appear comfortable when the second interview immediately started with a discussion of adherence. Therefore subjects were asked about the use of reminders for medication prior to questions about adherence.

9.0 Methods: data analysis

The first phase of analysis entailed describing the characteristics of the sample and the distribution of measures of adherence and candidate independent variables. Categorical variables with responses in only a few categories were transformed to binary coding. The mean (SD) of normally distributed, and the median (IQR) of skewed, continuously distributed variables were calculated. For categorical variables the number and percentage of subjects in each sub-group were calculated. Exact tests of significance were used. Data were analysed using the Statistical Package for the Social Sciences (version 9.5; SPSS Inc., 444 North Michigan Avenue, Chicago, Illinois.).

9.1 Identification of the best measure of adherence used in the whole sample

As described in section 8.1.7, the criteria used to define subjects as non-adherent from electronic monitoring were:-

- Missing medication on at least 20% days (non-adherence as 'missed medication')
- Having a standard deviation of inter-dose intervals of 6 hours or more (non-adherence as 'erratic timing')

Analyses were performed separately on these two types of non-adherence.

The sensitivity, specificity, positive and negative predictive values, positive likelihood ratio and mis-classification rate (see appendix B1) of the other measures were calculated using electronic monitoring as the gold standard. Receiver-operating curves (ROC curve) were used to identify the cut-off point on each measure that maximised the area under the curve.

The aim of identifying non-adherence is to detect patients whose risk of graft loss could be reduced by intervening to improve their adherence. The consequence of failing to detect non-adherence is severe (graft loss), so measures to detect non-adherence should be highly sensitive. However since non-adherence is likely to be relatively uncommon, increasing the sensitivity, and thus decreasing the specificity, of a measure will result in many patients being incorrectly identified as a non-adherent. An intervention targeted to patients classified as non-adherent will thus lead to many patients receiving unnecessary intervention. Although intervention is unlikely to be harmful, unnecessary intervention will add to the cost. The aim was to find a measure that had at least a sensitivity of 80% and a positive predictive value of 70%. These arbitrary figures were chosen to lead to an acceptable number of non-adherent 'cases' being missed, whilst targeting an intervention to a feasible number of patients.

9.2 Prevalence and correlates of non-adherence

The prevalence of non-adherence in the sub-sample receiving electronic monitoring was described directly. Adherence is likely to be continuously distributed but it was thought more important to identify correlates of clinically significant non-adherence than of non-adherence per se. Therefore logistic, rather than linear, regression was used to identify factors associated with non-adherence.

The large number of variables measured (appendix A11) increases the risk of a type one error (false positives). Therefore the first stage of model selection involved bivariate analyses with adherence to identify variables that were likely to have the largest impact on adherence ($p \leq 0.1$ significance). For continuously distributed variables an independent t-test or Mann-Whitney U test was used according to whether the variable had a parametric or non-parametric distribution. For categorical variables a Chi-squared test was performed. Significance was assessed using the exact two-sided p value for the test statistic. Interpretation of logistic regression models is difficult if covariates are strongly related. The exploratory nature of this study meant that many variables were measuring a similar concept and so might be strongly related. To test for such relationships, variables selected using bivariate analyses were compared using a Mann-Whitney U test, a Chi-squared test or Spearman's correlation coefficient. A significance of $p \leq 0.05$ or a significant correlation greater than 0.5 was used to define a 'strong' relationship.

Analyses of correlates of adherence were restricted to subjects with data from electronic monitors (see sections 11.6 and 11.7). This was a small sample for regression modeling ($n = 58$). A forward stepwise model was selected to provide a conservative estimate of variables that were associated with non-adherence. Variables were selected using the score statistic and retained if they remained significant using the likelihood ratio test. The model thus obtained was used to predict the level of adherence in patient groups with differing levels of modifiable factors such as belief in the need for medication.

The criteria from electronic monitoring used to classify a subject as non-adherent could not be related to known clinically important levels of non-adherence (as explained in section 8.1.7). A sensitivity analysis was performed to explore the strength of the relationship with adherence for variables identified in this study when different levels of adherence were used to classify a subject as non-adherent.

10.0 Results: description of the sample

The sample is described in this chapter to enable comparison with the population from which the sample was selected and with populations in other transplant units. Data related to the measurement of adherence and the prevalence of non-adherence are presented in chapter 11. Variables which may be associated with adherence are described in chapter 12 and the analysis identifying the major factors associated with non-adherence in this sample is presented in chapters 13 and 14. Analysis exploring the relationship of beliefs regarding the need for medication and adherence, and factors associated with these beliefs are explored in chapter 15.

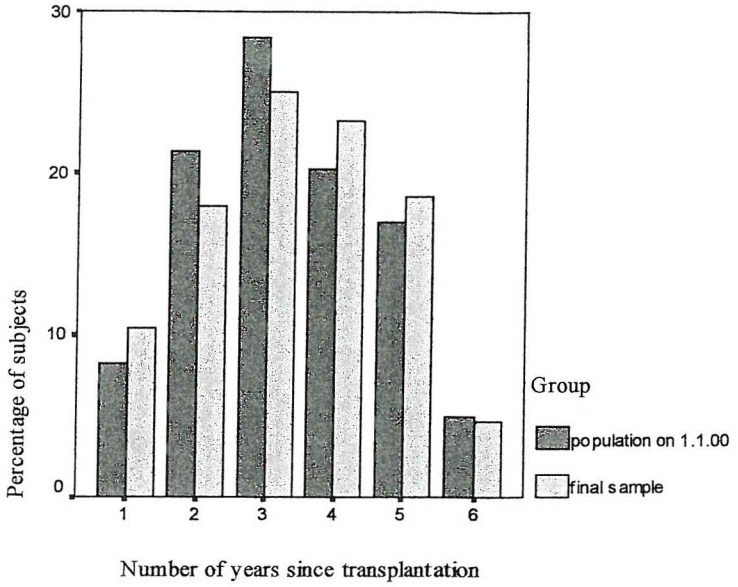
10.1 Characteristics of the study sample compared to the eligible population at the start of the study

Two hundred and seventy-seven subjects had been transplanted in the Wessex renal transplant unit 6-63 months prior to the start of the study. Thirty-eight (17%) had since died, 25 (11%) with a functioning graft. A further 31 (14%) had experienced transplant failure. Twenty-two subjects were excluded because their care had been transferred to an adjacent unit following re-organisation of regional boundaries (n = 20) or because they lived on the Channel Islands (n = 2). This left 186 eligible subjects at the start of the first wave of recruitment (table 10.1). The final sample of 172 subjects recruited from the population identified at the two census dates (1.1.00, 1.11.00, figure 7.5) was representative of the eligible population at the start of the study in terms of age, sex, type of transplant, number of re-grafts and duration of functioning of the current transplant (table 10.1, figure 10.1).

Table 10.1: Characteristics of the final sample recruited from two census dates compared to the population thought to be eligible at the first census date at the start of the study

	Sample	**Eligible population on 1.1.00**
Number of subjects	172	186
Mean age (SD) in years	48.1 (13.1)	48.3 (13.3)
Age range in years	20.4 – 77.5	19.4 – 76.6
Number (%) Caucasian	171 (99.3)	Not available
Number (%) male	105 (61.0)	117 (62.9)
Number (%) cadaveric grafts	151 (87.8)	163 (87.6)
Number (%) primary grafts	141 (82.0)	152 (81.7)
Mean (SD) number of months since transplantation	34.2 (16.0)	33.5 (15.7)
Range of months since transplantation	5.4 – 67.1	6.1 – 62.8

Figure 10.1: Distribution of time since transplantation for the sample and the eligible population at the start of



10.2 Recruitment to the study

From the 172 subjects asked to take part in the study, 19 (11%) refused and 153 (89%) consented although only 142 (83%) agreed to all parts of the study (figure 10.2, table 10.2a). Consultants failed to return assessments of adherence for three subjects and six General Practitioners failed to respond (table 10.2a).

Table 10.2a: Number of subjects with available data

	Number of subjects	
	Consenting to this part of the study	Data available
Agreed to at least some of the study	153	153
Consultant rating	153	150
General Practitioner report of current medication	152	146
Questionnaires	151	151
Interview	147	147*

* second interview data is only available for 146 because one subject died between the first and second interviews

There were no significant differences between the subjects consenting to the study and those who refused in terms of age, sex, type of transplant, number of transplants, time since the current transplant or consultant (table 10.2b).

Table 10.2b: Comparison of those who consented to the study and those who refused

Variable	Consented to study (n = 153)	Refused study (n = 19)	Test statistic (p value)
Number (%) male	94 (62)	11 (58)	0.09[1] (0.81)
Number (%) cadaveric transplants	134 (88)	17 (90)	0.06[1] (1.00)
Number (%) primary transplants	125 (82)	16 (84)	0.07[1] (1.00)
Number (%) with consultant 1	76 (50)	5 (26)	3.70[1] (0.09)
Mean age (SD)	48.2 (13)	46.9 (15)	0.34[2] (0.74)
Mean number of months since current transplant (SD)	34.7 (16)	31.4 (18)	0.79[2] (0.44)

[1]Chi squared statistic
[2]t statistic

10.2.1 Prescription of prednisolone

Prescription data were not available for 4/19 subjects refusing consent so comparison of subjects prescribed prednisolone with those withdrawn from the drug was carried out on 168/172 eligible subjects. Prescription of prednisolone did not affect consent. Age, type or duration of transplant and number of rejection episodes with the current transplant did not differ between subjects prescribed prednisolone and those withdrawn from steroids. However men were significantly more likely to remain on prednisolone ($X^2 = 7.14$, $p = 0.01$; table 10.2.1) and those on prednisolone were more likely to be under the care of consultant 1 ($X^2 = 24.08$, $p < 0.001$; table 10.2.1). There was no relationship between the consultant and gender of the subject.

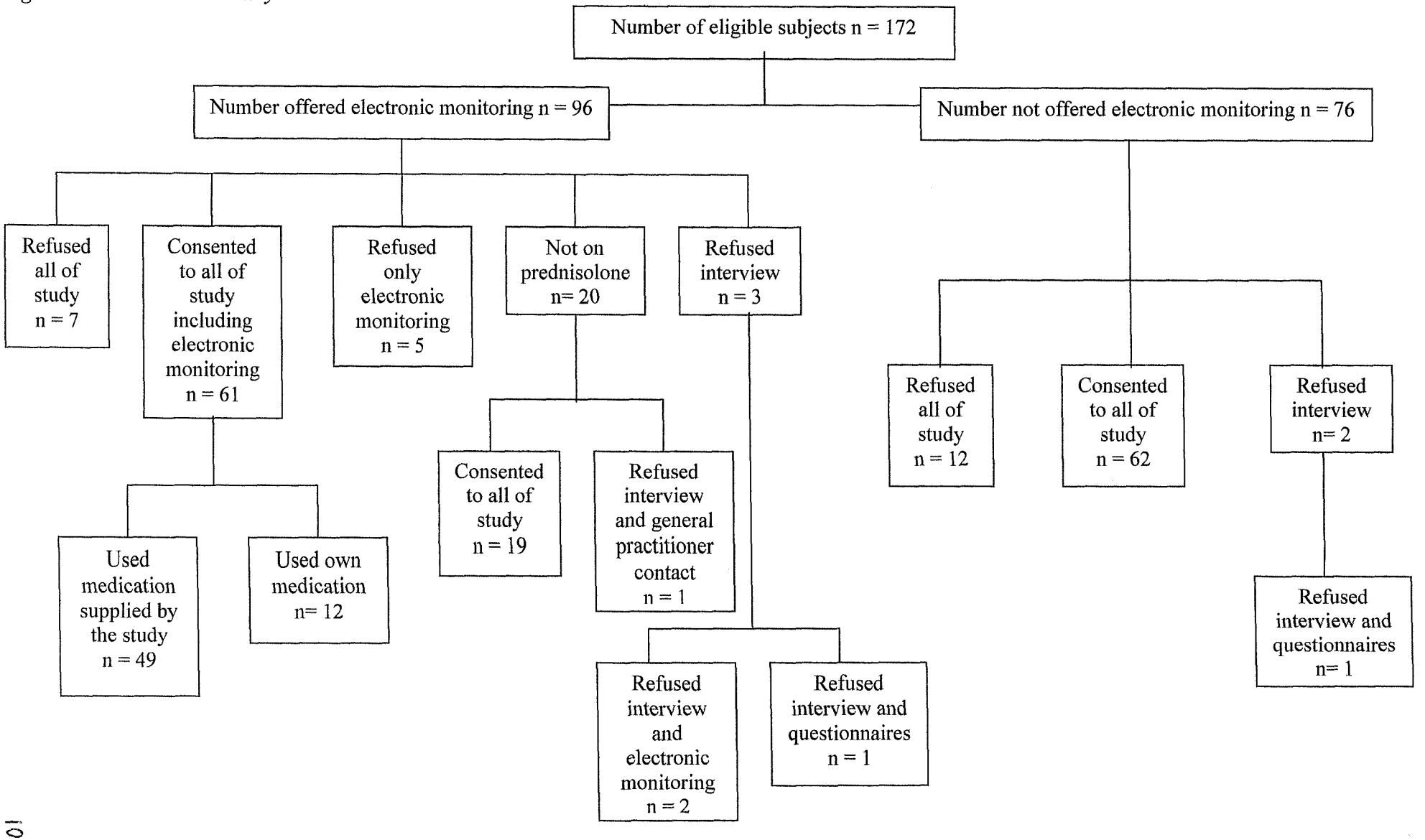
Table 10.2.1: Factors affecting prednisolone prescription

	Consultant		Gender	
	1	2-5	Male	Female
Number (%) subjects on prednisolone	76 (95)	57 (64)	88 (85)	45(68)

10.2.2 Sub-sample receiving electronic monitors

Sixty-one electronic monitors were distributed. Data could not be downloaded from one monitor so the monitor was replaced. Five eligible subjects refused to use the monitors and 20 subjects initially offered monitors had been withdrawn from prednisolone (figure 10.2). These monitors were offered to the next subject in the randomly ordered list of eligible subjects after stratification for time since transplantation (section 7.5.1). One subject died during the monitoring period and his monitor was not recovered. Data from another monitor was not used because at the end of the monitoring period the subject said that she had decanted her medication from the container once a week. Therefore 58 subjects had available data from electronic monitoring.

Figure 10.2: Consent to study



10.3 Characteristics of the sample

10.3.1 Socio-demographic factors

Of the 153 subjects consenting to the study, 94 (61%) were male. The mean (SD) age was 48 (13) years (range 21 - 77 years) and all but one subject was Caucasian. Further socio-demographic information was only available for the 147 subjects who agreed to an interview and social class could only be calculated for 140 subjects (table 10.3.1).

Table 10.3.1: Socio-demographic details of the 147 subjects who agreed to the research interview (140 with data to code social class)

	Number (%) in sample
Employment	
Number employed full-time	58 (39)
Number employed part-time	17 (12)
Number over retirement age	19 (13)
Number unemployed	37 (25)
Number medically retired or on long-term sick leave	16 (11)
Marital status	
Number living with a partner	106 (72)
Number never married or co-habiting	20 (14)
Number separated or divorced	19 (13)
Number widowed	2 (1)
Education	
Number leaving school $\geq$ 18 years	106 (72)
Number with no academic qualifications	15 (11)
Highest level of academic attainment at 'ordinary' level	47 (32)
Highest level of academic attainment at 'advanced' level	16 (11)
Number with an undergraduate or postgraduate degree	21 (14)
Number with vocational qualification	47 (32)
Social class	
Number in social class I or II	56 (40)

10.3.2 Transplant-related factors

Subjects predominantly had primary grafts from cadaveric donors and most had been dialysed prior to transplantation (table 10.3.2a). Only 41 (27%) subjects received an identical, beneficial or favourable tissue match (table 10.3.2b). Time since transplantation ranged from 5.4 - 67.1 months since practicalities of arranging interviews led to four subjects being slightly outside the planned 6 - 63 months post transplantation (table 10.3.2c). Sixty-three (69%) subjects had never experienced a rejection episode with their current transplant and of the rejection episodes that occurred, most were within the first year of transplantation (table 10.3.2d).

Table 10.3.2a: Transplant related characteristics of the sample

	Number (%) subjects
Cadaveric current transplant	142 (88)
Primary transplant	125 (82)
Experienced dialysis	129 (84)

Table 10.3.2b: Match of current transplant of subjects consenting to the study

Degree of mis-match at A, B and DR histocompatability antigens	**Number (%) subjects**
Identical (000)	10 (7)
Beneficial (100 or 010)	11 (7)
Favourable (110)	20 (13)
Other	110 (72)
Missing data	2 (1)
Total	153 (100)

Table 10.3.2c: Number of months on renal replacement therapy for subjects consenting to the study

Median (IQR) months since developing end-stage renal disease	49.7 (34.7-70.7)
Median (IQR) months in total with a transplant	41.1 (26.5-56.5)
Median (IQR) months in total on dialysis	15.3 (7.5-27.8)
Mean (SD) months with current transplant	34.7 (15.8)

Table 10.3.2d: Number of acute rejection episodes with the current transplant

Source of data	**Clinical notes**		**Patient report**	
Time period after transplantation	**1st year only**	**1st and subsequent years**	**1st year only**	**1st and subsequent years**
Number with no rejection episodes	98 (65)	96 (63)	107 (73)	101 (69)
Number (%) subjects with 1 rejection episode	34 (22)	33 (22)	19 (13)	22 (15)
Number (%) subjects with 2 rejection episodes	16 (10)	19 (12)	14 (10)	16 (11)
Number (%) subjects with 3 or more rejection episodes	3 (2)	3 (2)	5 (4)	6 (5)
Number (%) subjects with missing data	2 (1)	2 (1)	2 (1)	2 (1)
Total	153	153	147	147

11.0 Results: distribution of non-adherence

This chapter commences with a description of the distribution of measures of non-adherence. The relationship between the 'gold standard' (electronic monitoring) and other measures of adherence (biochemical monitoring, clinician rating, self-report by questionnaire and at interview and interviewer rating) using continuous and categorical definitions derived from the 'gold standard' measure is then investigated. Then the ability of other measures to detect non-adherent subjects classified as non-adherent in terms of both missing medication and taking it erratically using data from electronic monitoring is described. Finally the prevalence of non-adherence in the monitored sample is reported.

11.1 Distribution of non-adherence according to data from electronic monitoring

Subjects had the electronic monitor for between 35 and 77 days (median, IQR 45, 42-51 days). Subjects appeared to use the monitor (time between the first and last openings) for between 5 and 63 days (41, 39-42 days; figure 11.1a). The median (IQR) percentage of days with missed medication was zero (0.0 - 11.7) (table 11.1, figure 11.1b). The longest delay in dosing had a median value of 17.2 hours and the median standard deviation of inter-dose intervals was 4.8 hours (table 11.1, figure 11.1c).

Figure 11.1a: Length of time subjects appeared to use the electronic monitor

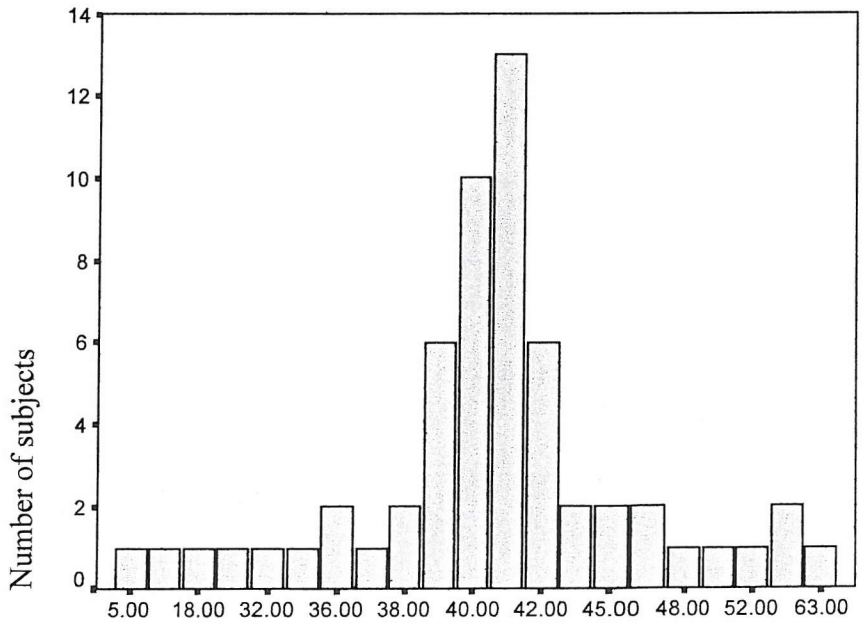


Table 11.1: Distribution of non-adherence according to data from electronic monitoring

Measure of non-adherence	Median	Inter-quartile range	Total range
Percentage missed days (days)	0.0	0.0 – 11.7	0.0 – 45.3
Longest delay in dosing (hours)	17.2	2.3 – 27.4	0.9 – 227.3
Standard deviation of inter-dose intervals (hours)	4.8	1.5 – 8.6	0.4 – 15.2

Figure 11.1b: Percentage of days without prescribed medication

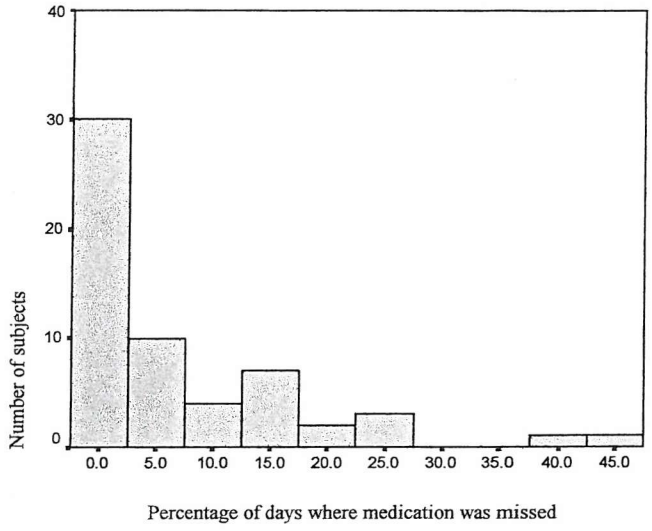
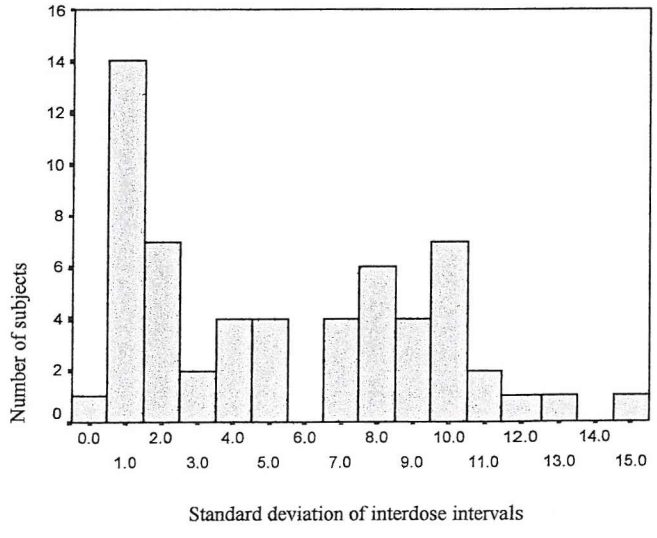


Figure 11.1c: Variability dose timing



11.2 Relationship between the different measures of adherence and electronic monitoring

Correlation of the three measures of adherence obtained from the electronic monitors suggested two patterns of non-adherence: missing medication and erratic timing of doses (table 11.2). The two measures of missing medication (percentage missed days and longest

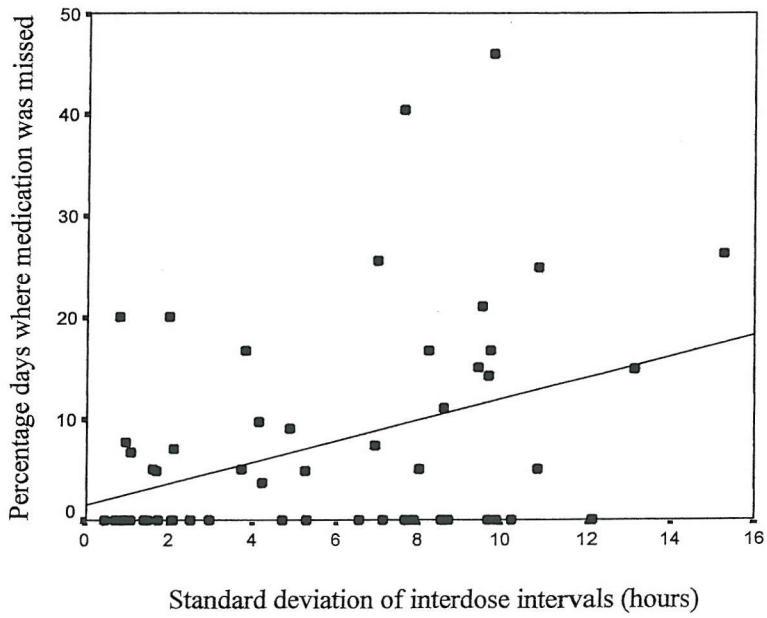
delay in dosing) were highly correlated with each other but weakly correlated (figure 11.2) with the measure of erratic timing of dosing (standard deviation of inter-dose intervals).

Table 11.2: Correlation of measures of non-adherence obtained from electronic monitors

	Spearman's correlation coefficient (p value)
Percentage missed days versus longest delay	0.86 (< 0.001)
Percentage missed days versus timing variability	0.35 (0.007)
Longest delay versus timing variability	0.30 (0.023)

Percentage days where medication was missed was used in further analyses as the variable reflecting missed doses. Since measures of missing doses correlated poorly with the measure of erratic timing of doses (figure 11.2), it was thought inappropriate to combine them into one non-adherence measure. Further analyses were therefore performed separately on the two variables representing missed medication and erratic timing.

Figure 11.2: Scatter plot of percentage missed days versus timing variability



11.3 Distribution of other measures of adherence

11.3.1 Cyclosporin levels

One hundred and thirty nine (91%) subjects consenting to the study were prescribed cyclosporin. The distribution of the two indicators of adherence obtained from the last six cyclosporin levels are shown in table 11.3.1 and figures 11.3.1a and b. The therapeutic range of cyclosporin will vary slightly with the length of time since transplantation and other

factors such as prior experience of rejection episodes, however a level under 90ng/ml is likely to be sub-therapeutic in all cases. Twenty-two (14%) subjects had their lowest cyclosporin level under 90 ng/ml.

Table 11.3.1 Distribution of cyclosporin plasma levels

Variable calculated from the last 6 levels	Median	Inter-quartile range	Range
Highest minus lowest level (ng/ml)	108	63 – 194	12 - 890
Lowest level (ng/ml)	119	97 – 146	35 – 239

Figure 11.3.1a: Range between the lowest and highest cyclosporin levels from the last 6 to be measured

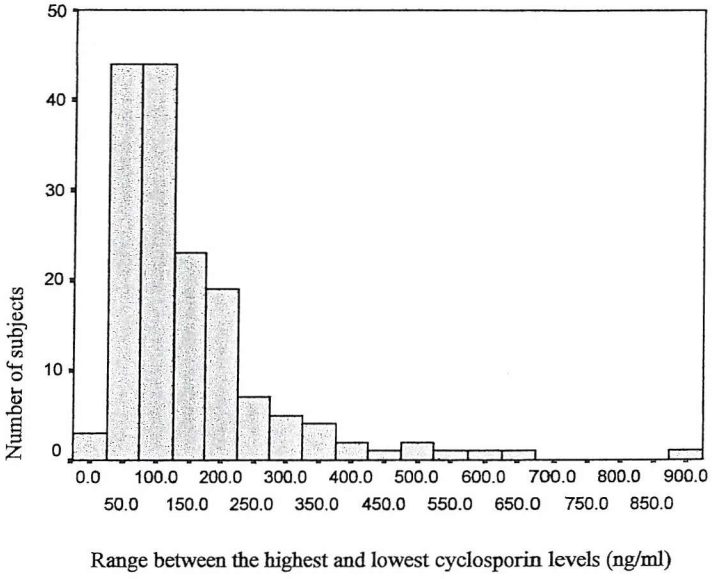
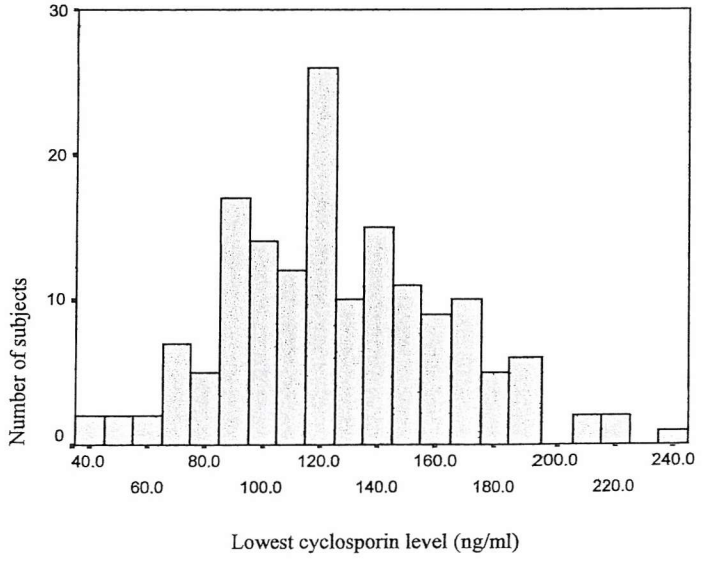


Figure 11.3.1b: Lowest of the last six cyclosporin levels



11.3.2 Morisky self-report questionnaire (n = 149)

Fifty (34%) subjects endorsed one or more items on the Morisky questionnaire, reflecting at least some non-adherence. From these subjects, 45 (90%) reported forgetting medication (table 11.3.2), making this the commonest reported reason for non-adherence. In this sample the questionnaire had poor internal reliability ($\alpha = 0.32$) which was not improved by deletion of any item. The internal reliability is lower than the quoted value of 0.61 derived from a study of anti-hypertensive medication (Morisky et al. 1986).

Table 11.3.2: Number of subjects endorsing different items, according to their total score, on the Morisky questionnaire relating to non-adherence with immunosuppressants

Item on questionnaire	**Total score on Morisky questionnaire**				**Total number of subjects endorsing this item**
	0	**1**	**2**	**3**	
Do you ever *forget* to take your medicines	0	31	11	1	45
Are you *careless* at times about taking your medicines	0	6	9	0	15
Sometimes *if you feel better do you stop taking* your medicines	0	0	0	1	1
Sometimes *if you feel worse do you stop taking* your medicines	0	1	2	1	4
Total number of subjects	99	38	11	1	149

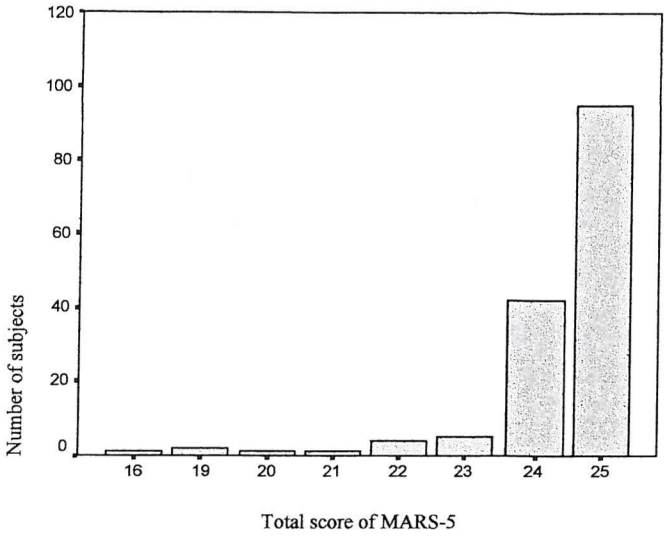
11.3.3 Medication adherence rating scale (MARS) (n = 151)

Scores for each item on the MARS range from 1 – 5, giving a total possible score of 5 to 25 (lower scores indicating poorer adherence). Total scores in this study ranged from 16 to 25 (median 25, IQR 24 – 25; figure 11.3.3). The majority of subjects scored 25 indicating 'perfect' adherence. Fifty-six subjects (37%) scored 24 or less and 14 (9%) scored 23 or less. The commonest reported reason for non-adherence was forgetting medication (table 11.3.3). The scale had an internal reliability (α) in this sample of 0.64.

Table 11.3.3: Number of subjects responding with 'never' to the five MARS items for the 151 subjects completing the questionnaire

Questionnaire item	**Number (%) of subjects who responded with 'never'**
I *forget* to take my anti-rejection medicines	101 (67)
I *alter the dose* of my anti-rejection medicines	144 (95)
I *take less* than instructed of my anti-rejection medicines	144 (95)
I *stop taking* my anti-rejection medicines for a while	147 (97)
I *decide to miss* a dose of my anti-rejection medicines	147 (97)

Figure 11.3.3: Distribution of scores on the MARS self-reported adherence questionnaire for immunosuppressants



11.3.4 Self-report on single questionnaire item

The item added to the MARS for this study ('I am more than 2 hours late taking my immunosuppressants', table 11.3.4) impaired internal reliability by reducing α from 0.64 to 0.57. Therefore this item was treated as a separate measure of non-adherence: 'self-report on a single questionnaire item' (table 11.3.4).

Table11.3.4: Self-report of taking immunosuppressants late on a single questionnaire item

Reported frequency of being at least 2 hours late taking immunosuppressants	**Number (%) of subjects**
Always	2 (1)
Often	9 (6)
Sometimes	42 (28)
Rarely	69 (46)
Never	29 (19)
Total	151 (100)

11.3.5 Clinician rating (n = 150)

Nephrologists thought 69 (46%) subjects were 'very rarely' or 'never' late taking their medication and 129 (86%) 'never' or 'very rarely' missed medication (tables 11.3.5a and b).

Table 11.3.5a: Frequency that subjects are late taking as assessed by nephrologists, a researcher and by self-report in a research interview

Reported frequency	Source of assessment		
	Clinician	Interviewer	Self-report
	Number (%) of subjects	Number (%) of subjects	Number (%) of subjects
Very often	1 (1)	14 (9)	6 (4)
Quite often	10 (6)	36 (25)	12 (8)
Occasionally	70 (47)	47 (32)	33 (23)
Very rarely	68 (45)	46 (31)	71 (49)
Never	1 (1)	4 (3)	24 (16)
Total	150 (100)	147 (100)	146 (100)

Table 11.3.5b: Frequency that subjects miss immunosuppressants as assessed by nephrologists and a researcher

Reported frequency	Number (%) of subjects	
	Assessment by clinician	Assessment by researcher
Very often	0 (0)	4 (3)
Quite often	3 (2)	10 (7)
Occasionally	18 (12)	29 (20)
Very rarely	77 (51)	95 (64)
Never	52 (35)	9 (6)
Total	150 (100)	147 (100)

11.3.6 Interviewer rating (n = 147)

At the end of the research interview, the researcher judged 50 (34%) subjects to be 'very rarely' or 'never' late taking their immunosuppressant medication and 104 (71%) were thought to 'very rarely' or 'never' miss tablets (table 11.3.5a and b).

11.3.7 Self report in interview

During the interview, 95 (65%) subjects reported that they only 'very rarely' or 'never' more than two hours late taking their immunosuppressants (table 11.3.5a). Despite admitting to taking medication late, almost all (138, 95%) subjects reported missing immunosuppressants only 'very rarely' or 'never'. Thus self-report in interview resulted in a lower estimate of non-adherence to dose frequency and timing than clinician or interviewer rating.

The question asking subjects how many days they were late taking immunosuppressants was added during the first wave of interviews therefore only 118 subjects were asked this question. One subject refused to answer, saying he didn't know, leaving 117 subjects with available data. Of these, 91 (78%) reported taking immunosuppressants late at least once a month. These general and specific definitions of non-adherence produced significantly different numbers of non-adherent subjects ($X^2 = 33.7$, $p < 0.001$; table 11.3.7).

Table 11.3.7: Frequency that subjects report being more than 2 hours late taking immunosuppressants using general and specific criteria

		Specific criteria		
		Number of subjects reporting late taking at least once a month	Number of subjects who are late less than once a month	Total (%)
General criteria	Number of subjects reporting late taking occasionally, quite often or very often	44	6	50 (43)
	Number of subjects reporting late taking very rarely or never	23	44	67 (57)
	Total (%)	67 (57)	50 (43)	

11.4 Sensitivity and specificity of measures used to detect non-adherence (missed days) defined as subjects missing at least 20% days medication according to electronic monitoring

Classification of subjects into adherent and non-adherent using each measure of adherence was compared to the reference measure, electronic monitoring, using a definition of missing at least 20% days medication for non-adherence. Tables comparing the sensitivity and specificity of different measures and graphical illustrations of the relationship using receiver operating curves (ROC curve) are given in appendix B4. The performance of measures was limited by large changes in sensitivity and specificity occurring with relatively small changes in the cut-off on the measurement scale (appendix B4). Table 11.4a shows the cut-off scores maximising sensitivity of each measure whilst maintaining specificity.

Cyclosporin levels were the poorest measure of adherence compared to electronic monitoring whether the variability, as defined by the range between the highest and lowest of the last six levels, or low trough levels were used. The 'best' criteria to define non-adherence produced positive predictive values of under 13%. Furthermore the definition for trough levels (under 150 ng/ml) was within the therapeutic range and is higher than would usually be desired for a patient after several years of transplantation.

Table 11.4a: Summary of other measures to detect the 7 subjects missing at least 20% days medication

Measure	Response or criteria defining non-adherence	sensitivity	specificity	PPV[1]	NPV[2]	+LR[3]	MCR[4]
Range of the last 6 cyclosporin levels	over 65 ng/ml	83.3	27.7	12.8	92.9	1.2	66.0
Lowest of the last 6 cyclosporin levels	150 ng/ml or less	66.7	17.0	9.1	77.8	0.8	79.2
Morisky questionnaire	total score of one or more	57.1	68.0	20.0	91.9	1.8	32.8
MARS questionnaire	total score of 24 or less	57.1	70.6	21.1	92.3	1.9	31.0
Single item on questionnaire	sometimes, often or always	42.9	68.6	15.8	89.7	1.4	34.4
Clinician rating of late taking	occasionally, quite often or very often	100.0	47.1	20.6	100.0	1.9	46.6
Clinician rating of missed medication	very rarely, occasionally, quite often or very often	100.0	33.3	15.9	100.0	1.5	58.6
Interviewer rating of late taking	quite often or very often	71.4	68.6	23.8	94.6	2.3	31.0
Interviewer rating of missed medication	occasionally, quite often or very often	57.1	72.5	22.2	92.5	2.1	29.3
Self-report of late taking at interview	occasionally, quite often or very often	85.7	72.5	30.0	97.3	3.1	25.9
Self-report of late taking at interview	once a month or more often	85.7	37.1	21.4	92.9	1.4	54.8

[1]positive predictive value; [2]negative predictive value

[3]positive likelihood ratio; [4]percentage of subjects mis-classified

The poor performance of low cyclosporin levels in predicting non-adherence assessed by electronic monitoring was unexpected. The results may have arisen because of difficulties in interpreting the levels. Although low trough levels are thought to indicate non-adherence, high levels also reflect inaccurate taking of medication - the level will be high if the cyclosporin was taken too close to the time of the blood test. To investigate this hypothesis, the lowest cyclosporin levels were split into three groups. According to clinicians in the unit, patients more than a year post-transplantation would generally be maintained with cyclosporin levels of between 80 and 130 ng/ml. Therefore subjects were split into groups according to whether their lowest cyclosporin level in the last six measurements was under

80.00 ng/ml, 80.00-130.00 ng/ml or over 130.0 ng/ml (table 11.4b). This categorisation was significantly related to missing 20% or more days medication ($X^2 = 6.70$, $p = 0.036$) but not to having a standard deviation of inter-dose intervals of 6 hours or more.

Table 11.4b: Low, acceptable and high trough cyclosporin levels in relation to missing prednisolone

Lowest cyclosporin level (ng/ml)	**Number of subjects missing at least 20% days prednisolone (non-adherent)**	**Number of subjects missing less than 20% days prednisolone (adherent)**
≤ 79.99	0	6
80.00 - 130.00	1	27
≥ 130.01	5	14

Higher trough levels were more likely to occur in non-adherent subjects; a trough level of over 130 ng/ml had 83.3% sensitivity and 70.0% specificity to detect subjects missing at least 20% or more days prednisolone (positive predictive value 26.3%, negative predictive value 97.0%, positive likelihood ratio 2.8 and mis-classification rate 28.3%). Thus high trough levels, indicating that a patient did not omit their cyclosporin prior to clinic, may be a better indicator of generally non-adherent subjects rather than low levels, suggestive of missed medication. However this is from a post-hoc analysis, is unexpected and from a relatively small sample so requires replication before the hypothesis can be accepted with confidence. Self-report of taking medication late at least occasionally in interview was the most accurate single measure of non-adherence used in the whole sample and so use of this measure, although mis-classifying 26% subjects, provided a larger sample. The three groupings of subjects according to their lowest cyclosporin level were not related to this measure of adherence, which does not support the hypothesis that high trough levels could be used to identify non-adherent subjects.

The Morisky and MARS self-report questionnaires had a similar ability to detect non-adherence (table 11.4a). On both questionnaires most subjects had scores reflecting perfect adherence (score 0 on Morisky and 25 on MARS questionnaire) or only scored one point towards non-adherence (score 1 on Morisky and 24 on MARS questionnaire). Thus although the MARS questionnaire has a greater range of potential scores, in this population it functioned more like a binary measure of adherence. As is expected with self-report measures, both questionnaires lacked sensitivity since about half the non-adherent subjects had scores at the adherent end of the questionnaire. (tables 11.4c and d).

Table 11.4c: Scores on the Morisky questionnaire according to whether subjects missed at least 20% days medication using electronic monitoring

Score on Morisky questionnaire[1]	Number (%) of non-adherent subjects using electronic monitoring	Number (%) of adherent subjects using electronic monitoring
0	3 (43)	34 (68)
1	4 (57)	13 (26)
2	0 (0)	3 (6)
Total number (%) of subjects	7 (100)	50 (100)

[1]order of increasing self-report of non-adherence

Table 11.4d: Scores on the MARS questionnaire according to whether subjects missed at least 20% days medication using electronic monitoring

Score on MARS questionnaire[1]	Number (%) of non-adherent subjects using electronic monitoring	Number (%) of adherent subjects using electronic monitoring
25	3 (43)	35 (71)
24	2 (29)	12 (23)
23	1 (14)	0 (0)
20, 21 or 22	0 (0)	3 (6)
19	1 (14)	0 (0)
Total number (%) of subjects	7 (100)	51 (100)

[1]order of increasing self-report of non-adherence

Clinicians and the researcher had a better ability to predict subjects who missed at least 20% days prednisolone, reflected in higher positive predictive values, if they judged how often subjects were late taking medication rather than how often a subject missed medication (table 11.4a). In contrast to this, the single questionnaire item asking the subject to report how often they were late taking immunosuppressants did not perform as well as the two questionnaire scales asking about a range of behaviour related to taking medication.

In the interview, which was confidential from the clinical team, 55 (95%) subjects with data from electronic monitors said they 'never' or only 'very rarely' missed immunosuppressants. Subjects were more likely to report being late taking medication. Twenty (34%) reported being more than 2 hours late taking immunosuppressants 'occasionally', 'quite often' or 'very often' (table 11.4e). This measure had the best ability to identify non-adherent subjects; it was the only measure with both sensitivity and specificity greater than 70% (table 11.4a). However, due to the relative infrequency of non-adherence, the positive predictive value was under 30%. If a subject was classified as non-adherent on the basis of this measure, there would be less than a 30% chance that they were truly non-adherent. Only 42 subjects given electronic monitors were asked to specify the number of days they took immunosuppressants

late. Twenty-eight (67%) reported being late at least once a month. However, although this was the optimal cut-off to define non-adherence in terms of the number of missed days (appendix B4), it was a less specific measure of adherence than asking subjects to report how often they were late in more general terms (table 11.4a).

Table 11.4e: Self-report of adherence at interview compared to whether subjects missed at least 20% days medication using electronic monitoring

Response to being asked 'how often do you take your anti-rejection medications more than 2 hours late'	**Number (%) of non-adherent subjects using electronic monitoring**	**Number (%) of adherent subjects using electronic monitoring**
Never	0 (0)	14 (27)
Very Rarely	1 (14)	23 (45)
Occasionally	4 (57)	9 (18)
Quite often	1 (14)	3 (6)
Very often	1 (14)	2 (4)
Total number (%) of subjects	7 (100)	51 (100)

As already discussed, the individual measure with the highest sensitivity and specificity to detect subjects missing at least 20% days medication was self-report at interview of taking immunosuppressants late at least 'occasionally' (table 11.4a). To investigate whether a composite measure would improve the positive predictive value, self-report at interview was combined with the best criteria on the other measures (using one measure of cyclosporin and clinician or interviewer rating) (table 11.4f). When non-adherence was defined by being assessed as non-adherent by the clinician and by self-report at interview, the sensitivity remained stable and the specificity improved (table 11.4f). However this combined measure of adherence still differed significantly from adherence classified by electronic monitoring ($X^2 = 18.43$, $p < 0.001$) and the positive predictive value only rose to 46%.

Table 11.4f: Self-report of taking medication late at least occasionally and non-adherent on other measures to identify subjects missing at least 20% days medication

Measure (from table 11.4a) combined with self-report at interview	**Sensitivity**	**Specificity**	**PPV[1]**	**NPV[2]**	**+LR[3]**	**MCR[4]**
Morisky questionnaire	57.1	90.2	44.4	93.9	5.8	13.8
MARS questionnaire	57.1	94.1	57.1	94.1	9.7	10.3
Clinician rating of late taking	85.7	86.2	46.2	97.8	6.2	13.8
Interviewer rating of late taking	85.7	58.8	22.2	96.8	2.1	37.9

[1]positive predictive value; [2]negative predictive value; [3]positive likelihood ratio; [4]percentage of mis-classified subjects

11.5 Sensitivity and specificity of measures used to detect non-adherence (erratic timing) defined as subjects with a standard deviation of inter-dose intervals of at least 6 hours according to electronic monitoring

Non-adherence (erratic timing) was defined as having a standard deviation of inter-dose intervals of at least 6 hours according to electronic monitoring. The ability of other measures to classify subjects (adherent and non-adherent) was calculated for different cut-off values of the other measures (appendix B5). Table 11.5a shows the criteria chosen to maximise sensitivity of each measure whilst maintaining specificity.

Table 11.5a: Sensitivity and specificity of other measures compared to non-adherence defined by a standard deviation of inter-dose intervals of 6 or more

Measure	Response or criteria defining non-adherence	sensitivity	specificity	PPV[1]	NPV[2]	+LR[3]	MCR[4]
Range of the last 6 cyclosporin levels	60 ng/ml or more	80.0	21.4	45.5	51.0	1.0	50.9
Lowest of the last 6 cyclosporin levels	160 ng/ml or less	88.0	17.9	50.0	66.6	1.1	43.9
Morisky questionnaire	1 or more	38.5	67.7	50.0	56.8	1.2	45.6
MARS questionnaire	24 or less	30.8	65.6	42.1	53.8	0.9	50.0
Single item on questionnaire	rarely, sometimes, often or always	92.3	25.0	50.0	80.0	1.2	44.8
Clinician rating of late taking	occasionally, quite often or very often	69.2	50.0	52.9	50.0	1.4	55.2
Clinician rating of missed medication	very rarely, occasionally, quite often or very often	84.6	40.6	53.7	76.5	1.4	39.7
Interviewer rating of late taking	occasionally, quite often or very often	76.9	53.1	57.1	73.9	1.6	36.2
Interviewer rating of missed medication	occasionally, quite often or very often	19.2	96.4	61.1	62.5	5.3	37.9
Self-report of late taking at interview	occasionally, quite often or very often	53.8	81.3	70.0	68.4	2.9	31.0
Self-report of late taking at interview	Once a month or more often	80.0	45.5	57.1	71.4	0.3	38.1

[1]positive and [2]negative predictive value; [3]positive likelihood ratio; [4]percentage of subjects mis-classified

The overall pattern of the ability of measures to accurately classify subjects as non-adherent if their standard deviation of inter-dose intervals was 6 or more was similar to their ability to identify subjects who missed 20% or more days medication. However all measures performed less well when used to detect erratic timing rather than missed doses.

Cyclosporin levels and the Morisky and MARS self-report questionnaires were particularly poor measures of erratic timing as indicated by the receiver-operator curve remaining close to the diagonal line indicating a performance no better than chance (appendix B5). The ability of clinician and interviewer ratings to detect erratic timing did not differ much according to whether clinicians and the researcher rated how often they thought the subject was late taking medication compared to how often they missed it completely (table 11.5a).

The best sensitivity and specificity occurred when, in the interview, subjects reported taking medication late at least 'occasionally'. However although the positive predictive value was 70%, the sensitivity was only 54% (table 11.5a). Six of the 7 subjects reporting taking immunosuppressants late 'quite often' or 'very often' were classified as non-adherent according to electronic monitoring (table 11.5b). Only 3 (5%) subjects reported that they missed immunosuppressants more frequently than 'very rarely' although all 3 were classified as non-adherent using electronic monitoring. Asking subjects to specify the number of days they were late was more sensitive but less specific and mis-classified more subjects than using general criteria (table 11.5a).

Table 11.5b:Self-report at interview of being more than 2 hours late taking immunosuppressants compared to having a standard deviation of inter-dose intervals of 6 hours or more

Response to being asked 'how often do you take your anti-rejection medications more than 2 hours late'	**Number (%) of subjects with this response classified as non-adherent by electronic monitoring**	**Number (%) of subjects with this response classified as adherent by electronic monitoring**
Never	4 (15)	10 (31)
Very Rarely	8 (31)	16 (50)
Occasionally	8 (31)	5 (16)
Quite often	4 (15)	0 (0)
Very often	2 (8)	1 (3)
Total number (%) of subjects	26 (100)	32 (100)

11.6 Failure to identify a categorical reference measure of adherence in the whole sample for further analyses

No measure had a sensitivity of at least 80% with a positive predictive value of at least 70% when used to detect either missed doses or erratic timing of doses as measured by electronic monitoring. Therefore assessment of the prevalence of non-adherence and analysis of the correlates of categorically defined non-adherence was confined to the sub-sample who received electronic monitoring.

11.7 Failure to identify a continuous measure of adherence for use in the whole sample

To identify correlates of non-adherence it is important to have an accurate classification of subjects according to their adherence. The number of subjects receiving electronic monitoring was too small to be likely to have large power for multivariate analysis (n = 60) and measures used in the whole sample did not accurately classify subjects (because they lacked acceptable levels of sensitivity and specificity). Therefore a continuous measure of adherence was sought to enable adherence to be used as the dependent variable in a linear regression model. This would enable data from the whole sample to be used thereby increasing the power of a model to identify possible predictors of non-adherence.

Scatterplots were inspected to assess the relationship of adherence measured by electronic monitoring compared to that measured by other methods. When compared to electronic monitoring of missed medication (appendix B6) or erratic timing (data not shown but plots similar to those for missed medication), a strong relationship was not seen. Using Spearman's correlation, all measures correlated poorly with electronic monitoring (table 11.7).

Table 11.7: Correlation of other measures of adherence with electronic monitoring

Other adherence measure	Spearman's correlation coefficient (p value) for % missed days	Spearman's correlation coefficient (p value) for timing variability
Cyclosporin range	0.16 (0.264)	-0.05 (0.718)
Lowest cyclosporin level	-0.11 (0.428)	-0.09 (0.538)
Single item self-report on questionnaire	-0.19 (0.146)	-0.24 (0.074)
MARS questionnaire	-0.17 (0.216)	0.07 (0.612)
Morisky questionnaire	0.18 (0.176)	0.02 (0.873)
Self-report of lateness item in interview	-0.38 (0.003)	-0.40 (0.002)
Clinician rating late taking	-0.18 (0.188)	-0.15 (0.264)
Clinician rating missed doses	-0.27 (0.043)	-0.28 (0.034)
Interviewer rating late taking	-0.26 (0.047)	-0.31 (0.018)
Interviewer rating missed doses	-0.24 (0.067)	-0.37 (0.005)

The best correlations were with self-report by interview for both missed doses (r = - 0.38) and timing variability (r = - 0.40). Furthermore, apart from measures derived from cyclosporin levels, rated adherence tended to cluster amongst only 2-3 responses on the other measures, thus suggesting that adherence should be defined categorically when using these other measures. Thus a continuous measure of adherence, used in the whole sample, was not found and analysis of the correlates of non-adherence was confined to subjects having received electronic monitoring.

11.8 Prevalence of non-adherence according to the reference measure of adherence

Adherence and non-adherence are continuously distributed so the prevalence of non-adherence will vary according to the criteria used to define non-adherence. Tables 11.8a and b show the prevalence of non-adherence in the sub-sample allocated electronic monitors with different thresholds being used to define non-adherence.

Seven (12%; 95% confidence intervals 4 - 20%) of the 58 subjects with data available from electronic monitors missed at least 20% days medication and 26 (45%; 95% confidence intervals 32 - 58%) had a standard deviation of inter-dose intervals of at least 6 hours. Thirty-seven subjects (64%) were classified in the same way (either adherent or non-adherent) by both these measures (table 11.8c). All but one of the subjects (86%) who missed at least 20% days prednisolone also had a standard deviation of at least 6 hours.

Table 11.8a: Number of subjects receiving electronic monitors classed as non-adherent according to different percentages of days of missed medication

Classification	**Number (%) subjects missing prednisolone on more than**			
	10% days	**15% days**	**20% days**	**25% days**
Non-adherent	15 (26)	12 (21)	7 (12)	5 (9)
Adherent	43 (74)	46 (79)	51 (88)	53 (91)

Table 11.8b: Number of subjects receiving electronic monitors classed as non-adherent according to different values of inter-dose standard deviation

Classification	**Number (%) subjects with an inter-dose standard deviation of**		
	at least 2 hours[1]	**at least 4 hours[2]**	**at least 6 hours[3]**
Non-adherent	39 (67)	32 (55)	26 (45)
Adherent	19 (33)	26 (45)	32 (55)

[1] Non-adherent subjects took medication outside a 4 hour period 32% of the time
[2] Non-adherent subjects took medication outside an 8 hour period 32% of the time
[3] Non-adherent subjects took medication outside a 12 hour period 32% of the time

Table 11.8c: Non-adherence to number of doses compared to non-adherence to dose timing

	Number of subjects missing at least 20% days prednisolone	Number of subjects missing under 20% days prednisolone
Number of subjects with a standard deviation of inter-dose intervals of 6 at least hours	6	20
Number of subjects with a standard deviation of inter-dose intervals of under 6 hours	1	31

11.9 Summary of chapter eleven

According to electronic monitoring, the median (IQR) percentage of days subjects missed prednisolone was 0 (0 – 12)% and the maximum missed was 45%. The median (IQR) standard deviation of inter-dose intervals was 5 (2 – 9) hours. These two types of non-adherent behaviour were only moderately correlated (r = 0.35) so were analysed separately. Non-adherence was defined as missing at least 20% days medication or having a standard deviation of inter-dose intervals of 6 hours or more respectively.

Ninety-one percent of subjects were prescribed cyclosporin. The variation (i.e.: range) between the highest and lowest levels in the last six measurements was highly skewed with most subjects having little variation in their cyclosporin levels (median 108 ng/ml, IQR 63 – 194 ng/ml). The pattern of adherence on all other measures was also skewed with most subjects being classified at the adherent end of the measure. Despite having a greater range of possible responses, most subjects scored the MARS self-reported adherence questionnaire in a similar manner to the Morisky questionnaire. Sixty-three and 66% subjects reported perfect adherence on the MARS and Morisky questionnaires respectively. Only 9% subjects scored 23 or less on the MARS questionnaire. Fifty-seven percent of subjects reported taking immunosuppressants more than 2 hours late at least once a month and, as expected, subjects reported less non-adherence than estimated by clinicians. Compared to electronic monitoring, the best indirect measure of adherence was self-report in the research interview of taking immunosuppressants more than 2 hours late at least occasionally. However even this measure did not have 80% sensitivity and a positive predictive value of 70% when used to detect subjects missing at least 20% days medication or having a standard deviation of inter-dose intervals of 6 hours or more. No continuous measure of adherence correlated well with the continuous description of adherence from electronic monitors. Therefore estimation of the prevalence of non-adherence and subsequent analysis of the correlates of non-adherence was restricted to the 58 subjects with data available from electronic monitoring.

Seven (12%, 95% confidence intervals 4 – 20%) monitored subjects missed at least 20% days prednisolone and 26 (45%, 95% confidence intervals 32 – 58%) had a standard deviation of inter-dose intervals of 6 hours or more. All but one subject who missed at least 20% days medication were also classified as non-adherent to dose timing.

12.0 Results: distribution of possible factors associated with non-adherence

This chapter describes the distribution of factors that may be associated with non-adherence. After discussing the use of reminders for medication, functional health status, social support and depression the chapter will concentrate on description of the distribution of health beliefs as assessed by the Beliefs about Medicines Questionnaire (BMQ), the Illness Perception Questionnaire (IPQ), the pros and cons questionnaires and semi-structured interview.

12.1 Number of medications and use of reminders for medication

Subjects reported prescription of a median (IQR) of 6 (5-7) medicines per day resulting in 12 (10-17) tablets per day. The question asking about aids to medication taking was added during the first wave of interviews, so only 139/147 interviewed subjects were asked this question. One hundred and two (73%) subjects reported using a reminder. The commonest reminder was being reminded by a partner (32%). For the 56 subjects who used a reminder and were prescribed prednisolone on alternate days, the commonest aid was using a calendar to mark alternate days (77%).

12.2 Functional health status assessed using the SF36 (n = 151)

Subjects reported low levels of energy, a poor perception of their general health, high levels of pain and high levels of limitations due to physical problems (table 12.2).

Table 12.2: Scores of subjects on the SF36 scales (higher scores reflects less disability)

Scale	Number completing all items on the scale	Median (IQR)	Mean (SD)	Population norms for mean (SD)[1]
Role limitation due to emotional problems	147	100.0 (33.3-100.0)	70.5 (41.7)	82.5 (32.0)
Social functioning	151	77.8 (55.6-100.0)	72.6 (28.5)	87.8 (19.6)
Pain	151	77.8 (44.4-100.0)	68.0 (27.5)	81.2 (21.7)
Mental health	151	72.0 (60.0-84.0)	70.9 (19.1)	72.9 (17.2)
Physical functioning	150	70.0 (38.8-90.0)	63.8 (29.8)	88.9 (16.5)
Energy / vitality	151	55.0 (30.0-70.0)	51.0 (23.3)	60.1 (19.4)
Role limitation due to physical problems	150	50.0 (0.0-100.0)	50.8 (43.8)	86.1 (29.3)
General health perception	151	50.0 (35.0-70.0)	51.0 (22.5)	74.3 (19.5)

[1]norms for social class III non-manual workers from Jenkinson et al. 1993

12.3 Social support

One hundred and fifty subjects completed the significant others questionnaire. Subjects tended to score at the upper end of each sub-scale and about 70% reported receiving as much practical and emotional support as they desired (table 12.3). At least as much actual support as their ideal amount of support was reported by 102 (68%) subjects for emotional support and by 107 (71%) subjects for practical support.

Table 12.3: Scores of subjects on each of the four sub-scales (scored 2-14) in the significant others questionnaire

Sub-scale	Median score	IQR	Total range	Number (%) with actual support ≥ ideal support
Actual emotional support	14	12 – 14	2-14	102 (68)
Ideal emotional support	14	13 – 14	4-14	
Actual practical support	14	11 – 14	2-14	107 (71)
Ideal practical support	14	12 - 14	5-14	

12.4 Psychological symptoms and psychiatric illness

The 147 subjects agreeing to be interviewed all completed the revised Clinical Interview schedule (CIS-R). Subjects tended to have low scores (median 6; inter-quartile range 3-11) indicating good psychological health (table 12.4). However 44 (30%) subjects were depressed and 28 (64%) of these had depression of moderate or severe severity (table 12.4). For 10 subjects the response to probes in the CIS-R meant that less questions had been asked than were needed to make a firm ICD-10 diagnosis. These subjects were therefore classified as having mild or no depression according to the data available.

Table 12.4: Number of subjects who were 'cases' on the CIS-R

Definition used to define 'a case'	Number of subjects with available data	Number (%)of 'cases'
Total score on CIS-R ≥ 11	147	34 (23)
ICD-10 diagnosis of depressive illness	145	44 (30)
a) mild depressive illness	145	16 (11)
b) moderate depressive illness	145	15 (10)
c) severe depressive illness	145	13 (9)

12.5 Health beliefs

12.5.1 Beliefs about Medicines Questionnaire

One hundred and fifty one subjects completed the Beliefs about Medicines Questionnaire (BMQ) with the specific section relating to immunosuppressants and 111 of these completed the specific section of the BMQ relating just to prednisolone. Internal consistency (α) of

scales was consistent with published values (0.58 – 0.88 on different scales, table 12.5.1a). The two extra items added to the concerns scale did not impair α (table 12.5.1a) suggesting that they measured the same concept as the other items on the scale. This original concerns score plus the two added items was used as the BMQ concerns scale in this study.

Table 12.5.1a: Internal reliability of Beliefs about Medicines Questionnaire (BMQ) sub-scales in this sample of 151 subjects who completed the questionnaire compared to published values

BMQ section	**BMQ Scale**	**Number of items**	**Cronbach's alpha in this sample**	**Cronbach's alpha when BMQ was designed[6]**
General	Overuse	4	0.73	0.60 – 0.80
	Harm	4	0.58[1]	0.47 – 0.83
	Benefit	4	0.65	Not applicable
Specific relating to immunosuppressants as a group	Necessity	5	0.80	0.55 – 0.86
	Concern	5	0.67[3]	0.63 – 0.80
	Concern with 2 items added for this study	7	0.70[5]	Not applicable
Specific relating to prednisolone only	Necessity	5	0.88	0.55 – 0.86
	Specific-concern	5	0.73[2]	0.63 – 0.80
	Concern with 2 items added for this study	7	0.79[4]	Not applicable

[1]increased to 0.63 if delete item 'all medicines are poisons'
[2]increased to 0.80 if delete item 'my prednisolone is a mystery to me'
[3]increased to 0.76 if delete item 'my immunosuppressants are a mystery to me'
[4]increased to 0.82 if delete item 'my prednisolone is a mystery to me'
[5]increased to 0.74 if delete item 'my immunosuppressants are a mystery to me'
[6]Horne et al. 1999

Scores were distributed across the range of possible scores on the general-harm, general-overuse and specific-concerns scales (table 12.5.1b). However more than 95% subjects scored in the top half of the general-benefit and specific-need relating to immunosuppressants scales and more than 75% scored in the top half of the specific-need scale relating to prednisolone (table 12.5.1b). This indicates that subjects varied more in their beliefs regarding problems with medicines in general or specifically with their immunosuppressants but all tended to strongly believe in the benefits of medicines in general and in the need for immunosuppressants. One hundred and forty-seven (97%) subjects had greater necessity scores than concern scores for immunosuppressants.

Subjects reported less belief in the need for prednisolone than immunosuppressants as a group ($Z = -8.0$, $p < 0.001$; figures 12.5.1a and b). The median (IQR) necessity scale score

was 18 (16-21) for prednisolone and 22 (20-25) for immunosuppressants as a group. However subjects had similar scores on the BMQ concerns scale (modified by adding the two items for this study) for prednisolone as for immunosuppressants as a group (table 12.5.1b).

Table 12.5.1b: Subjects responses to scales on the Beliefs about Medicines Questionnaire (151 for immunosuppressants as a group, 111 for prednisolone only)

Scale (range of possible scores)	**Specified medication**	**Median (IQR)**	**Subjects' range of scores**	**Number (%) of subjects scoring in the upper half of the scale**
Overuse (4-20)	n/a	11 (9-13)	4 – 19	59 (39)
Harm (4-20)	n/a	8 (7-10)	4 – 17	7 (5)
Benefit (4-20)	n/a	16 (15-17)	10 – 20	150 (99)
Necessity (5-25)	Immunosuppressants[2]	22 (20-25)	10 – 25	147 (97)
Concerns (5-25)	Immunosuppressants[2]	13 (10-15)	6 – 23	33 (22)
Modified Concerns[1] (7-35)	Immunosuppressants[2]	20 (16-23)	9 - 33	62 (41)
Necessity (5-25)	Prednisolone[3]	18 (16-21)	9 – 25	86 (78)
Concerns (5-25)	Prednisolone[3]	14 (12-17)	6 – 25	41 (37)
Modified Concerns[1] (7-35)	Prednisolone[3]	21 (17-24)	8 – 35	62 (56)

[1]Concern scale plus 2 items for this study
[2]151 subjects completed BMQ scales for immunosuppressants
[3]111 subjects completed BMQ scales for prednisolone

Figure 12.5.1a: Distribution of scores on the BMQ necessity scale for immunosuppressants as a group

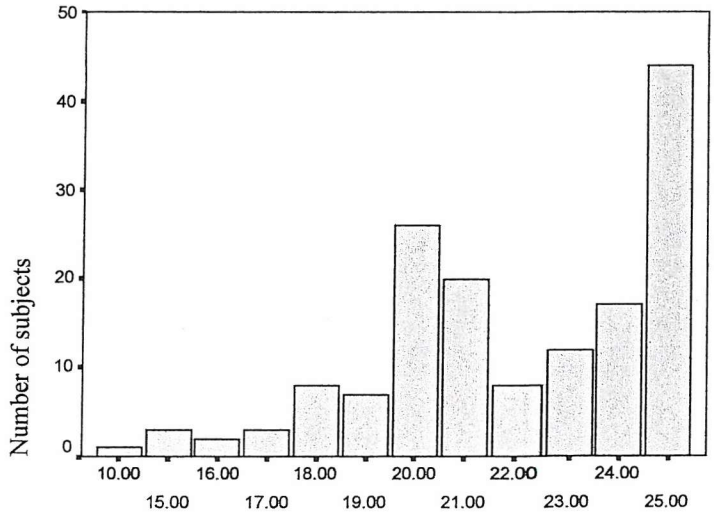
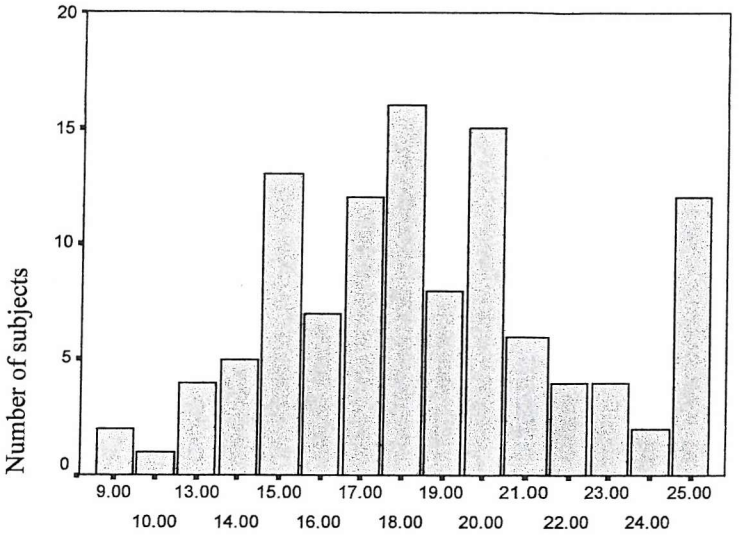


Figure 12.5.1b: Distribution of scores on the BMQ necessity scale for prednisolone



BMQ necessity scale score for prednisolone

12.5.2 Illness Perception Questionnaire

One hundred and fifty one subjects completed the Illness Perception Questionnaire (IPQ). One subject did not complete the identity scale (list of symptoms) but from the remaining 149 subjects the mean (SD) number of symptoms endorsed was 5 (3). Subjects believed that a median of 33% (IQR 0 – 67) of these symptoms were due to their transplant and a median of 59% (IQR 22 – 88) were due to their immunosuppressants.

Table 12.5.2a: Strength of belief in the ability of different factors to cause transplant failure

Possible cause item on the Illness Perception Questionnaire	Number (%) subjects scoring in the upper half of the scale rating belief in this possible cause
Poor medical care	129 (85)
Germs	115 (76)
My behaviour	99 (66)
Chance	92 (61)
Diet	88 (59)
My state of mind	80 (53)
Stress	66 (44)
Other people	30 (20)
Pollution	23 (15)
Hereditary factors	23 (15)

Subjects were most likely to believe that 'germs' or 'poor medical care' could cause their transplant to fail, with over 70% subjects scoring in the upper half of the scale rating belief in these possible causes of transplant failure. The things least likely to cause transplant failure were 'pollution' and 'hereditary factors' (table 12.5.2a).

The internal consistency of the IPQ was lower than expected for the consequences and control-cure scales (see table 12.5.2b) in this sample. This indicated that subjects did not 'view' the items as relating to the same construct. The three added items improved the internal consistency of the consequences scale, particularly if the item 'my transplant has not had much effect on my life' was removed. Therefore this new consequences sub-scale of nine items was used in analyses of the relationship between health beliefs and non-adherence.

Table 12.5.2b: Internal reliability of Illness Perception Questionnaire (IPQ) scales in this sample of 151 subjects completing the questionnaire

Scale of the IPQ	**Number of items**	**Cronbach's alpha when IPQ was designed[1]**	**Cronbach's alpha in this sample**
Time-line	3	0.73	0.75
Consequences	7	0.82	0.34[2]
Modified consequences[3]	10	Not applicable	0.72
Control-cure	6	0.73	0.41[4]
Emotions	8	Not applicable	0.85

[1]Weinman et al. 1996
[2]0.49 if delete 'my transplant has not had much effect on my life'
[3]three items added for this study and deleted 'my transplant has not had much effect on my life'
[4]0.45 if delete item 'my kidney function will improve with time'

Subjects' scores ranged across all possible scores on the time-line and emotions scales (table 12.5.2c). Seventy-nine and 82% subjects respectively scored in the lower half of these scales, indicating that most subjects thought their transplant would last a long time and that they experienced few negative emotions attributable to their transplant. In contrast, 121 (80%) subjects scored in the upper half of the control-cure scale (table 12.5.2b), indicating that most subjects believed treatment and behavioural factors could greatly affect transplant survival.

Table 12.5.2c: Subjects responses to sub-scales on the Illness Perception Questionnaire (IPQ) for the 151 subjects completing the questionnaire

Scale (range of possible scores)	**Subjects' range of scores**	**Mean (SD) scale score**	**Number (%) of subjects scoring in the upper half of the scale**
Time-line (3-15)	3 –15	9 (2.2)	40 (26.5)
Consequences (7-35)	13 – 30	21 (3.3)	62 (41.1)
Consequences plus 3 added items without 'my transplant has not had much effect on my life' (9-45)	13 – 41	24 (5.2)	47 (31.1)
Control-cure (6-30)	12 – 28	21 (2.8)	121 (80.1)
Emotions (8-40)	8 – 35	19 (5.9)	28 (18.5)

12.5.3 Pros and cons of a transplant or immunosuppressants questionnaires

The pros and cons questionnaires were given to all 146 subjects completing the second interview and were sent to two subjects who completed questionnaires but refused the interview. If a subject missed an item on the scale, their data were excluded when calculating the total score on that scale. All scales had good internal consistency ($\alpha = 0.77$ for cons of transplant; 0.81 for pros of transplant; 0.84 for cons of immunosuppressants and 0.78 for pros of immunosuppressants respectively). On the questionnaire, most subjects reported many benefits and few concerns with their transplant and medication (table 12.5.3).

Table 12.5.3: Subjects responses to the pros and cons questionnaires

Scale (range of possible scores)	**Number of subjects completing the scale**	**Median (IQR) of scale**	**Subjects' range of scores**	**Number (%) of subjects scoring over half-way on the scale**
Cons of transplant (13-65)	146	25 (21-33)	15 – 59	16 (11)
Pros of transplant (11-55)	148	40 (33-43)	11 – 55	105 (71)
Cons of immunosuppressants (16-80)	140	29 (25-37)	16 – 63	14 (10)
Pros of immunosuppressants (3-15)	148	14 (12-15)	6 – 15	136 (92)

12.5.4 Number of reported problems and benefits from their transplant and immunosuppressants reported by subjects in the interview

One hundred and forty-seven subjects consented to the interview but five did not list benefits from their medicines. Almost all subjects reported more benefits than problems from their transplant but 78 (54%) reported more problems than benefits from their immunosuppressants (table 12.5.4).

Table 12.5.4: Benefits and problems associated with their transplant and immunosuppressants reported by subjects in the interview

	Median number of problems/benefits reported by each subject (range)	**Number (%) of subjects reporting more problems than benefits**
Problems with transplant	1 (0 – 8)	9/147 (6.1)
Benefits from transplant	4 (1 – 15)	
Problems with immunosuppressants	2 (0 – 10)	78/144 (54.2)
Benefits from immunosuppressants	1 (0 – 4)	

12.5.5 Belief in the importance of medication and estimates of the number that could be missed without harm

Estimates of the importance of medication were obtained from all 146 subjects completing the second interview. Ninety-one of these were taking anti-hypertensive medication. Subjects all thought immunosuppressants were important for their transplant's survival but there was greater variation in their beliefs regarding the need for anti-hypertensives (table 12.5.5). They also thought that they could miss more anti-hypertensives than immunosuppressants before their transplant was damaged. Subjects had more belief in the importance of anti-hypertensives to control their blood pressure than to maintain their transplant (table 12.5.5).

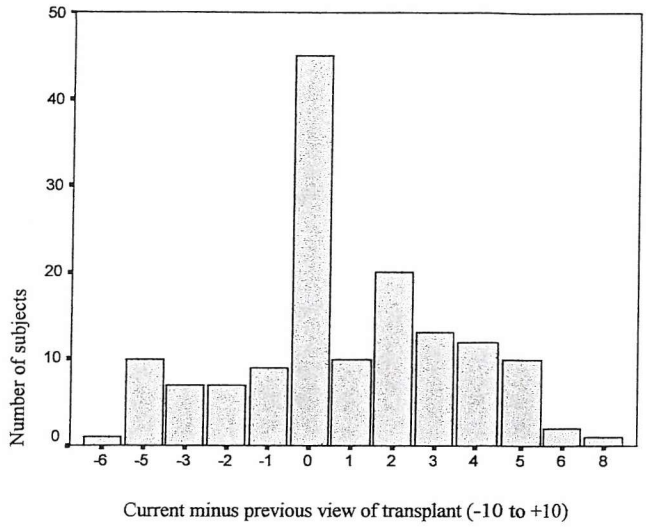
Table 12.5.5: Subjects beliefs in the importance of immunosuppressant and anti-hypertensive medication and their estimates of how many days medication could be missed without impairing their transplant or blood pressure

Drug	Drug to maintain	Number of subjects	Median percentage importance of drugs (IQR)	Median number of consecutive days that could be missed (IQR)	Median number of days that could be missed in one year (IQR)
Immunosuppressants	Transplant	146	90 (75-100)	3 (2-8)	12 (5-52)
Anti-hypertensives	Transplant	91	40 (15-75)	10 (4-72)	60 (18-194)
Anti-hypertensives	Blood pressure	91	80 (50-100)	2 (103)	20 (6-72)

12.5.6 Change in view of the overall benefits of a transplant

All 147 subjects agreeing to the interview were asked to rate, on a 0-10 scale, how good they had expected a transplant to be and how good they now thought a transplant was. The median (IQR) scores were 8 (7-10) and 9 (8-10) respectively but 34 (23%) subjects reported a less positive view of their current transplant than they had expected prior to transplantation (figure 12.5.6).

Figure 12.5.6: Change in subjects' views of the benefits of a transplant at the time of interview compared to what they had expected prior to transplantation



12.6 Summary of chapter twelve

The median (IQR) number of prescribed medicines taken each day was 6 (5 – 7) and 73% subjects used a reminder for their medication. Subjects reported more functional disability than found in general population surveys on all scales of the SF36 except for mental health. Disability was particularly pronounced on the physical functioning, role limitation due to physical problems and general health perception scales. Subjects tended to report high levels of emotional and practical social support but 30% fulfilled ICD10 criteria for a depressive illness. The BMQ scales had acceptable internal reliability in this sample. Subjects expressed strong beliefs in the general benefits of medicines and the specific necessity for immunosuppressants or prednisolone. There was a wider range of views regarding the general overuse of medicines and concerns with both immunosuppressants and prednisolone. In comparison with their views about immunosuppressants as a group, subjects tended to perceive less need for, and more problems associated with, prednisolone. The internal reliability of the IPQ control-cure and consequences scales was poor although the latter was improved by adding items thought to be relevant to transplant recipients. Most subjects believed that their transplant would last a long time and that behavioural and treatment factors could influence transplant survival. Eighteen percent reported a lot of negative emotions attributed to the transplant. Seventy-five percent of subjects thought immunosuppressants were clearly the most important factor contributing to the survival of their transplant but they thought a median (IQR) of 12 (5 – 52) days per year could be missed without risk of a rejection episode.

13.0 Results: factors associated with missed days (non-adherence defined by missing at least 20% days medication according to electronic monitoring)

The data presented in this chapter follows the sequence of analysis used to identify the main correlates of non-adherence (the rationale for this is described in section 9.2): bivariate analysis to identify variables that are related to non-adherence (with $p \leq 0.1$), followed by checking for strong relationships between these variables to try to avoid using two variables exhibiting strong collinearity and finally, forward stepwise selection of variables in a logistic regression model with non-adherence as the dependent variable.

13.1 Relationship of individual variables with missed days

An arbitrary value of missing at least 20% days medication measured by electronic monitoring was used to reflect non-adherence according to number of doses of medication taken. Variables significantly related to missed days ($p \leq 0.05$) in binary analyses were (tables 13.1a and b)

- first transplant from a live-related donor
- current transplant from a live-related donor
- living alone
- younger age
- less belief in the general benefits of medicines (BMQ benefits scale)
- less belief in the need for immunosuppressants as a group (BMQ necessity scale)
- less belief in the need for prednisolone (BMQ necessity scale)

Variables that were less strongly related to missed days, but still significant at the $p \leq 0.1$ level, were (tables 13.1a and b)

- pre-emptive transplantation (i.e. transplanted prior to dialysis)
- left full-time education aged under 18 years
- more negative emotions attributed to the transplant (IPQ emotion scale)
- less desired practical support (social support questionnaire)
- functional limitations attributed to emotional factors (SF36 role limitation due to emotional factors scale)

Table 13.1a: Continuous variables related to missing at least 20% days medication

Variable	Z statistic* (p value)	More non-adherence if:-
i-need	-3.27 (0.001)	less necessity
p-need	-2.92 (0.002)	less necessity
Benefits	-2.88 (0.004)	less benefit
Age	-2.52 (0.010)	younger
Emotion	-1.94 (0.052)	more emotion
Practical support	-2.08 (0.081)	less desired support
i-(need-concern)	-1.74 (0.086)	concerns greater than belief in necessity
Role-emotion	-1.98 (0.091)	more limited

*calculated from the Mann-Whitney test statistic
i-need: total score on BMQ necessity scale for immunosuppressants
p-need: total score on BMQ necessity scale for prednisolone
i-(need-concern): total score on necessity scale - total score on concern scale for immunosuppressants
Emotion: total score on IPQ emotion scale
Benefit: total score on BMQ benefit scale
Practical support: total ideal practical support from social support scale
Role-emotion: SF36 scale total for role limitation due to emotional factors

Table 13.1b: Categorical variables related to missing at least 20% days medication

Variable	Odds of non-adherence (category associated with non-adherence)	Odds 1	Odds 2	Relationship to non-adherence, X^2 (p value)*
Type first transplant	12.3 (Live transplant)	4/5	3/46	10.52 (0.008)
Type current transplant	10.0 (Live transplant)	4/6	3/45	8.88 (0.013)
Live alone	8.1 (Live alone)	5/12	2/39	6.82 (0.019)
Pre-emptive transplantation	9.8 (Pre-emptive transplant)	2/2	5/49	5.83 (0.067)
Age left full-time education	n/a (Under 18 years old)	7/33	0/18	3.58 (0.087)

Odds 1: odds of non-adherence (number non-adherent/number adherent) in the group strongly associated with non-adherence
Odds 2: odds of non-adherence (number non-adherent/number adherent) in the group associated with adherence
*all with 1 degree of freedom

There was no significant relationship with missed days for gender, recalling one or more rejection episodes with the current transplant, social class, having two or more transplants, frequency of prednisolone dosing, length of time since transplantation, use of reminders for medication, number of symptoms perceived to be due to the transplant or medication, BMQ scales relating to belief in the general harm or overuse of medicines or specific concerns with immunosuppressants or prednisolone and depressive illness or overall psychological distress.

13.1.1 Investigation of collinearity between variables selected for multivariate analysis

Table 13.1.1a shows the variables that were strongly related ($p \leq 0.05$ on a Chi-squared test; $p \leq 0.05$ on a Mann-Whitney U test; or $r \geq 0.5$ and $p \leq 0.05$ using Spearman's rank correlation) when bivariate statistics were used on variables that were related to missing at least 20% days medication at $p \leq 0.10$ level of significance (table 13.1.1b).

Table 13.1.1a: Strongly related variables

Strongly related pairs of variables	Test statistic (p value)
Type of first and current transplant	$X^2 = 51.14$ (< 0.001)
Type of first transplant and age	$Z = 43.00$ (< 0.001)
Type of current transplant and age	$Z = 56.00$ (<0.001)
Live alone and ideal practical support	$Z = -3.82$ (<0.001)
Type of current transplant and ideal practical support	$Z = -2.91$ (0.004)
BMQ benefit scale and BMQ necessity scale for immunosuppressants	$r = 0.50$ (0.001)
BMQ necessity minus concerns scales for immunosuppressants and BMQ necessity scale for immunosuppressants	$r = 0.67$ (<0.001)

X^2: Chi squared statistic, Z: Z statistic from a Mann-Whitney U test, r: Spearman's rank correlation

To minimise collinearity, where strongly related pairs of variables were judged to be measuring a similar concept (such as type of current transplant and type of first transplant), only one of the pair was included in regression modelling. If pairs of related variables were judged to be measuring different concepts (such as type of transplant and age), both variables were included.

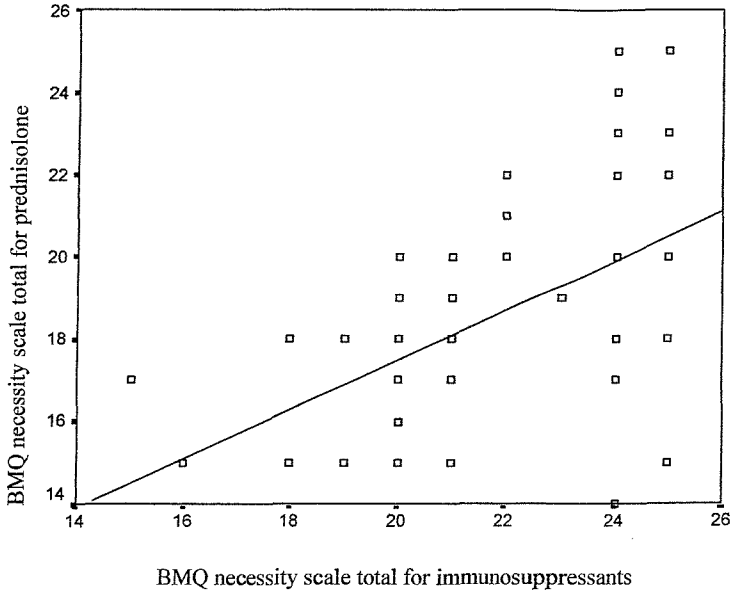
It was initially assumed that subjects would have similar beliefs regarding prednisolone specifically and immunosuppressants as a group. This did not appear to be the case since the two measures were only moderately correlated and the sample had scores reflecting less belief in the need for prednisolone than for immunosuppressants as a group (figure 13.1.1). Therefore both scales were included in regression modelling.

Table 13.1.1b: Relationship between variables that are related to missing 20% or more days at $p \leq 0.1$ level of significance

	Tx-1	Tx-c	Dialysis	Partner	Education	Age	p-need	i-need	i-(n-c)	Benefits	Emotion	SF36	Support
Tx-c	X^2 = 51.14***												
Dialysis	ns	ns											
Partner	ns	ns	ns										
Education	ns	ns	ns	ns									
Age	Z = -3.81***	Z = -3.79***	ns	Z = -2.43*	ns								
p-need	ns	ns	ns	ns	ns	r = 0.28*							
i-need	ns	ns	ns	ns	ns	ns	r = 0.45**						
i-(n-c)	ns	ns	ns	ns	ns	ns	r = 0.28*	r = 0.67***					
Benefits	ns	ns	ns	ns	ns	ns	r = 0.42***	r = 0.50***	r = 0.37**				
Emotion	ns	ns	ns	ns	ns	r = -0.43***	r = -0.39**	ns	r = -0.34**	ns			
SF36	ns	ns	ns	ns	-2.0*	ns	ns	ns	0.2**	ns	-0.3***		
Support	ns	-2.9**	ns	-2.90**	ns	0.3***	ns	ns	ns	0.2**	-0.2*	ns	

ns: not significant; ***p<0.001; **p<0.01; *p<0.05; r: Spearman's rank correlation, X^2: Chi squared statistic, Z: Z statistic from a Mann-Whitney U test
Tx-1: type of first transplant; Tx-c: type of current transplant; Dialysis: pre-emptive transplantation; Partner: live alone;
Education: leaving full-time education under 18 years old; i-need: total score on BMQ necessity scale for immunosuppressants;
p-need: total score on BMQ necessity scale for prednisolone; i-(need-concern): total score on necessity scale - total score on concern scale for immunosuppressants
Benefits: total score on BMQ benefit scale; Emotion: total score on IPQ emotion scale; SF36: total score on SF36 scale for role limitation due to emotional factors
Support: total ideal practical support from social support scale

Figure 13.1.1 Relationship between the BMQ necessity scales for immunosuppressants as a group and for prednisolone alone



BMQ necessity scale for prednisolone inter-quartile range 17-20 (range 9-25)
BMQ necessity scale for immunosuppressants inter-quartile range 20-24 (range 15-25)
Spearman's correlation $r = 0.45$, $p<0.01$

Therefore the variables that were included in logistic regression modelling with missing at least 20% days medication as the dependent variable were

- type of current transplant
- pre-emptive transplant
- report of living alone
- age of leaving full-time education
- age
- BMQ benefits scale
- BMQ necessity scale for immunosuppressants as a group
- BMQ necessity scale for prednisolone
- IPQ emotions scale
- SF36 scale for role limitations due to emotional factors

13.2 Selection of the best model to predict missed days

The logistic regression model fitted to all variables, listed above, that were associated with missed days ($p < 0.1$) showed that three variables remained significant predictors: pre-emptive transplantation and belief in the necessity for both immunosuppressants as a group and prednisolone specifically. However the adjusted odds ratio for pre-emptive transplantation had very wide 95% confidence intervals (2.16 to over 6 million).

This instability in the model was thought likely to be largely due to the small number of subjects with pre-emptive transplantation (4/58). Therefore a model was fitted to the variables significantly related to missed days after excluding pre-emptive transplantation. The variables that remained significant were the BMQ necessity scales for immunosuppressants and prednisolone and type of current transplant (table 13.2). The model correctly classified 97% subjects. It correctly categorised 6/7 non-adherent subjects (positive predictive value of 86%) and 50/51 adherent subjects (negative predictive value 98%). According to the model, the odds of non-adherence increase 32-fold with a transplant from a live donor compared to a cadaveric donor and decrease 0.5-fold and 0.6-fold with each unit increase on the BMQ necessity scale score for immunosuppressants and prednisolone respectively.

Table 13.2:Predictors of missing at least 20% days medication (excluding pre-emptive transplantation)

Variable	**Crude odds ratio (95% CI)**	**Adjusted odds ratio (95% CI)**	**Likelihood ratio test (P value)**	**Homer & Lemeshow goodness of fit X^2 (P value), number of outliers***
Type current tx	10.0 (1.79-55.95)	31.63 (1.20-827.11)	0.038	
i-need	0.47 (0.27-0.82)	0.49 (0.27-0.90)	0.022	
p-need	0.60 (0.41-0.87)	0.57 (0.35-0.94)	0.030	
Final model				6.93 (0.44), 1

* cases with studentised residuals greater than 2

Converting the odds to predicted adherence aids interpretation of the effect of the variables. Figures 13.2a, b and c suggest that the importance of the type of transplant in predicting adherence to prednisolone tends to decrease as the belief in the necessity for prednisolone or immunosuppressants as a group increases. The small sample size meant that it was not statistically valid to include an interaction between beliefs and type of transplant in the regression model.

Figures 13.2a,b and c: Logistic Regression Model fitted to variables related to missing 20% or more days medication excluding pre-emptive transplantation when BMQ necessity scale score for immunosuppressants is 17 (figure 13.2a), 21 (figure 13.2b) or 24 (figure 13.2c)

Figure 13.2a: Low belief in the need for immunosuppressants (BMQ necessity score 17)

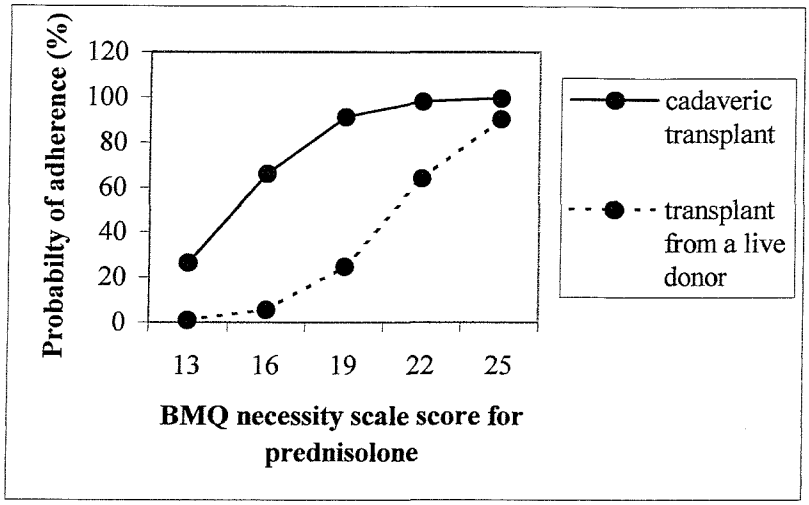


Figure 13.2b: Moderate belief in the need for immunosuppressants (BMQ necessity score 21)

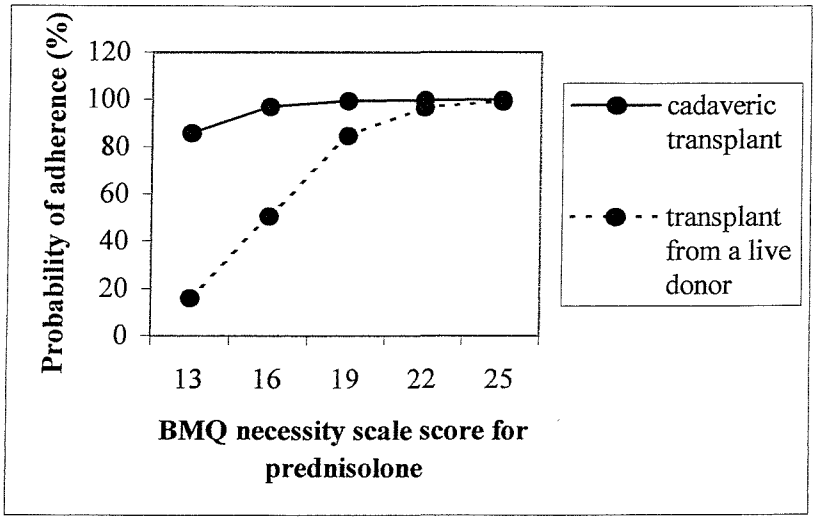
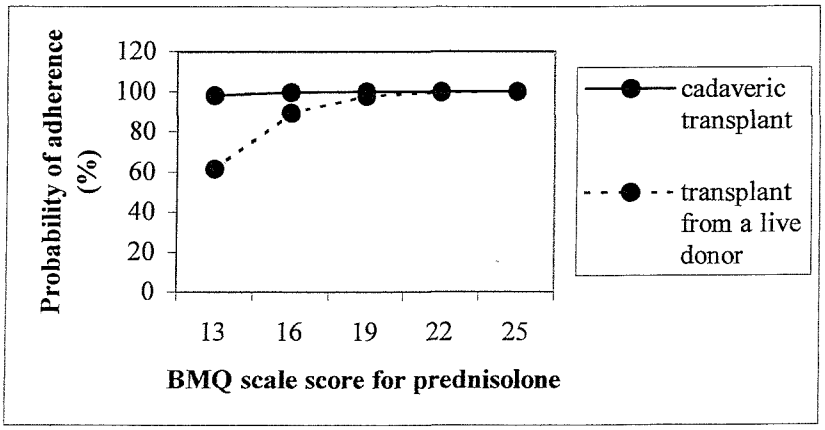


*Figure 13.2c: Strong **belief in the need for immunosuppressants (BMQ necessity score 17)***



13.3 Sensitivity analysis using different cut-offs to define non-adherence

Missing at least 20% days medication is the most restrictive definition of non-adherence used in previous studies (see section 5.2.1). However choice of a different cut-off did not greatly chance the results. All but three of the 13 variables that were related to missing at least 20% days medication at $p \leq 0.1$ significance were similarly related to both missing at least 10% or 25% days medication (table 13.3). Two variables (BMQ necessity scale score for immunosuppressants and the BMQ benefit scale) became more strongly associated with non-adherence as the threshold for defining non-adherence increased (table 13.3).

Table 13.3: Ability of variables associated with missing at least 20% days medication at $p \leq 0.1$ significance to predict other levels of adherence

Variables	Minimum number of missed days				Significance (p value)		
	10%	20%	25%		for 10%	for 20%	for 25%
i-need	+	+	+		0.027	0.001	<0.001
p-need	+	+	+		0.039	0.002	0.044
BMQ-benefit	-	+	+		0.090	0.004	0.004
Type 1st tx	+	+	+		0.006	0.008	0.023
Age	+	+	+		0.005	0.010	0.066
Type current tx	+	+	+		0.013	0.013	0.032
Live with partner	-	+	-		0.747	0.019	0.144
IPQ-emotions	+	-	+		0.033	0.052	0.009
Pre-emptive tx	+	-	+		0.049	0.067	0.034
Practical support	-	-	-		0.070	0.081	0.478
i-(need-concern)	-	-	-		0.081	0.086	0.058
Age left education	-	-	-		0.384	0.087	0.172
SF36 role emotion	+	-	+		0.009	0.091	0.048

+ $p \leq 0.05$; - $p > 0.05$

As a more comprehensive analysis, the data analysis in the current study was repeated after classifying subjects as non-adherent if they missed at least 10% days prednisolone (instead of at least 20% days). Bivariate analysis produced similar results to when the cut-off of missing at least 20% days had been used, the only differences being that there was a trend for the number of spontaneously reported cons of a transplant to be associated with non-adherence ($p = 0.064$) and living with a partner and age of leaving education were not associated. Forward stepwise logistic regression produced a model with no major differences to that most strongly associated with missing at least 20% days medication; the selected variables were having a transplant from a live donor and having less belief in the need for immunosuppressants as a group.

13.4 Summary of chapter thirteen

The variables with the strongest relationship with missed days on bivariate testing were having a first or current transplant from a live donor (odds ratio 12 and 10 respectively), living alone, younger age and having a lower score on the benefits and necessity scales of the BMQ. Belief in the need for immunosuppressants or prednisolone were both related to adherence. These two necessity scale scores were only moderately correlated with each other, indicating that subjects had different beliefs about their prednisolone compared to immunosuppressants as a class. Gender, time since transplantation, depression and the number of symptoms reported on the IPQ were not significantly associated with adherence. After controlling for other variables in logistic regression, the main factors associated with missing at least 20% days prednisolone were having a transplant from a live donor and having low belief in the need for both immunosuppressants as a group and for prednisolone specifically. The influence of the type of transplant diminished as belief in the need for either immunosuppressants as a group or prednisolone specifically increased.

14.0 Results: factors related to erratic timing (non-adherence defined by a standard deviation of inter-dose intervals of at least 6 hours according to electronic monitoring)

14.1 Relationship of individual variables to erratic timing

A mean standard deviation of inter-dose intervals of six or more was used to reflect erratic timing (non-adherence according to the timing of medication; see 8.1.7). Variables significantly related to erratic timing ($p \leq 0.05$) in binary analyses were (tables 14.1a and b)

- alternate day dosing of prednisolone
- pre-emptive transplantation
- more symptoms reported on the IPQ
- disappointment in the experience of transplantation from what was expected

Variables that were less strongly related but still significant at the $p < 0.1$ level, included having a first or current transplant from a live-related donor, younger age and functional limitations thought to be due to emotional factors (tables 14.1a and b).

There was a non-significant relationship with erratic timing of doses for concerns about immunosuppressants or prednisolone, belief in the general overuse of medicines, number of transplants, number of recalled rejection episodes, percentage of symptoms attributed to the transplant, belief in the general harm of medicines, gender, social class, years of education, length of time since transplantation, percentage of symptoms attributed to medication, depression and overall psychological distress.

Table 14.1a: Categorical variables significantly related to erratic timing

Variable	Odds ratio (group with larger odds of non-adherence)	Odds 1	Odds 2	X^2 (P value)*
Dose frequency	9.17 (Alternate day)	22/12	4/20	13.13 (<0.001)
Type first transplant	5.16 (Live transplant)	7/2	19/30	4.68 (0.064)
Type current transplant	3.56 (Live transplant)	7/3	19/29	3.10 (0.095)
Pre-emptive transplant	n/a (Pre-emptive transplant)	4/0	22/32	5.29 (0.035)

Odds 1: odds of non-adherence (number non-adherent/number adherent) in the group strongly associated with non-adherence
Odds 2: odds of non-adherence (number non-adherent/number adherent) in the group associated with adherence
*all with 1 degree of freedom

Table 14.1b: Continuous variables significantly related to erratic timing

Variable	Z statistic* (p value)	More non-adherence if:-
Change in view of transplant	-2.26 (0.023)	less good than expected
Number of symptoms	-1.97 (0.049)	more symptoms
Functional limitation from emotional factors	-1.76 (0.079)	more limitation

* calculated from the Mann-Whitney U statistic

14.1.1 Investigation of collinearity between variables selected for multivariate analysis

The only significant relationships ($p < 0.05$) between variables that were related to erratic timing at $p < 0.1$ significance were between type of first and current transplant ($p < 0.001$), between change in view of the transplant compared to what had been predicted and the number of symptoms experienced ($r = -0.18$, $p < 0.05$) and between dosing frequency and having a pre-emptive transplant ($X^2 = 5.22$, $p < 0.04$). Type of current transplant was used in regression modelling in preference to type of first transplant since the current transplant was hypothesised to be the most related to current adherence. Both the other related pairs of variables were used since they were judged to be measuring different concepts and they were only weakly related. Therefore the variables that were included in regression modelling were:-

- dosing regime
- pre-emptive transplantation
- type of current transplant
- number of symptoms reported on the IPQ
- change in view of a transplant
- age
- functional limitations thought to be due to emotional factors (SF36 scale)

14.2 'Predictors' of erratic timing

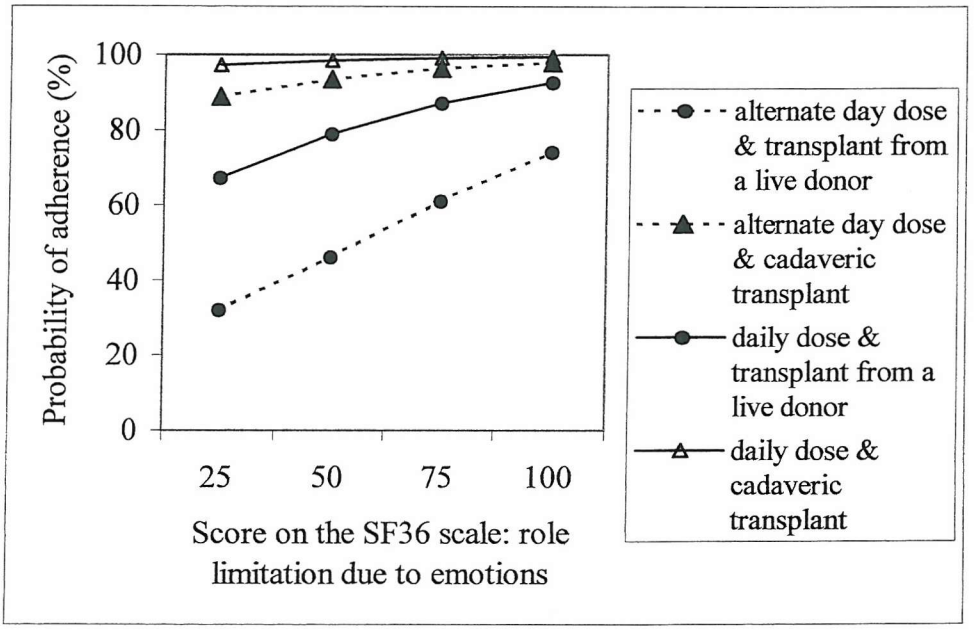
Table 14.2 shows the logistic regression model fitted to the variables related erratic timing at $p < 0.1$ significance. Three variables remained significant predictors: dosing frequency of prednisolone, type of transplant and the SF36 scale for 'role limitations due to emotional factors'. The model correctly classified 74% subjects. It indicated that that the odds of erratic timing increase 47-fold for subjects prescribed prednisolone on alternate days compared to those prescribed the medication daily, the odds increase 17-fold for those with a transplant from a live-related donor compared to a cadaveric donor and the odds decrease 0.2-fold for each unit increase on the SF36 scale. Figure 14.2 illustrates this graphically.

Table 14.2 Predictors of erratic timing from variables that were significant at the $p < 0.1$ level

Variable	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Likelihood ratio test (P value)	Homer & Lemeshow goodness of fit X^2 (P value), number of outliers*
Dose frequency	8.71 (2.40-31.55)	47.16 (4.39-506.21)	0.002	
Type of current transplant	3.44 (0.79-14.99)	16.83 (1.38-205.3)	0.027	
SF36 scale	0.98 (0.97-1.00)	0.98 (0.96-1.00)	0.030	
Final model				2.91 (0.71), 1

NA: number correctly predicted from 26 non-adherent subjects
A: number correctly predicted from 31 adherent subjects
* cases with studentised residuals greater than 2
SF36 scale: SF36 score for role limitation due to emotional factors

Figure 14.2: Relationship between adherence and reported functional limitations attributed to emotional factors after controlling for the type of first transplant and prescribed dosing frequency of prednisolone



14.3 Summary of chapter fourteen

The variables with the strongest relationship with erratic timing on bivariate testing were alternate day dosing of prednisolone, pre-emptive transplantation, more reported symptoms and reporting disappointment in the transplant compared to what had been expected. After controlling for other variables in logistic regression, the main factors associated with erratic timing were having a transplant from a live donor, being prescribed prednisolone on alternate days rather than daily and reporting more disability on the SF36 scale role limitation attributed to emotional factors.

15.0 Results: exploratory analyses conducted after initial data analysis

Although the current study addressed specific objectives (6.2), the lack of existing high quality research studies in the field led to exploratory analyses designed to generate hypotheses for future work. Since these analyses were based on observation of the initial data, and were not the result of a priori hypotheses, the results are presented in this separate chapter.

15.1 Wording of items to detect non-adherence to immunosuppressants

The other measures performed poorly when compared to detection of non-adherence by electronic monitoring. Possible reasons for this are discussed in section 16.2.2. One reason, that items are not sufficiently well phrased so as to minimise social desirability effects, required further exploration of the data. This analysis is presented here.

In the interview, more subjects reported being late taking immunosuppressants than missing them (table 15.1) and the subjects' rating of how often they were late was a better predictor of missing at least 20% days medication than their rating of how often they missed immunosuppressants. A similar pattern occurred for clinician ratings (table 15.1).

Table 15.1 Clinician rating and self-report of subjects taking immunosuppressants more than 2 hours late or missing them completely

	Number (%) subjects reporting 'very often', 'quite often' or 'occasionally'	**Sensitivity to detect subjects missing at least 20% days prednisolone (%)**	**Specificity to**
Clinician rating of taking immunosuppressants late, n=150	81 (54)	100	47
Clinician rating of missing immunosuppressants, n=150	21 (14)	14	88
Self-report of taking immunosuppressants late, n=146	51 (35)	86	73
Self-report of missing immunosuppressants, n=146	8 (5)	14	96

This may suggest that patients may be more likely to disclose missed medication if the question is phrased to ask about 'late taking' and clinicians may be more likely to accept that patients are late rather than miss medication completely. The results cannot be explained just

by the fact that more subjects took medication late than missed it, as reflected in the prevalence of erratic timing being higher than that of missing immunosuppressants, because self-report or clinician rating of late taking were more sensitive measures of non-adherence defined by missing at least 20% days prednisolone than self-report or clinician rating of the frequency of missed doses (table 15.1).

15.2 Belief in the need for medication

15.2.1 Necessity scale of the Beliefs about Medicines Questionnaire and adherence to immunosuppressants

As stated in section 6.2, the initial plan of analysis was based on the assumption that another adherence measure, ideally a self-report measure, would compare favourably to adherence measured by electronic monitoring. However no measure reached the pre-defined level of sensitivity with an acceptable positive predictive value (tables 11.4a and 11.5a, section 11.6).

It would be clinically useful to have a simple measure of adherence. Beliefs regarding the need for medication were identified from logistic regression modelling as major predictors of missing at least 20% days medication (missed days). It was hypothesised that, compared to questions asking directly about adherence, subjects would be less likely to think questions about the need for medication were related to assessment of adherence. Therefore questions about the need for immunosuppressants may be less affected by social desirability and may thus be better indicators of missed days. Therefore a pragmatic analysis was performed to investigate the ability of scores on the BMQ necessity scale to identify subjects who missed at least 20% or more days medication according to electronic monitoring.

The distribution of belief in the need for immunosuppressants as a group and for prednisolone specifically, as reflected in the total BMQ scale score, differed according to missed days ($p = 0.001$ and $p = 0.002$ respectively; table 15.2.1a; figures 15.2.1a and b) but not to erratic timing.

Table 15.2.1a: Belief in the need for immunosuppressants and prednisolone according to whether subjects missed 20% or more days prednisolone

Non-adherent	**Median (IQR)**	**Range**	**Mean (SD)**
i-need	19 (17 - 20)	15 – 21	18 (2)
p-need	15 (13 - 18)	9 – 18	15 (3)
Adherent	**Median (IQR)**	**Range**	**Mean (SD)**
i-need	21 (20 - 24)	16 – 25	22 (2)
p-need	19 (17 - 20)	13 – 25	19 (3)

Belief in the need for immunosuppressants (figure 15.2.1a) or prednisolone (figure 15.2.1b) according to whether subjects missed 20% or more days prednisolone

Figure 15.2.1a

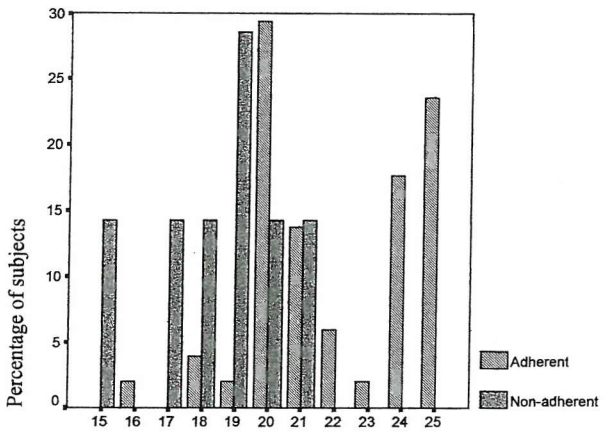
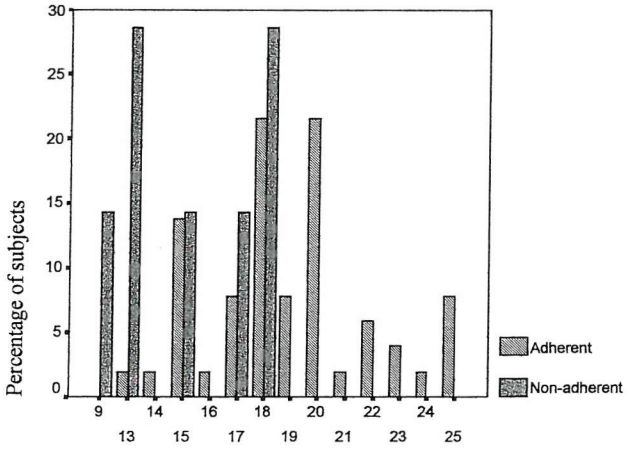


Figure 15.2.1b



Receiver operator curves were drawn for the BMQ necessity scales for immunosuppressants as a group and for prednisolone specifically. The sensitivity and specificity of the measures were calculated (table 15.2.1b).

Table 15.2.1b: The optimal cut-off on the BMQ necessity scale to identify subjects missing at least 20% days prednisolone

Criteria used to define non-adherence	**Sensitivity**	**Specificity**	**PPV[1]**	**NPV[2]**	**+LR[3]**	**Mis-classification rate**
p-need (total score ≤ 17)	71.4	72.5	26.3	94.9	2.6	27.6
i-need (total score ≤ 19)	71.4	92.2	55.6	95.9	9.2	10.3

[1]positive predictive value, [2]negative predictive value, [3]positive likelihood ratio
p-need: BMQ necessity scale relating to prednisolone
i-need: BMQ necessity scale relating to immunosuppressants as a group

Belief in the need for medication had better sensitivity and specificity when used to detect subjects missing at least 20% days prednisolone compared to the Morisky or MARS questionnaires (table 15.2.1c, table 11.5a). The BMQ necessity scale score related to immunosuppressants as a group was a better measure than the scale relating specifically to prednisolone (table 15.2.1c).

Figure15.2.1c: Relationship between percentage of days where medication was missed and the score on the BMQ necessity scale for prednisolone

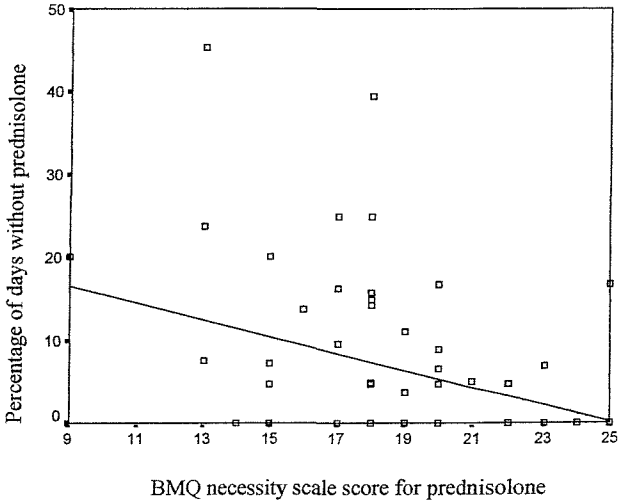
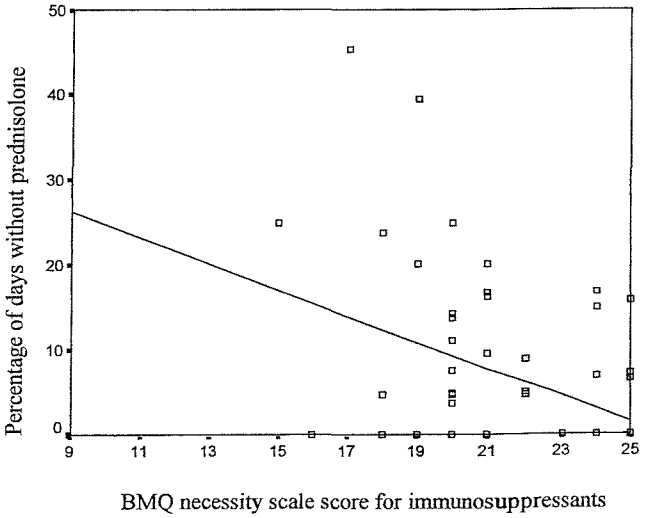


Figure15.2.1d: Relationship between percentage of days where medication was missed and the score on the BMQ necessity scale for immunosuppressants



15.2.2 Individual items of the Beliefs about Medicines Questionnaire and adherence to immunosuppressants

The other published study of belief in the need for immunosuppressants and adherence in renal transplant recipients (Greenstein & Siegel 1998) reported a relationship between individual beliefs and self-reported missed medication. Therefore the relationship between missed days and individual items on the BMQ necessity scale for immunosuppressants was examined. Most subjects answered 'agree' or 'strongly agree' to items on the BMQ. The proportion of subjects 'strongly agreeing' with each item was compared to their adherence assessed by electronic monitoring. Three of the individual items were significantly related to missed days (table 15.2.2).

Table 15.2.2: Relationship of not strongly agreeing with individual items on the BMQ necessity scale for immunosuppressants and missing at least 20% days prednisolone

BMQ necessity scale item	Number of subjects disagreeing with this item[1] (n = 151)	P value (X^2 value)
My health at present depends on my anti-rejection medicines	59	0.075 (3.33)
My life would be impossible without my anti-rejection medicines	85	0.034 (4.52)
Without anti-rejection medicines I would be very ill	76	> 0.100
My health in the future strongly depends on anti-rejection medicines	81	0.034 (4.52)
Anti-rejection medicines protect my kidney from failing	56	> 0.100

[1]not rating it as 'strongly agree'

15.2.3 Factors associated with belief in the need for immunosuppressants

Less belief in the need for immunosuppressants, as assessed by the BMQ necessity scale, was a strong predictor of missed days. Therefore factors strongly associated with the total score on the BMQ necessity scale relating to immunosuppressants were investigated using linear regression. The first stage of model selection included identifying variables that were related at $p \leq 0.1$ significance (table 15.2.3).

Table 15.2.3: Variables related to BMQ necessity scale for immunosuppressants at $p \leq 0.1$ significance

Variable	Test statistic (p value)	Less belief in the need for immunosuppressants if:-
Dose frequency	-2.37 (0.018)[1]	Daily dose
Pre-emptive transplant	-2.17 (0.030)[1]	Had dialysis[3]
Recalled one or more rejection episodes	-1.84 (0.065)[1]	No rejection recalled
Duration of current transplant	0.16 (0.048)[2]	Shorter time
Score on BMQ benefit scale	0.41 (<0.001)[2]	Lower score
Score on pros of medicines questionnaire	0.38 (<0.001)[2]	Lower score
Score on IPQ control-cure scale	0.30 (<0.001)[2]	Lower score[3]
Score on pros of transplant questionnaire	0.26 (0.001)[2]	Lower score
Score on BMQ overuse scale	0.19 (0.020)[2]	Higher score

[1]Z statistic calculated from the Mann-Whitney U statistic
[2]Pearson's correlation coefficient
[3]Association with non-adherence was in the opposite direction

The direction of effect of pre-emptive transplantation and dosing frequency was in the opposite direction to that predicted by association of the variables with adherence. Not having experienced dialysis (pre-emptive transplantation) was associated with both missed days and erratic timing but having received dialysis was associated with lower belief in the need for immunosuppressants. Although not associated with missed days, dosing frequency was associated with chaotic timing but it was alternate day dosing that was associated with chaotic timing whereas daily dosing was associated with less belief in need for immunosuppressants. Duration of transplantation was also associated with belief in the need for immunosuppressants in a direction that was not consistent with the hypothesised relationship with adherence. Since the items on the pros of medicine questionnaire were similar to those to those assessed in the BMQ necessity scale, the pros of medicine score was not used in regression modelling. Similarly the BMQ benefit scale is moderately correlated with the necessity scale so was not included in regression modelling. IPQ control-cure scale had poor internal reliability in this sample so also was not used in regression modelling.

A linear regression model, excluding cases pairwise, indicated that endorsing more pros of transplantation, alternate day dosing and recalling more than one rejection episode were the main predictors of the score on the BMQ necessity scale for immunosuppressants. Together these variables explained 12.4% variance in the scale score. The variable 'dosing frequency' related to prednisolone but not all subjects were taking this medication. If the 'dosing frequency' was removed from the model, not having had dialysis replaced dosing frequency and the final model explained slightly less variance (10.3%).

15.3 Depression

15.3.1 Depression and adherence

A surprising finding of this study was that depression was not associated with non-adherence. Depression and psychiatric illness in general are thought to be major predictors of non-adherence by clinicians (Hathaway et al. 1999; Bunzel & Laederach-Hofmann 2000) and depression has been related to non-adherence in previous studies of renal transplant recipients (Rodriguez et al. 1991; Kiley et al. 1993; Frazier et al. 1994).

The results of this study may have been due to lack of power since only 13 (22%) subjects with data from electronic monitors were moderately or severely depressed and only 7 (12%) were non-adherent according to missed doses. A diagnosis of severe (but not lesser degrees of) depression was associated with missing medication assessed by self-report of late taking of immunosuppressants in the interview ($X^2 = 4.53$, $p = 0.037$) where data on more subjects were available (144 compared to 58 subjects). Also clinicians' and the researcher's ratings of whether a subject was late taking immunosuppressants at least occasionally was related to the subject being severely depressed ($X^2 = 5.23$, $p = 0.038$; $X^2 = 4.63$, $p = 0.038$ respectively).

These findings suggest that either severe depression is associated with non-adherence if there is sufficient power in the study or that low mood in the patient influences self-report and clinicians assessment of non-adherence.

15.3.2 Depression and factors associated with non-adherence

The sample in this study was too small to statistically investigate interactions between variables. However, depression may exert its influence on adherence by influencing other variables related to non-adherence. Table 15.3.2 shows the relationship of adherence to variables that were found to be related to non-adherence in this study.

Table 15.3.2: Relationship of depressive illness to factors that were associated with non-adherence

Variable	Relationship to non-adherence	Relationship to depression
Live first transplant	M**, T*	Neither
Live current transplant	M**, T*	Neither
Living alone	M**	Severe**
Younger age	M**, T*	Neither
Less belief in the general benefits of medicines (BMQ benefit scale)	M**	Moderate or severe**
Less belief in the need for immunosuppressants (BMQ necessity scale)	M**	Neither
Less belief in the need for prednisolone (BMQ necessity scale)	M**	Neither
Pre-emptive transplantation	M*, T**	Neither
Left full-time education aged 18 years or less	M*	Neither
More negative emotions attributed to the transplant (IPQ emotions scale)	M*	Both**
Less desired practical support	M*	Neither
Functional limitations attributed to emotional factors (SF36 role limitations due to emotional factors scale)	M*, T*	Both**
Alternate day dosing of prednisolone	T**	Moderate or severe**
More negative view of the transplant than remembered prior to transplantation	T**	Severe*
More current symptoms (IPQ identity scale)	T**	Both (Severe**, moderate or severe*)

**$p \leq 0.05$; *$p \leq 0.1$ but > 0.05
M: related to missing 20% or more days prednisolone
T: related to a standard deviation of inter-dose intervals of 6 hours or more
Neither: $p > 0.05$ for severe and moderate or severe depression
Both: $p \leq 0.05$ for severe and moderate or severe depression
Severe only: $p \leq 0.05$ for severe depression
Moderate or severe: $p \leq 0.05$ for moderate or severe depression

15.4 Functional health status

15.4.1 Functional health status and expectations of a transplant

Subjects in this study had considerably more disability, assessed by the SF36, than the general population (Jenkinson et al. 1993). The discrepancy may relate to disappointment some subjects felt with the performance of their transplant, if they expected to feel 'normal' rather than just much better than on dialysis, they were likely to be disappointed. In support of this hypothesis was the finding that having a more negative view of the transplant than the subject remembered prior to transplantation, was strongly associated with the score on the SF36 scales for pain ($Z = -2.84$, $p = 0.005$), mental health ($Z = -2.42$, $p = 0.016$) and energy ($Z = -$

2.27, p = 0.023) and there was a trend to significance for general health perception (Z = -1.63, p = 0.103). However being a cross-sectional study, this study cannot determine the direction of any link.

15.5 Summary of chapter fifteen

Belief in the need for either immunosuppressants or prednisolone was a better predictor of missed days (but not erratic timing) than adherence measures. When used to identify subjects with missed days, belief in the need for prednisolone had a sensitivity of 71%, specificity of 92%, positive predictive value of 56% and only mis-classified 10% subjects. The mean score on the necessity scale scores for either immunosuppressants or prednisolone differed by 4 units between adherent and non-adherent subjects, with non-adherent subjects reporting less belief in the need for medication. On bivariate testing, the factors most strongly associated with greater belief in the need for immunosuppressants were alternate day dosing of prednisolone, pre-emptive transplantation, longer duration of transplantation, recalling one or more rejection episodes, score on the pros of medicines or pros of transplant questionnaire and scores on the BMQ benefit or control-cure scale. However dosing frequency and pre-emptive transplantation were associated with believed necessity in the opposite direction predicted by associations with adherence. Despite bivariate associations, the variables accounted for relatively little of the explained variance in the BMQ necessity scale score.

Although depression was not associated with adherence as measured by electronic monitoring on bivariate testing, it was associated with several factors associated with non-adherence, particularly for adherence to dosing frequency. Furthermore, in the whole sample, severe depression was related to self-reported adherence at interview. Thus depression may influence adherence by interacting with other variables or the current study may have lacked sufficient power to find a relationship between depression and adherence.

Self-reported functional health status of subjects was lower than that reported by community samples. Post hoc analysis indicates that this may be related to transplant recipients feeling disappointed with the performance of their transplant.

16.0 Discussion

The study used a cross-sectional design to investigate adherence to immunosuppressants in adult renal transplant recipients using electronic monitoring as the 'gold standard' measure of adherence. The main results related to the measurement of adherence, the prevalence of non-adherence and the identification of major factors associated with non-adherence. Regarding the measurement of adherence, self-report, clinician rating and cyclosporin levels were all poor predictors of missed days or erratic timing assessed using electronic monitoring. Self-report at interview was the most sensitive and specific of these measures but, since the researcher was independent of the clinical team, this measure could not be generalised to a clinical setting. Secondary analysis of the results indicated that belief in the need for immunosuppressants as a group or for prednisolone specifically may be a more valid indicator of adherence. Regarding the prevalence of non-adherence, amongst monitored subjects, 12% missed at least 20% days medication and 45% took their prednisolone outside a 12 hour period 32% of the time. Regarding major factors associated with adherence, having a transplant from a live donor was strongly associated with non-adherence defined by missed medication or by erratic timing of doses, less belief in the need for immunosuppressants as a group or for prednisolone specifically was strongly associated with missing medication and alternate day dosing of prednisolone and self-reported role limitation attributed to emotional factors was associated with erratic timing.

However the results need to be interpreted in the light of methodological features of the study. Therefore this chapter will commence with a discussion of the strengths and weaknesses of the study in relation to the use of electronic monitoring, other adherence measures, the definition of non-adherence and measurement of other variables. The results of the current study will then be discussed and related to findings from previous research. Finally the main clinical and research implications will be outlined.

16.1 Strengths and weaknesses of the methodology

16.1.1 Benefits of using electronic monitoring to measure adherence

Electronic monitoring is now widely thought to be the best overall measure of adherence and it is unique in enabling a continuous description of adherence. This is the first study in Europe to use electronic monitoring to assess adherence in renal transplant recipients and is the first study in this population to compare the performance of other measures of adherence to electronic monitoring. Subjects were not told the function of monitors thus minimising the

chance of social desirability bias or the Hawthorne effect distorting the results. However although only two subjects appeared to have guessed the function of the monitor it is not possible to be sure that others were not aware that adherence was being monitored.

16.1.2 Problems resulting from the use of electronic monitoring

The size and cost of electronic monitoring bottles and their use as the 'gold-standard' measure of adherence led to the two main limitations of the study, namely reduced power and availability of 'gold-standard' adherence data only for prednisolone.

The cost of the monitors and feasibility of filling them with medication restricted the use of monitors to 60 subjects. Other measures performed poorly against electronic monitoring so the number of subjects for the main analyses was restricted. This reduced the power of the study, especially for the multivariate analyses. The wide 95% confidence intervals of the estimate of the prevalence of non-adherence (4-20%) are also due to the relatively small sample size. However the study had sufficient power to detect the difference in belief in the need for immunosuppressants between adherent and non-adherent subjects. It was estimated that a standard deviation of 0.95 between skewed scale scores in the adherent and non-adherent groups could be detected with 80% power in a sample of 58 (7.4). The actual difference in mean scale scores between the adherent and non-adherent subjects was 4. The standard deviation was 2 so a difference of 1.9 could have been detected with 80% power.

Local pharmacists told the research team that cyclosporin would deteriorate if removed from its foil packaging and, in this packaging, cyclosporin tablets were too large to fit a six week supply into electronic monitoring bottles. Nevins and colleagues (2001) may also have been unable to use cyclosporin in electronic monitors since they report using azathioprine and they did not give a reason for not using cyclosporin. However other groups (De Geest et al. 1998; Feldman et al. 1999) have used cyclosporin in electronic monitors with one group reporting that the tablets remained in foil packaging.

Although they are both immunosuppressants in widespread use, prednisolone differs in several ways from cyclosporin and this may have affected the results of the study. Cyclosporin is the main immunosuppressant in triple therapy regimes and several subjects in the current study reported viewing cyclosporin as more important than prednisolone. There is controversy within the medical profession about the need for long-term prednisolone within immunosuppressant regimes. Clinicians within the renal unit differed in the proportion of

patients they maintained on steroids, which may reflect differences in the perceived importance of prednisolone amongst the staff. The proportion of males maintained on steroids was greater than the proportion of females. The different prescribing patterns within the unit may have contributed to subjects' uncertainty regarding the need for prednisolone, as found in an earlier study by Siegel & Greenstein 1997. Perceived importance, or need, was found to be associated with adherence in the current study. Therefore lower perceived need for prednisolone may mean non-adherence is greater for prednisolone than cyclosporin. Other measures of adherence measures adherence to cyclosporin (cyclosporin levels) or immunosuppressants as a group (self-report, clinician rating, interviewer rating). The lower perceived need for prednisolone compared to cyclosporin may have contributed to the poor performance of these other adherence measures in comparison with electronic monitoring of adherence to prednisolone.

Furthermore cyclosporin is prescribed twice daily whereas prednisolone is prescribed daily or on alternate days. Dosing frequency is known to affect adherence and was related to erratic timing of prednisolone in this study. Therefore the findings relating to the frequency of adherence to prednisolone may not be generalisable for all immunosuppressants. However the only other comparative study using electronic monitoring, found adherence to prednisolone to be greater than adherence to cyclosporin (Feldman et al. 1999) and a study using pill counts reported adherence to be the same between the two drugs (Hilbrands et al. 1995). Thus adherence to prednisolone does not appear to be worse than adherence to cyclosporin.

Other problems also occurred due to the use of electronic monitors. Many subjects were anxious that the study was a drug trial and refused consent due to fear the monitor may contain placebo tablets. This fear requires further investigation and may be a particular problem for the use of electronic monitoring in transplant recipients who are likely to have strong belief in the need for medication. To overcome the difficulty, subjects were given the opportunity of being given an empty monitor. This may have been a confounding variable and it would have been better to do this for all subjects. However post hoc analysis did not find a relationship between adherence and refusal to use medication supplied by the researchers. Use of an empty container in future studies would have the advantage of putting all the subject's medication in the monitor, ensuring they did not have other supplies of that medication and so increasing the chance of a missed opening reflecting a missed dose and not being due to the subject taking the tablet from another source.

16.1.3 Benefits of the use of other measures of adherence

A strength of the study is the use of standardised questionnaires (Morisky and MARS) to assess self-reported adherence. Previous studies have used instruments designed expressly for that study and have failed to specify the exact wording of the questionnaire. Furthermore the current study is the first in renal transplant recipients to report measurement of self-reported adherence using both general and specific terms such as 'rarely' and 'once a month' respectively. This enabled comparison of results with previous studies using either type of definition of non-adherence and enabled the performance of both forms of wording to be tested against electronic monitoring. Cyclosporin levels are widely held by clinicians to be indicators of adherence and this is the first study to compare the prediction of non-adherence using cyclosporin levels with that assessed using electronic monitoring.

16.1.4 Problems with the other adherence measures

Although the Morisky and MARS questionnaires are standardised, neither specifies the number of days used to define the response categories. Therefore different subjects may interpret the questions differently. The interviewer and clinician questionnaires did not specify numbers of missed tablets and they were designed just for this study. However they were quick and simple to use and are likely to reflect the way clinicians think of non-adherence in their patients.

16.1.5 Attempting a clinically significant definition of non-adherence is a strength of the study

This is the first study measuring adherence in transplant recipients that attempted to identify a clinically significant level of non-adherence; an 'expert' consensus was sought. Medical staff in the unit were surveyed (table 8.1.7) since they would have given the subjects in the study information about their medication. The questions were asked in relation to an 'average' patient in terms of risk factors for rejection to improve generalisability and the pattern (consecutive or sporadic missed doses) and timescale of non-adherence was specified.

16.1.6 Problems with the survey of renal staff

The survey would have been more generalisable if it had included clinicians from other renal units and other staff who may give the patients information such as general practitioners and renal nurses. More consensus may have been reached if specific case scenarios had been given and particular drugs specified; for example 'what are the maximum number of doses of cyclosporin that could be missed without increased risk of rejection in a 40 year old,

otherwise fit man, with an identically matched primary cadaveric transplant, two years post-transplantation, with no previous episodes of rejection and receiving an immunosuppressant regime of cyclosporin twice daily, prednisolone daily and azathioprine daily'.

16.1.7 Strengths of the definitions of non-adherence used in the current study

A staff consensus did not occur therefore an arbitrary definition of non-adherence was used. However the definition, based on data from electronic monitors, was standardised and included an assessment of both missed doses and timing variation. Because the definition of non-adherence was arbitrary, conservative criteria were chosen to both identify missed days and to define the threshold for non-adherence. Analyses from electronic monitoring only included data between the dates of the first and last opening. All other studies of immunosuppressant adherence using electronic monitoring imply that the monitored period was calculated as all the days the subjects had the monitor. Only one study, in heart transplant recipients (De Geest et al. 1998) reports questioning subjects regarding the actual days that they used the monitor.

16.1.8 The definitions of non-adherence may have underestimated the proportion of subjects at increased risk of rejection

The use of missing 20% or more days to define non-adherence is a conservative definition since all but one previous study of adherence to immunosuppressants in transplant recipients uses a definition of missing 0-10% doses (tables 5.2.2b,c and d). Furthermore, in heart transplant recipients, the risk of rejection appears to increase when as few as 3% doses are missed (De Geest et al. 1998) which has led to the suggestion that transplant recipients require 100% adherence to immunosuppressants (De Geest et al. 1999). This lower level is similar to that used in studies which used questionnaires asking subjects to specify how many days in the last month they missed medication. The commonest threshold to define non-adherence in renal transplant recipients was missing immunosuppressants 'at least once' in the last month (5.2.1). This definition classifies a subject on daily dosing a non-adherent if they miss 3% doses. The other definition of non-adherence in the current study, a standard deviation of 6 hours or more, is even more conservative in comparison to studies reporting clinicians estimate of the required adherence to dose timing (Hathaway et al. 1999).

16.1.9 Strengths and weaknesses related to the measurement of factors potentially associated with non-adherence

The investigation of factors that were potentially related to adherence was an exploratory aspect of the study so all relevant variables were assessed. However the large number of variables made it likely that some apparent associations with adherence on bivariate testing would be due to type one error. Due to this risk, only the variables that were most strongly associated were entered into a logistic regression model and a conservative method of modelling was used. However the possibility of type one errors in the study, means that results relating to factors associated with adherence should be interpreted cautiously.

A difficulty for the study related to the concepts of a transplant and transplant failure. The BMQ is designed to assess beliefs about medicines used to treat an illness and the IPQ is designed to assess the constructs which people use to organise their beliefs about an illness. However a transplant is itself a treatment for end-stage renal disease, and is not an illness itself. Thus the immunosuppressants transplant recipients receive are to prevent transplant failure, or 'treatment failure' rather than to directly treat a disease. The constructs used by patients to organise their views about a transplant are not known but may not be the same as those used to organise beliefs about an illness per se. Some constructs within the IPQ, such as emotional response or negative consequences, seem to be applicable to a transplant but others, such as controllability, seem less applicable and need to be applied to the risk of transplant failure rather than the transplant itself. Although there may be less difficulty with assessing beliefs about immunosuppressants in the same way as beliefs about other medications, patients may have different or additional constructs, such as risk of omitting tablets, when organising beliefs about preventative medication.

These conceptual difficulties may partly explain the poor internal reliability of the consequences and control-cure scales in this sample compared to the populations in which the IPQ was tested (table 12.5.2b). The control-cure scale has also been shown to have poor internal reliability in another study of renal transplant recipients (Stabler, personal communication 1999). The conceptual difficulties may also relate to the finding in the current study that unlike other illness groups (Horne, personal communication 2002), the difference between scores on the necessity and concerns scales did not have a stronger relationship with non-adherence than the score on either scale alone.

16.2 Discussion of results relating to the frequency of non-adherence and comparison with previous studies

16.2.1 Distribution of non-adherence according to electronic monitoring

This is the first study to describe the distribution of adherence to the number of prescribed doses and the timing of medication in renal transplant recipients. The percentage of days prednisolone was missed was highly skewed (figure 11.1b) with the majority of subjects missing little, if any, medication. However a significant minority of subjects (12%) missed at least 20% days prednisolone and just over a quarter (26%) missed at least 10% days medication (fuller discussion in 16.2.3). The distribution of the standard deviation of inter-dose intervals was much less skewed (figure 11.1c), indicating that although relatively few subjects miss medication, many take it at erratic times. Twenty-five percent of subjects had a standard deviation of inter-dose intervals of 8.6 hours or more (table 11.1) indicating that they took prednisolone outside a 17 hour period 32% of the time. Using a standard deviation of inter-dose intervals of at least 6 hours or missing at least 20% days prednisolone to define non-adherence, almost all the subjects who missed medication (6/7, 86%) also took their prednisolone at erratic times. However most subjects who took prednisolone erratically (31/51, 61%) did not miss 20% of doses.

A survey of clinicians indicates that staff think that both missing medication and taking it erratically can increase the risk of rejection (Hathaway et al. 1999). However only two previous studies of adherence in renal transplant recipients have defined non-adherence in terms of either missing medication or being late taking tablets (Sketris et al. 1994; Teixeira de Barros & Cabrita 2000). It is not clear to what degree each aspect of non-adherence contributes to clinical risk or whether subjects who both miss medication and take it erratically have a higher risk than subjects who only miss it.

16.2.2 Comparison of adherence measures with electronic monitoring

The other measures of adherence were not good at accurately detecting subjects who either missed 20% or more days prednisolone or who had a standard deviation of inter-dose intervals of 6 hours or more according to electronic monitoring.

Cyclosporin levels were particularly poor whether the range between the highest and lowest levels or the lowest level was used. This is surprising since cyclosporin levels reflect immunosuppressant levels directly. The results could be explained by subjects having taken their cyclosporin differently in the days prior to the clinic visit, so called 'white coat

compliance'. However there is medical debate about the levels of medication required with increasing time post-transplantation and the results may be explained by some subjects not requiring high levels of cyclosporin to prevent rejection. The study design may also have contributed to the poor performance. Prednisolone was monitored by electronic monitoring so if adherence to cyclosporin and prednisolone differed, cyclosporin levels would not reflect adherence to prednisolone.

As previously discussed (11.4) trough levels in the current study may have been poor indicators of adherence since both low and high trough levels could indicate non-adherence. Subjects with their lowest cyclosporin level in the last six measurements being at least 130.0 ng/ml were more likely to miss at least 20% days prednisolone (table 11.4b). However this is from a post-hoc analysis, is unexpected and from a relatively small sample. Furthermore there was not a significant relationship with self-reported adherence and the finding is dependent upon the criteria used to categorise subjects. Thus the association of trough cyclosporin levels with adherence requires replication before confidence can be expressed in the hypothesis that high trough levels indicate non-adherence.

The self-report questionnaires performed poorly compared to electronic monitoring. The Morisky and MARS questionnaires produced similar results. Subjects tended to answer the MARS questionnaire in a binary manner despite being able to report a greater range of adherence behaviour (rated 'always' to 'never' rather than just 'yes' or 'no') and not specifying the reason that they may alter medication. This response pattern to the MARS has not occurred in samples with other medical conditions (Horne 2002, personal communication). However significant skewing of responses is reported in most other studies of renal transplant recipients (e.g. Greenstein & Siegel 1998). Self-reported adherence is recognised to be sensitive to social desirability effects and there are reasons to think that such effects may be particularly strong in a transplant population. Comments made by subjects to the researcher suggest that they believe that they should be grateful for their transplant and that they are aware that transplants are a scarce and costly commodity. Several subjects also reported memories of conversations between staff and patients where staff were perceived to be angry at patients they thought had suffered rejection due to non-adherence with immunosuppressants. All the self-report, clinician and interviewer measures rated adherence to immunosuppressants in general, so if adherence to prednisolone differed this could account for some of the results.

Within the MARS questionnaire more subjects reported forgetting medication (reflected in an answer greater than 'never') more often than altering the dose, taking less or stopping or missing immunosuppressants. 'Forgetting' has been found to be the most commonly reported reason for missing immunosuppressants given by subjects in other studies (Sketris et al. 1994; Kory 1999). However forgetting does not appear to be a random, and thus unavoidable, event since subjects are also able to associate factors, such as being tired or away from home, with an increased likelihood of forgetting medication (Valentine 2000).

Self-report yielded lower estimates of non-adherence than assessment by clinicians or a researcher but self-report in interview had the highest agreement with electronic monitoring. The benefit of disclosure in an interview setting rather than by questionnaire cannot be explained by independence from the clinical team since subjects were reassured that none of their answers would be conveyed to clinicians. There was no more disclosure of non-adherence in the interview since similar proportions of subjects reported being late sometimes or occasionally on the single questionnaire item and in the interview (35% on both). The better performance of the interview measure was thus due to more accurate reporting. This suggests that the MARS and Morisky questionnaires are not worded in the most appropriate way to detect non-adherence to immunosuppressants. Exploratory analyses presented in 15.1, suggest that better detection may occur if interviewed subjects are asked about taking medication late rather than missing it completely. The same may be true regarding the phrasing of questionnaire items.

An interesting finding of the study was that belief in the need for immunosuppressants in general or prednisolone specifically were better predictors of non-adherence than other measures (table 15.1a). As discussed in chapter 15, this may be because subjects are less likely to associate the questions with measurement of adherence and thus the questions will be less prone to social desirability effects.

16.2.3 The level of non-adherence that is thought clinically significant by renal staff

Lack of consensus between staff was also found in the study by Hathaway and colleagues (1999). They report estimates given by a single clinician (nephrologist, surgeon or nurse transplant co-ordinator) from different transplant centres throughout, predominantly, the United States. Although the median percentage days of immunosuppressants that could be missed without clinical harm was estimated to be 10%, answers ranged from 0 - 100% days. Similarly the median timing variation that would lead to increased risk was estimated to be 2

hours but answers ranged from 0 - 48 hours. However, unlike the study by Hathaway and colleagues, this study only surveyed nephrologists, all of whom came from the same renal unit, thus more consensus may have been predicted. The lack of agreement between staff (table 8.1.7) is a significant issue not only for the definition of non-adherence but also needs to be considered when patient beliefs are reported. It is also a clinically important finding (see below 16.5).

16.2.4 Frequency of non-adherence

This study found that 12% (95% confidence intervals 4 – 20%) subjects missed at least 20% days medication. This is a lower frequency of non-adherence than found in most previous cross-sectional studies (median 22%, IQR 18-26%, table 5.2.3b).

As discussed above (16.1.7) the definition of non-adherence in the current study was chosen to produce a conservative estimate of non-adherence. In contrast to the current study, the two other studies of adherence following renal transplantation using electronic monitoring did not report how data from monitors were analysed. Nevins and colleagues (2001) reported that monitored days started from the first day of hospital discharge but also reported that days were excluded if 'the monitor cap malfunctioned or it was physically lost' and they did not report whether they excluded days where monitors were in the post to subjects. Feldman and colleagues (1999) reported that two subjects 'began to use the monitored medications 5 to 7 days later than instructed' and '2 of the 63 monitors failed to record data correctly' but it is not clear how this affected analysis of the data. Neither study reported whether subjects could have used other supplies of medication. If either study included days where the subject took medication from another source, this could incorrectly inflate their measure of non-adherence. The current study aimed to minimise the risk of that error by only including days between the first and last openings.

The dosing regime may also account for differences between the current and previous studies. Feldman and colleagues (1999) included subjects on daily and twice daily cyclosporin regimes and found that there was a trend for subjects on twice daily prescriptions to miss more doses of both azathioprine and cyclosporin. This difference was more apparent when 'non-compliant days' were calculated since missing either of the two doses on one day was counted as a non-compliant day. Nevins and colleagues (2001) only assessed adherence in the first 6 months of transplantation, a period excluded from this study, and had a greater percentage of subjects with transplants from live-related donors (55% compared to 12%) than this study. This study found that a live donor increased the risk of missing medication.

Furthermore Nevins and colleagues (2001) may have had biased results due to a large number of eligible subjects not taking part or being without available data (205, 60%).

Table 16.2.4a: Results of electronic monitoring in the current study compared to previous studies in renal transplant recipients

Study	Monitored drug	Median percentage of days medication was missed (range)
Feldman et al. 1999	cyclosporin	5.3 (0.0 – 37.5)
	azathioprine	3.6 (0.0 – 67.3)
Nevins et al. 2001	azathioprine	2.8 (0.0 – 84.0)
Current study	prednisolone	0.0 (0.0 – 45.3)

Nevins and colleagues (2001) reported that over a 4 year follow up, 'lower compliance rates during the first 6 months were associated in a dose-response fashion with acute rejection and graft loss' ($p = 0.006$ and 0.002 respectively). Death with function was included as 'graft loss' but the authors report that this was not associated with adherence.

Like other studies, the current study was unable to base the definition of non-adherence on a clinically significant level of non-adherence. Subjects missing at least 20% days were classed as non-adherent. The proportion of non-adherent subjects identified in this manner is substantially lower than that found by Chisholm and colleagues (2000) who also used the same definition. However the study by Chisholm and colleagues was very small (n=18), only assessed adherence in the first year of transplantation and measured adherence by comparing pharmacy refill data with the prescription in the medical notes. This measure is prone to error due to errors in entering prescription refill data on the computer system and by clinicians not recording all changes to medication in the notes.

Table 16.2.4b: The percentage of missed medication in the current study compared to previous studies

Study	Percentage of subjects missing at least 10% days medication	Percentage of subjects missing at least 20% days medication
Hilbrands et al. 1995[1]	23	n/a
Chisholm et al. 2000	n/a	67
Nevins et al. 2001	20	n/a
Current study	26	12

[1]defined non-adherence as taking either 10% extra doses or less than 10% of doses

Two previous studies have defined non-adherence as missing 10% or more days medication. The level of non-adherence using this definition was similar to the current study. Although the

median level of non-adherence was greater in Nevins and colleagues' (2001) study than in the current one, the percentage of subjects missing at least 10% days medication was slightly lower (table 16.2.4b).

Table 16.2.4c: Results of the current study compared to previous studies defining non-adherence as forgetting or missing immunosuppressants more often than 'never'

Study	Percentage of non-adherent subjects
Frazier et al. 1994	45
Kory 1999	25
Raiz et al. 1999	26
Valentine 2000	26
Current study:-a) Morisky questionnaire item	30
b) MARS questionnaire item	33
c) self-report in interview	46

As discussed above, asking subjects how often they are late taking immunosuppressants may be a more acceptable question for patients than asking how often medication is missed. Sixty-seven (57%) subjects reported taking medication more than 2 hours late at least occasionally in the last month. This is a much larger percentage than found in other studies when subjects were asked how often they miss, forget or alter the dose medication in a month (table 16.2.4d) and is much larger than the percentage missing 10 or 20% days assessed using electronic monitoring. These comparisons suggest that asking about late taking may be too sensitive to use as the sole indicator of non-adherence since it may incorrectly identify many subjects who are actually adherent ('false positives'). However previous studies, using reported non-adherence in the last month, may also have mis-classified many subjects as non-adherent when they were truly adherent because in this study (table 11.4a) a definition including a specific time-scale had a lower specificity compared to a definition using general terms such as 'rarely'.

Table 16.2.4d: Results of previous studies defining non-adherence as missing, forgetting or altering the dose of immunosuppressants at least once in the last month using a self-report questionnaire

Study	Percentage of non-adherent subjects
Didlake et al. 1988	19
Sketris et al. 1994	26
Siegel & Greenstein 1997	19
Greenstein & Siegel 1998	22
Raiz et al. 1999	26
Teixeira de Barros & Cabrita 2000	17

16.3 Discussion of results relating to possible factors associated with non-adherence and comparison with previous studies

16.3.1 Reminders for medication

The mean of 6 medicines per day was consistent with other studies in renal transplant recipients (5.4 in Kiley et al. 1993 and 5.5 in Sketris et al. 1994). A large proportion of subjects (73%) reported using a reminder for their medication but this was not associated with a greater likelihood of adherence. In a previous study (Kory 1999) the majority of subjects reported using a reminder for their immunosuppressants but this percentage decreased with time post-transplantation. Reminders may only help to a small degree and so their use may only differentiate subjects with lower degrees of non-adherence. Subjects in this study reported that the most common reminder for their medication was comments from their partner. Partners may be subject to the same difficulties as patients regarding remembering medication since other studies document that patients report forgetting immunosuppressants when they are busy or their daily regime changes, such as when they are away from home (Frazier et al. 1994; Valentine 2000). However against this hypothesis is the finding that, in subjects using a reminder, adherence assessed by electronic monitoring or self-report in interview did not relate to being reminded about medication by a partner. Although alternate day dosing was associated with non-adherence to dose timing, use of a calendar, to mark days to take prednisolone, was not associated with adherence.

16.3.2 Functional health status

The finding of greater levels of disability than the general population replicates earlier findings in renal transplant recipients (Fujisawa et al. 2000; Manu et al. 2001; table 16.3.2).

Subjects in this study reported more disability than those in previous studies (table 16.3.2). However samples in previous studies differed from that in the current study in ways that would be predicted to reduce disability in the other studies. Fujisawa and colleagues (2000) included a greater proportion of subjects with transplants from live donors (74% versus 12%), only included subjects with a primary graft (compared to 82% in the current study) and had a lower proportion of subjects with diabetes (4% versus 9%). Manu and colleagues (2001) excluded patients with a history of rejection or 'other complications'.

Table 16.3.2: Scores on the SF36 scales in the current study compared to previous studies (higher scores reflects less disability)

Scale	Current study mean (SD)	Previous studies in renal transplant recipients		Population norms for mean (SD)[3]
		mean (SD)[1]	Mean[2]	
Role limitation due to emotional problems	70.5 (41.7)	78.0 (37.2)	79.1	82.5 (32.0)
Social functioning	72.6 (28.5)	82.1 (19.7)	80.2	87.8 (19.6)
Pain	68.0 (27.5)	80.2 (21.6)	78.6	81.2 (21.7)
Mental health	70.9 (19.1)	70.0 (19.7)	68.8	72.9 (17.2)
Physical functioning	63.8 (29.8)	86.2 (14.8)	84.6	88.9 (16.5)
Energy / vitality	51.0 (23.3)	63.3 (20.3)	64.1	60.1 (19.4)
Role limitation due to physical problems	50.8 (43.8)	77.6 (35.0)	77.4	86.1 (29.3)
General health perception	51.0 (22.5)	56.4 (19.0)	56.3	74.3 (19.5)

[1]Fujiswa et al. 2000; [2]Manu et al. 2001 (SD not given)
[3]norms for social class III non-manual workers from Jenkinson et al. 1993

16.3.3 Psychological symptoms and psychiatric illness

Depressive illness was common in this sample with 28 (19%) subjects completing the CIS-R having a moderate or severe depressive disorder according to ICD-10 criteria. Nine (6%) of the interviewed subjects were taking anti-depressant medication, only one of whom currently fulfilled criteria for depression, so the actual prevalence of depressive illness in the sample may be higher than reported. There are no other studies of the prevalence of depression assessed using standardised diagnostic interviews in renal transplant recipients. Two studies of referrals to psychiatrists from a renal unit (House 1989; Rustomjee & Smith 1996) report that mood disorder diagnosed according to DSM-III criteria was the commonest diagnosis, occurring in 22 and 24% subjects respectively. However the majority of referrals were of patients on dialysis, not with a transplant and psychiatric disorders are thought to be more prevalent amongst dialysis patients than transplant patients (Petrie 1989).

Twenty-seven (96%) subjects with moderate or severe depression were not on anti-depressants. This represents significant untreated morbidity. However the current study is unable to determine the cause for absent treatment: depression may have been missed by clinicians, clinicians may not have prescribed anti-depressants or the patient may have refused psychotropic medication. Depression is important to address since effective treatments exist and depression impairs quality of life and may increase the risk of transplant loss and mortality.

16.3.4 Beliefs about medicines

All questionnaires assessing belief in the need for immunosuppressants (BMQ necessity scale and pros and cons questionnaires) found that subjects tended to have strong beliefs in the need for immunosuppressants as indicated by the majority of subjects scoring in the upper half of the questionnaire relating to the benefits of medication (tables 12.5.1b and 12.5.3). The proportion scoring in the upper half of the BMQ necessity scale for immunosuppressants was similar to that found in an unpublished study by Stabler (personal communication 1999) in renal transplant recipients (97 and 91% respectively).

Subjects also tended to express stronger belief in the need for immunosuppressants than concerns with the medication as reflected in more subjects scoring in the upper half of the BMQ necessity or pros of medicines scale than in the BMQ concerns or cons of medicines scale (tables 12.5.1b and 12.5.3). The proportion of subjects scoring in the upper half of the BMQ concerns scale, indicating strong concerns, was 22% for immunosuppressants as a group and 37% for prednisolone. When two extra items were added that seemed especially relevant to immunosuppressants, the proportion of subjects scoring in the upper half of the scale increased to 41% and 56% for immunosuppressants and prednisolone respectively. These latter proportions are similar to the 42% found by Stabler who also added three items related specifically to immunosuppressants. One of the additional items in the current study asked about concerns with changed appearance. More women than men agreed with this concern as has been found in other studies of patient concerns due to immunosuppressant side effects (Stabler personal communication 1999; Moons et al. 1998; Teixeira be Barros & Cabrita 1999).

However cued responses (where subjects are asked to endorse specific benefits or problems rather than generate benefits and problems themselves) may not reflect how patients spontaneously think about their medicines. When asked to list all the reasons they took immunosuppressants and all the problems they experienced with their medicines, 54% subjects reported more problems than benefits (table 12.5.4). However a simple subtraction of the number of reported problems from the number of reported benefits does not take into account the differential importance of answers, for example one reason to take immunosuppressants may be to prevent rejection and this may be more important to a subject than several concerns related to minor side effects. Furthermore the median number of answers given in relation to questions about the need for immunosuppressants and concern with the medication was small, making interpretation of the results tentative.

Although scores tended to be skewed, previous studies by the group designing the BMQ have reported mean (SD) scale scores. The mean score on the necessity and concerns scales in this study is similar to that found in diabetic subjects and reflects greater belief in the need for medication and less concerns with the medication than found in asthmatic, cardiac and psychiatric patients or those on renal haemodialysis. The only other identified study using the BMQ in renal transplant recipients is an unpublished MSc. thesis (Stabler, personal communication 1999). This also found a high mean score on the necessity scale for immunosuppressants (mean 22.2, SD 2.8; Stabler, personal communication 1999) but the concerns scale in Stabler's study included three extra items so the mean score cannot be compared to those given in table 16.3.4a.

Unlike the pilot study, the main study found that subjects commented that they did not perceive prednisolone to be as important as cyclosporin and some subjects did not know that it was an immunosuppressant at all. This led to all the remaining subjects who were prescribed prednisolone ($n = 111$) being given the BMQ necessity scales relating to immunosuppressants as a group and prednisolone specifically. Subjects tended to have lower scores on the scale relating to prednisolone alone, reflecting less belief in the need for prednisolone ($Z = -8.00$, $p < 0.001$ on Wilcoxon rank test). However subjects had generally high belief in the need for both immunosuppressants as a group and prednisolone specifically with 97% and 78% subjects respectively scoring in the upper half of the necessity scale.

Subjects also reported belief in the need for medication when they were asked the relative importance of immunosuppressants as a percentage of all things that keep their transplant working. The median importance of immunosuppressants was 90% in relation to transplant survival but this measure did not relate to missed days or erratic timing of prednisolone. However the median importance of anti-hypertensives was 80% in relation to blood pressure control and 40% in relation to transplant survival (table 12.5.5). The corresponding number of days in a year that subjects estimated anti-hypertensives could be missed before their blood pressure rose or the risk of rejection increased was 20 and 80 respectively. Thus greater belief in the importance of medication appeared to be related to believing less tablets could be missed before clinical harm occurs.

Table 16.3.4a: Comparison of mean (standard deviation) BMQ scale scores in the current study with those found by Horne et al (1999) in other illness groups

Study	**Horne et al. 1999**					**This study**
Medicine specified in specific section	My medicines					My immunosuppressants
Sample	Out-patient asthma	Out-patient diabetes	Out-patient general psychiatry	In-patient cardiac	Hospital haemodialysis	Out-patient renal transplant
Sample size	78	99	85	116	47	151
Necessity scale	19.67 (3.23)	21.26 (2.98)	17.72 (3.75)	18.72 (3.02)	19.45 (2.78)	21.95 (2.86)
Concerns scale	15.76 (4.09)	12.91 (3.38)	15.60 (3.36)	13.95 (3.73)	13.77 (4.28)	12.77 (3.39)
Harm scale	10.24 (2.30)	9.29 (2.43)	9.92 (2.81)	9.98 (2.32)	9.91 (3.76)	8.46 (2.40)
Overuse scale	11.64 (2.59)	11.43 (2.77)	12.25 (2.84)	12.80 (2.90)	12.66 (3.19)	11.02 (2.77)

One of the main analyses in the current study found that lower total BMQ necessity scale scores were significantly related to missing at least 20% days medication (13.1). From the five items on the scale, the three individual items that were most strongly related to adherence were (from table 15.1.2):-

- 'having to take anti-rejection medicines worries me'
- 'my life would be impossible without anti-rejection medicines'
- 'my health in the future depends on anti-rejection medicines'

Two previous studies, from the same research group, assessed belief in the need for immunosuppressants and non-adherence following renal transplantation (Siegel & Greenstein 1997; Greenstein & Siegel 1998). Both studies used single items to assess belief in the need for medication and, like this study, both found an inverse relationship with non-adherence. The BMQ, used in this study, has items relating belief in the need for immunosuppressants to general health. In contrast, the items asked by Siegel and Greenstein's group (1997, 1998) related questions about the need for immunosuppressants specifically to transplant failure. Greenstein and colleagues (1997) report the frequency of different beliefs about immunosuppressants. Their results are shown in table 16.3.4b.

Table 16.3.4b: Percentage of subjects agreeing with statements related to their renal transplant (from Greenstein et al. 1997)

Statement	Percentage of subjects agreeing with the statement
Post-transplant medications should never be delayed or missed	92
The advantages of the kidney transplant outweigh the drug side effects	90
Cyclosporin must be taken to keep the kidney	75
When the dose of the post-transplant medication was reduced, the drug was no longer needed; but the transplant professional was afraid to stop this drug completely	25
The kidney transplant is functioning so well that the post-transplant medications are not needed	20

Greenstein and Siegel (1998) investigated different beliefs and found that the following beliefs were associated with non-adherence on bivariate testing:-

- 'I need my immunosuppressants even if my transplant is functioning well'
- 'Immunosuppressants stay active in the body for longer than 24 hours'
- 'My drugs should never be delayed'
- 'I need cyclosporin to keep my kidney'

The first three beliefs significantly contributed to the explained variance in adherence after controlling for socio-demographic and transplant-related factors. However there were sub-group differences. 'I need my immunosuppressants even if my transplant is functioning well' did not appear significant in subjects with a cadaveric transplant and 'Immunosuppressants stay active in the body for longer than 24 hours' was not significantly related to non-adherence in subjects with a transplant from a live donor. The fact that subjects differed in which beliefs about the need for immunosuppressants related to adherence is interesting in the light of the finding from the current study that both type of transplant and belief in the need for medication were related to adherence. The current study did not find a relationship between BMQ necessity scores and type of transplant. This may have been due to the beliefs only differing if the need for immunosuppressants is related specifically to the risk of transplant failure as occurred in the study by Greenstein and Siegel (1998).

16.3.5 Beliefs about the transplant

Subjects rated their belief in the ability of different factors to cause transplant failure on the IPQ cause scale. Most believed poor medical care could cause transplant failure. This is not surprising in view of the significant degree of medical input into transplantation. The belief

could be detrimental to adherence in patients who believe that staff could easily treat rejection but the belief could be beneficial if it led to patients trying harder to follow advice. A surprising number (53%) of subjects scored highly on the belief that their state of mind could cause transplant failure.

The mean (SD) number of symptoms on the IPQ identity scale was 5 (3) and reporting more symptoms on this scale was associated with a standard deviation of inter-dose intervals of 6 hours or more and with a more negative view of the transplant than remembered prior to transplantation. However the number of symptoms attributed to the transplant or immunosuppressants was not related to non-adherence.

Negative emotions attributed to the transplant but not other beliefs measured by the IPQ were associated with missing at least 20% days medication. Depression is strongly related to the IPQ emotion score and from this cross sectional study it is not possible to say whether depression leads to experience of a lot of negative emotions that, in transplant recipients get attributed to the transplant or whether experiencing unpleasant mood changes post-transplantation leads to increased risk of a depressive illness.

Forty-one percent of subjects scored in the upper half of the concerns scale on the IPQ, indicating strong concerns about the transplant. However this may have been due to the items not accurately measuring transplant related concerns because only 11% scored in the upper half of the cons of transplant scale, where all items related experience of the transplant to dialysis (table 12.5.3), and the median number of unprompted problems listed by subjects was only one (table 12.5.4).

16.3.6 Multivariate analysis to identify the major factors associated with non-adherence

The factors associated with non-adherence in monitored subjects at $p \leq 0.1$ significance on bivariate testing are shown in table 16.3.6.

Younger age has been consistently related to increased risk of non-adherence in other studies of renal transplant recipients (table 5.3a). A surprising finding in this study was the lack of relationship of either depression or duration post-transplantation with adherence.
Beliefs relating to the need for immunosuppressants were found to be related to adherence by Greenstein & Siegel (1998) and differed according to the type of transplant. Post hoc analysis in this study did not find a relationship between type of current transplant and belief in the

need for either immunosuppressants as a group or prednisolone specifically, belief in the general benefits of medicines, emotional response to the transplant or change in view of a transplant from what was remembered prior to transplantation. There was a non-significant trend for subjects with a transplant from a live donor to report more functional limitations attributed to emotional factors than subjects with a cadaveric graft ($Z = -1.77$, $p = 0.077$).

Table 16.3.6: Summary table showing the factors associated with non-adherence

	P value (missed days)[1]	**P value (erratic timing)[2]**
Less belief in the need for immunosuppressants	0.001	ns
Less belief in the need for prednisolone	0.002	ns
Less belief in the general benefits of medicines	0.004	ns
First transplant from a live donor	0.008	0.064
Younger age	0.010	ns
Current transplant from a live donor	0.013	0.095
Living alone	0.019	ns
More negative emotions attributed to the transplant	0.052	ns
Pre-emptive transplantation	0.067	0.035
Left full-time education under 18 years old	0.087	ns
Less desired practical support	0.081	ns
Functional role limitations attributed to emotional factors	0.091	0.079
Alternate day dosing of prednisolone	ns	< 0.001
Change in view of the transplant from what is remember prior to transplantation	ns	0.023
Number of physical symptoms	ns	0.079

[1]Significance with missing 20% or more days prednisolone
[2]Significance with having a standard deviation of inter-dose intervals of 6 hours or more

Three variables were identified which accounted for the explained variance in missed days:-

- transplant from a live donor
- strong belief in the need for immunosuppressants
- strong belief in the need for prednisolone

Three variables also accounted for the explained variance in erratic timing:-

- alternate day dosing
- transplant from a live donor
- functional limitations attributed to emotional factors

Thus the current study found that, even after controlling for non-modifiable factors, beliefs related to medication are significant predictors of missing immunosuppressants. Larger studies are needed to investigate causal pathways between factors associated with adherence

and to determine their relationship with non-adherence and graft function in a prospective manner.

Cluster analysis of the bivariate associations with adherence in the study by Greenstein & Siegel (1998) identified three groups of non-adherent subjects. 'Invulnerables' were identified as subjects who believed they did not need to take their immunosuppression regularly. They had less belief in the efficacy of immunosuppressants, were younger, less educated, tended to have been transplanted more recently and tended to have a transplant from a live donor. In contrast, 'decisive non-compliers' were identified as subjects who decided not to take immunosuppressants. They had stronger belief in the statement 'Immunosuppressants stay active in the body for longer than 24 hours', tended to have higher levels of education, be in white-collar occupations and have a longer time since transplantation. Greenstein & Siegel (1998) reported other differences between sub-groups in the same study. In addition to the importance of different beliefs, recipients of different transplant types differed in the effect of time since transplantation and occupation - these were only related to adherence for those with a cadaveric transplant. There were also different associations with adherence for beliefs about medication, experience of physical symptoms and type of transplant according to gender and ethnicity.

A follow up to the cross-sectional study by Greenstein & Siegel (1998) found that a logistic regression model including age (older), occupation, time post-transplantation and the beliefs 'I need my immunosuppressants even if my transplant is functioning well', 'My drugs should never be delayed' and 'Immunosuppressants stay active in the body for longer than 24 hours' was a good predictor of non-adherence at 18 months follow-up (Greenstein & Siegel 2000).

16.4 Determinants of belief in the need for immunosuppressants

This study found that the main determinants of increased belief in the need for immunosuppressants were:-

- alternate day dosing of prednisolone
- pre-emptive transplantation (no experience of dialysis)
- recalling one or more rejection episodes
- reporting more benefits of transplantation on the pros of a transplant questionnaire

The direction of effect of dosing frequency and pre-emptive transplantation were in the opposite direction predicted from their association with adherence. This may reflect type one

errors in the analyses or may reflect a complicated relationship between the variables and it requires further exploration in future studies. Scores on the BMQ benefits and overuse scales were also related on bivariate analysis to belief in the need for immunosuppressants. Thus, in this population, beliefs about medicines in general appear related to beliefs about specific medication. More reported benefits of a transplant reported on the pros of a transplant questionnaire were also related to increased belief in the need for immunosuppressants. The cross-sectional nature of this study means that the direction of relationship is not clear, a more favourable experience of transplantation may increase motivation to keep the transplant and thus a lead to greater belief in the need for medication or perhaps believing you need the medication and, therefore adhering more, leads to a better experience of transplantation.

Other beliefs, such as the predicted number of tablets that could be missed without rejection, were not related to the BMQ necessity scale. This is in contrast to the one previous study (Siegel & Greenstein 1997) which also found belief in the need for immunosuppressants predicted adherence. The authors investigated predictors of the belief by including four open-ended questions in their study. Responses given by subjects who had less belief in the need for immunosuppressants were:-

- Side effects are greater than the benefits of a functioning kidney
- Knowledge of other patients whose transplant functions well despite them having been taken off, or never received, cyclosporin
- The kidney function is great so the immunosuppressant drugs are not needed
- The healthcare team decreases the dose of post-transplant immunosuppressants, meaning that the drugs are not needed (and the staff are too cautious to stop them completely)

These answers given in Siegel & Greenstein's study (1997) suggest that belief in the need for immunosuppressants is primarily determined by other beliefs and experiences directly related to the transplant rather than other transplant or socio-demographic factors as investigated in the current study. In support of this hypothesis were comments, not collected in a standardised format but which were made by several subjects to the researcher in this study; subjects commented that they were not sure of the need for their prednisolone because they knew another patient who had been withdrawn from steroids without suffering any adverse effects. Siegel & Greenstein (1997) did not collect data in a format to allow linear regression modelling to estimate the explained variance of belief in the need for medication, so like the current study, they may not have identified predictors of significant amounts of variance in

beliefs. Furthermore Siegel & Greenstein (1997) looked at single item measures of belief in the need for immunosuppressants with the items being relatively specific to immunosuppressants. This was in contrast to the current study which used a generic measure of beliefs about medication.

16.5 Implications for clinical practice

This study demonstrates that a significant minority of patients miss at least 20% days prednisolone and most take prednisolone at a very variable time in the day. Although adherence to other immunosuppressants was not measured, other studies have indicated that adherence is similar to that for prednisolone. Therefore many patients appear to be missing immunosuppressants at levels that have been associated with an increased risk of graft failure in previous studies. This study shows that clinicians are poor at detecting which subjects are non-adherent and, assuming that adherence to cyclosporin is similar to that for prednisolone, cyclosporin levels are also poor indicators of adherence. In view of the difficulty identifying non-adherent patients and evidence from a study in heart transplant recipients that missing as little as 3% doses of immunosuppressants increases the risk of rejection (De Geest et al. 1998), clinicians should be alert to the possibility of non-adherence in all subjects.

Recipients of a transplant from a live donor and those who have not experienced dialysis appear to be at greater risk of non-adherence. This is a major clinical concern in view of calls to increase the numbers of transplants from live donors (Royal College of Surgeons 1999) and an increasing number of pre-emptive transplants. If the association with non-adherence is real, then the prevalence of non-adherence may be expected to increase with increasing proportions of live and pre-emptive transplants. Both these procedures are generally associated with better transplant survival but non-adherence will become an even more important factor. Although the association of live and pre-emptive transplantation with non-adherence needs replicating and the reasons for the association require further explanation, current results suggest that clinicians should be particularly sure to discuss the need for immunosuppression in patients with a transplant from a live donor. They should emphasise that although transplant survival is generally better than with a cadaveric graft, the benefits of a live transplant may be further increased by adequate immunosuppression. Similarly, extra attention may be needed in those who have had pre-emptive transplantation. It is possible that these patients view the problems related to immunosuppression as relatively greater, the chance of transplant failure as less likely or the consequences of dialysis as less problematic than those who have experienced dialysis.

In view of the importance of beliefs in the need for immunosuppressants as a group and for the specific drugs that are being taken, the results of this study indicate that beliefs relating to medication should be explored in all patients and mis-understandings explained. An example of such a mis-understanding is reported by Greenstein and colleagues (1997) who found that some patients with a lower belief in the need for their immunosuppressants had developed this view after interpreting the fact that clinicians reduce the dose of immunosuppression post-transplantation as an indication that the medication is actually not needed but clinicians' caution stops them withdrawing it completely. If renal staff recognise that patients may hold different views about medicines to staff and that these beliefs may occur due to inappropriate interpretations of various sources of evidence such as the routine reduction of immunosuppressant levels, they may be more likely to facilitate disclosure of such beliefs and then discuss them in a non-judgemental manner that enables the patient to reassess the evidence and therefore change their beliefs.

The results of the staff survey highlight a difference in levels of non-adherence that are perceived as important by surgeons compared to physicians, with the surgeons tending to estimate that many fewer tablets could be missed before the risk of rejection increases. The difference may be partly explained by surgeons tending to see patients early in the life of their transplant when there is clear evidence that immunosuppression is important whereas physicians see patients over a longer time where there is medical debate about the necessary levels of immunosuppression and the long term side effects of drugs, such as malignancy, occur. However the subject requires further study in view of the finding of a previous study (Hathaway et al. 1999) that surgeons are significantly more likely than other members of the transplant team to remove a patient they assess as non-adherent from the transplant list and comments made by several subjects in the current study about memories of surgeons being reported to shout at patients they thought had suffered a rejection episode due to non-adherence. Clinicians should understand the benefits of exploring non-adherent behaviour in a non-judgemental manner since if patients expect a negative response they are unlikely to disclose their own non-adherence.

The staff survey and the difference between consultants in the prescription of prednisolone highlights considerable differences in beliefs about the need for immunosuppressants between clinicians within one unit. Such differences are likely to be identified by patients who, in a renal unit, tend to discuss their treatment with other patients. This may cause confusion and reduce the perceived need in medication that is prescribed differently by other doctors.

Support for this hypothesis comes from comments made by participants in the current study and from the study by Greenstein and colleagues (1998). The latter found that some patients explained less belief in the need for immunosuppressants as being due to their observation that other patients were on different immunosuppressant regimes without one of the drugs they were prescribed. Protocols for immunosuppression within a unit, as recommended by the British Transplantation Society (1998), may reduce differences between consultants.

The current study demonstrates significant untreated morbidity due to depression, with moderate or severe depression occurring in 19% subjects. Although depression was not related to non-adherence, it is likely to impair quality of life and effective treatments exist. Clinicians should be aware of the possibility of a mood disorder and discuss anti-depressant medication with patients if depression is detected. Clinicians may also need educating that even in those with significant physical illness, depression can still be successfully treated. The levels of untreated psychiatric illness suggest that such disorders are often missed by renal staff. Closer involvement of liaison psychiatry or health psychology services should occur for all renal units. This would provide specialist staff to train renal teams in the detection and routine management of common mental disorders and would have the added advantage of providing a psychiatric specialist with particular expertise in the range of psychological problems presented by patients with end-stage renal disease.

16.6 Implications for future research

16.6.1 Clinically significant definition of non-adherence

One of the biggest problems for this study, and others in the field, is the lack of a definition of non-adherence that is known to relate to clinically significant outcomes. Studies to address this issue are urgently needed. However such studies would be difficult to design since graft loss is a relatively rare event and the number of readily available subjects is relatively small. Even at five years post-transplantation less than 30% grafts are expected to have failed (The Renal Association 2002) and the majority of these will be due to death with function which is less likely to be due to non-adherence. Each regional transplant unit in England and Wales performs 40-90 transplants per year, which would only give an expected 10-23 transplant failures if an entire region's transplant recipients were followed up for five years. This difficulty probably partly explains the fact that most studies to date relating adherence to graft function have been retrospective. However such studies, by design, have to rely on retrospective assessment of adherence which introduces more error into the identification of non-adherent subjects than in cross sectional or prospective studies.

Despite these difficulties prospective studies using electronic monitoring and assessing graft function over time are needed. Electronic monitoring is the only method able to measure the effect of different amounts of missed medication and different patterns of non-adherence so that these can be related to graft survival. The study by Nevins and colleagues (2001) has used electronic monitoring continuously in renal transplant recipients from the time of transplantation and has followed subjects for five years. However the study was undertaken in the United States, only assessed adherence to azathioprine and was only able to recruit 53% eligible subjects. A further 26% had incomplete data or dropped out so it is difficult to generalise the findings. Furthermore the results are unlikely to be applicable to British healthcare, may not reflect the pattern of adherence to the main immunosuppressants such as cyclosporin or tacrolimus. The current study, using electronic monitoring will allow a follow-up study to investigate the number of missed doses and / or timing variation that increases the risk of graft function. However since electronic monitoring was restricted to 60 subjects a follow-up study is unlikely to have sufficient power to definitively answer the question.

16.6.2 Measurement of adherence

More research into the effects of using electronic monitors is needed. De Geest and colleagues (1998) provided some data from a study of heart transplant recipients when they reported that 35% subjects admitted to opening their monitor inappropriately when questioned at the end of the study. Similarly, although not formally questioned about the monitor, several subjects in this study reported taking medication out for two days to avoid taking the monitor away for a weekend. It may be difficult to get subjects to accurately report discrepancies between monitor openings and tablet ingestion unless they are aware of the function of the monitor. Furthermore there is an understandable but increasing demand by the public to be fully informed about clinical and research events in which they are involved. Although previous studies have shown non-adherence to be less if a subject is aware their adherence is being monitored, it is not known how long this effect lasts or to what degree it changes behaviour. Studies are therefore needed to address these issues. Future studies can then use electronic monitoring to assess adherence in fully informed subjects with the impact of this being known. Such a design would also make the explanation of follow up studies easier.

However although electronic monitoring is the most sensitive measure of adherence to use in research studies, it is unlikely to be feasible to monitor adherence in clinical practice. Self-report measures are probably the most cost-effective way to monitor adherence and do detect a proportion of non-adherent subjects (De Geest et al 1999). Research studies tend to

maximize disclosure of non-adherence by maintaining the confidentiality of subjects responses but the results of this are not generalisable to the clinical setting. Future studies could investigate whether clinicians could be trained to facilitate disclosure of non-adherence and whether this would be better than self-report questionnaires given back to the clinical team. There is a suggestion from this study that enquiring about delayed taking enabled subjects to more accurately disclose missed medication than by asking about missed medicine directly. However this was most effective when the question was asked in an interview with a researcher independent to the clinical team. Further research exploring patients reasons for not disclosing non-adherence may identify better ways to phrase questionnaire items or deliver the questionnaires within routine practice.

16.6.3 Depression in renal transplant recipients

In view of the prevalence of untreated depression in this study, further studies should confirm the prevalence and identify reasons for lack of treatment. Although depression was not directly related to non-adherence, its frequency and relation to some of the factors that were associated with adherence, imply that further research is required. There are effective treatments for depression and this may be easier to alter than some of the other correlates of non-adherence such as emotional response to the transplant or functional limitations attributed to emotional factors.

16.6.4 Determinants of non-adherence

The determinants of non-adherence are still not clear. Like other studies using multivariate techniques, this study found that potentially modifiable factors are associated with non-adherence after controlling for socio-demographic and transplant-related factors. The difficulty is that different studies have studied different combinations of variables. Studies need to be designed to assess the causal pathways relating such variables.

In view of beliefs relating to the need for immunosuppressants being so important in both this study and that reported by Greenstein & Siegel (1998), there needs to be further exploration of the determinants of beliefs relating to immunosuppressants and the key beliefs that are important. Because the BMQ, used in this study, is a generic measure and immunosuppressants are essentially preventative medication, several items do not appear relevant to transplant recipients. Specific items, such as those used by Greenstein & Siegel (1998) may be better.

16.6.5 Interventions to improve adherence

There are currently no generalisable and successful interventions to improve adherence in chronic disease. In a thorough literature review, Haynes and colleagues (1996) found only 13 controlled trials of interventions to improve adherence to treatment that met their strict inclusion criteria. The trials included subjects with hypertension, schizophrenia, asthma, epilepsy and acute infection but not renal disease. Interventions differed in all studies and tended to be multi-faceted. Despite such complex interventions, only seven were associated with significantly improved adherence. Authors did not clearly describe all aspects of the intervention and did not appear to explore the key components of their intervention.

Reviews about interventions to improve adherence to immunosuppressants in renal transplant recipients (Newton 1999; De Geest et al. 1999; Laederach-Hofmann & Bunzel 2000) show that authors tend not to base their suggestions on a theoretical model of adherence behaviour. Suggested interventions have tended to be simple and based on changing routine clinical practice, such as ensuring regular follow up of patients by the same healthcare worker (De Geest et al. 1999). There are no controlled trials of interventions in renal transplant recipients.

De Geest and colleagues (1999) classify interventions into those aiming to initiate adherence, maintain adherence or remedy problems with adherence. Changing routine practice is likely to address the first two categories. As discussed above, the results of the current study suggest adherence may be improved in this manner by changing information given to recipients of transplants from live donors and those who have pre-emptive transplantation. However the third category of intervention suggested by De Geest and colleagues (1999) requires a detailed understanding of factors leading to problems with adherence.

Beliefs regarding the need for medication appear to be related to increased risk of missing medication and role limitations attributed to emotional factors appear to be related to an increased risk of erractic timing. Both these variables are potentially modifiable and so may be targets for an intervention to improve adherence. However before an intervention would be suitable for large scale clinical trials, several questions need to be answered:-

- can beliefs or role limitations be changed sufficiently to alter adherence?
- what is a clinically significant amount of change?
- how does the risk of graft loss relate to different degrees of non-adherence?
- can the current assessment of predictors of adherence be improved such that a greater degree of behavioural change may be expected?

The questions will need addressing through a series of research studies. An effective intervention to produce behavioural and clinical change is likely to include several interconnected components. Such interventions have been termed 'complex interventions', and the Medical Research Council has stated that their development requires the use of quantitative and qualitative methodologies with the intervention being refined through an iterative process involving several 'phases' of research and being grounded in a theory of behaviour (Campbell et al. 2000). The phases involve theoretical developments, defining the components of an intervention such as increase in the belief in the need for medication or treating depression, exploratory trials to assess the feasibility and key components of an intervention and finally a definitive trial with clinically important end-points (Campbell et al. 2000).

Several theoretical models of health behaviour have been applied to adherence and could be used as a theoretical starting point to develop interventions to improve adherence. As discussed in section 4.3.4, the Self-Regulatory Model has an advantage over other models in that it integrates several elements of cognition and emotion that are related to behaviour and includes an appraisal stage. However, before it can be directly used to develop an intervention to improve adherence to immunosuppressants, the model needs further theoretical refinement. The emotional pathway has not been understood as well as the cognitive pathway. This is important since depression is common and is related to many of the variables associated with adherence in the current study. The Self-Regulatory Model is a model to understand behaviour related to an illness but behaviour related to a transplant may have different determinants (as discussed in section 16.1.9). For example, although the components of the illness representation in the Self-Regulatory Model can be assessed using a validated, standardised questionnaire (IPQ, Weinman et al. 1996), these components may not be exactly the same as components of patients' representation of their transplant. Support for this hypothesis comes from the finding of poor internal reliability of some scales on the IPQ in renal transplant recipients in the current study and an earlier, unpublished study (Stabler 1999, personnal communication). Another difficulty in using the current Self-Regulatory Model used to design an intervention to improve adherence to medication is that beliefs about medicines do not clearly fit into the model. Horne (1997) suggested that their inclusion will increase the explanatory power of the model and he developed the BMQ to test this view. In the current study, belief in the need for medication assessed using the BMQ was associated with missing medication but only contributed to a small proportion of the variance.

The IPQ and BMQ are generic measures of health beliefs. Beliefs which are more specific to transplants or immunosuppressants may be better predictors of adherence in renal transplant recipients. The nature of such beliefs should be explored in qualitative studies. As discussed above, comments made by subjects in this study and in an earlier study by Siegel and Greenstein (1997) suggest that specific beliefs about immunosuppressants and beliefs associated with interactions with the clinical team may be important.

16.7 Summary of the findings and research implications of the study

Existing studies indicate that non-adherence to immunosuppressants is a major cause of renal transplant failure. The current study confirms that many renal transplant recipients in the United Kingdom do not take theirs medication as prescribed. Erratic timing of doses is more common than missing immunosuppressants but a significant minority of patients miss substantial amounts of medication. The question of how many missed immunosuppressants increase the risk of graft loss, and how erratic timing relates to this risk, could not be addressed in this cross-sectional study but it remains an important question to answer.

Interventions to improve adherence require identification of potentially modifiable predictors of non-adherence. If a high risk group can be identified, specific interventions may be targeted to patients at the greatest risk of non-adherence. The current study indicates that recipients of a transplant from a live donor and, possibly, those who have never received dialysis may be at particularly high risk of non-adherence. However this hypothesis is tentative due to the small sample size of the current study and it requires addressing in future studies. Beliefs regarding the need for medication have been identified as major determinants of adherence to immunosuppressants in this population the beliefs assessed using the BMQ only explain a small proportion of the variance in adherence. Although development of a definitive intervention requires much further research, results of this study suggest that application of cognitive-behavioural principles addressing beliefs in the need for medication may improve adherence.

The emotional impact of transplantation also appears an important factor associated with adherence. This is important in view of the prevalence of untreated depression found in this study. Furthermore depression is disabling and requires treatment in its own right and effective treatments already exist. Further research is therefore needed into the causes of depression in renal transplant recipients, the reasons behind the current lack of treatment and

interventions to improve the treatment of depression should be assessed for their impact on adherence.

The main findings from the study and the main areas of future research that these findings lead to are summarised in table 16.7.

Table 16.7: Future research studies suggested by the main results of this study

Main finding	**Research study to develop knowledge in relation to the current finding**
There is a lack of a clinically significant definition for non-adherence to immunosuppressants	Prospective observational study with adherence measured (including electronic monitoring) repeatedly over time and acute rejection episodes and graft failure as outcome measures
Electronic monitoring appears to be the best measure of adherence	Controlled trial to assess the size and duration of impact of knowing adherence is being monitored by electronic monitoring compared to not knowing the purpose of the monitors
Beliefs about medication are major, potentially modifiable factors associated with non-adherence	Pilot study to show that beliefs about medication can be changed Qualitative study to explore beliefs about medication and transplants that are salient to adult renal transplant recipients Use of the results of the qualitative study to improve the standardised questionnaire measurement of illness and medication beliefs in renal transplant recipients Pilot studies to determine the most effective and feasible intervention to alter beliefs, or to determine who needs to be targeted with different 'levels' of intervention such as information leaflets or groups and group or individual cognitive behavioural sessions Controlled trial of an intervention to improve adherence
Recipients of a transplant from a live donor may be at higher risk of non-adherence	Qualitative study to explore beliefs about the transplant and medication in recipients of transplants from a cadaver compared to a live donor
Depression is common and usually untreated	Qualitative studies to explore the reasons for lack of treatment Education of renal unit staff regarding the detection and management of depression Controlled trials of interventions for depression in transplant recipients Trial to assess change in adherence following treatment of depression Development of understanding of the emotional pathway in the self-regulatory model, assessment of the emotional pathway by standardised questionnaires and understanding how the emotional and cognitive pathways interact

Appendix A1: Illness Perception Questionnaire

IPQ: YOUR VIEWS ABOUT YOUR TRANSPLANT

Listed below are a number of symptoms that you may or may not have experienced since your transplant. Please indicate by circling yes or no, whether you have experienced any of these symptoms since your transplant, and whether you believe any of these symptoms are related to either your transplant or your anti-rejection medicines.

SYMPTOM	**I have experienced this symptom since my transplant**		**I believe this symptom is related to my transplant**		**I believe this symptom is related to my anti-rejection medicine**	
			Please answer both these columns if you answered "yes" to having the symptom			
Pain	Yes	No	Yes	No	Yes	No
Nausea (feeling sick)	Yes	No	Yes	No	Yes	No
Breathlessness	Yes	No	Yes	No	Yes	No
Weight loss	Yes	No	Yes	No	Yes	No
Fatigue (tiredness)	Yes	No	Yes	No	Yes	No
Stiff joints	Yes	No	Yes	No	Yes	No
Sore eyes	Yes	No	Yes	No	Yes	No
Headaches	Yes	No	Yes	No	Yes	No
Upset stomach	Yes	No	Yes	No	Yes	No
Sleep difficulties	Yes	No	Yes	No	Yes	No
Dizziness	Yes	No	Yes	No	Yes	No
Loss of strength	Yes	No	Yes	No	Yes	No

We are interested in your own personal views of how you now see your kidney transplant. Please indicate how much you agree or disagree with the following statements about your kidney transplant.

	VIEWS ABOUT YOUR KIDNEY DISEASE	**STRONGLY AGREE**	**AGREE**	**NEITHER AGREE NOR DISAGREE**	**DISAGREE**	**STRONGLY DISAGREE**
IPQC1	A germ or virus could make my transplant fail					
IPQC2	My diet is important to keep my transplant working					
IPQE1	Symptoms related to my transplant are distressing to me					
IPQT1	My transplant will last a short time					
IPQO1	My transplant is a serious medical procedure					
IPQO2	My transplant has had major negative consequences on my life					

IPQ: YOUR VIEWS ABOUT YOUR KIDNEY TRANSPLANT (CONTINUED)

	VIEWS ABOUT YOUR KIDNEY DISEASE	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE
IPQC3	Pollution of the environment could make me lose my transplant					
IPQU1	My kidney function will improve with time					
IPQE2	I get depressed when I think about my transplant					
IPQC4	Hereditary factors could make me lose my transplant					
IPQC5	I could lose my transplant by chance					
IPQT2	My transplant is likely to last for ever					
IPQE4	My transplant makes me feel angry					
IPQU2	There is a lot which I can do to control my symptoms					
IPQO4	My transplant has not had much effect on my life					
IPQO5	My transplant has strongly affected the way others see me					
IPQC6	Stress could be a major factor causing my transplant to fail					
IPQC7	My transplant could fail largely due to my own behaviour					
IPQT3	My transplant will last for a long time					
IPQU4	My treatment will be effective in maintaining my transplant					
IPQU5	Keeping my transplant is largely a matter of chance or fate					

IPQ: YOUR VIEWS ABOUT YOUR KIDNEY TRANSPLANT (CONTINUED)

	VIEWS ABOUT YOUR KIDNEY DISEASE	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE
IPQC9	I could lose my transplant by poor medical care					
IPQE3	When I think about my transplant I get upset					
IPQE5	My transplant does not worry me					
IPQC10	My state of mind plays a large part in keeping my transplant working					
IPQO3	My transplant has become easier to live with					
IPQO6	My transplant has made me financially worse off					
IPQO7	My transplant has strongly affected the way I see myself as a person					
IPQC8	Other people could play a large part in my transplant failing					
IPQO8	My transplant causes difficulties for those who are close to me					
IPQO9	My transplant has a negative impact on me					
IPQO10	My transplant is not a problem for me					
IPQU3	There is very little that can be done to keep my transplant working					
IPQU6	What I do can determine whether my transplant lasts or fails					
IPQE6	Having a transplant makes me feel anxious					
IPQE7	I worry a lot about my transplant					
IPQE8	My transplant makes me feel afraid					

Appendix A2: Beliefs about Medicines Questionnaire

YOUR VIEWS ABOUT MEDICINES IN GENERAL

- These are some statements other people have made about medicines in general.
- Please show how much you agree or disagree with them by ticking the appropriate box

There are no right or wrong answers
We are interested in your personal views

	Views about MEDICINES IN GENERAL	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
BMQO1	Doctors use too many medicines					
BMQH2	People who take medicines should stop their treatment for a while every now and then					
BMQH3	Most medicines are addictive					
BMQO4	Natural remedies are safer than medicines					
BMQH5	Medicines do more harm than good					
BMQH6	All medicines are poisons					
BMQO7	Doctors place too much trust on medicines					
BMQO8	If doctors had more time with patients they would prescribe fewer medicines					
BMQA9	Medicines help people to live better lives					
BMQA10	In the future medicines will be developed to cure most diseases					
BMQA11	In most cases the benefits of medicines outweigh the risks					
BMQA12	Medicines help many people to live longer					

YOUR VIEWS ABOUT YOUR ANTI-REJECTION MEDICINES
(eg: cyclosporin, azothiaprine, prednisolone)

- We would like to ask you about your personal views about medicines prescribed for you.
- These are some statements other people have made about their medicines.
- Please show how much you agree or disagree with them by ticking the appropriate box

There are no right or wrong answers
We are interested in your personal views

	Views about ANTI-REJECTION MEDICNES	**Strongly agree**	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
BMQN13	My health at present depends on anti-rejection medicines					
BMQC14	Having to take anti-rejection medicines worries me					
BMQN15	My life would be impossible without anti-rejection medicines					
BMQN16	I sometimes worry about the long term effects of anti-rejection medicines					
BMQC17	Without anti-rejection medicines I would be very ill					
BMQC18	Anti-rejection medicines are a mystery to me					
BMQN19	My health in the future depends on anti-rejection medicines					
BMQC120	Taking anti-rejection medicines disrupts my life					
BMQC21	I sometimes worry about becoming too dependent on anti-rejection medicines					
BMQN22	Anti-rejection medicines protect me from my kidney failing					
BMQA23	I sometimes worry about changes in my appearance caused by my anti-rejection medicines					
BMQA24	I have experienced unpleasant side-effects due to my anti-rejection medicines					
BMQA25	I have been given enough information about how to take my anti-rejection medicines					

Appendix A3: Morisky and 'MARS' Self-reported Adherence Questionnaires

QUESTIONS ABOUT USING YOUR ANTI-REJECTION MEDICINES

- We know that many people find a way of using their medicine which suits them
- This may differ from the instructions on the label or from what their doctor has said
- We would like to ask you some questions about how you use your anti-rejection medicines (cyclosporin, prednisolone, azothiaprine)

- **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**
- **As with all the information you give us, your answers will remain confidential to the research and will not be disclosed to any staff in the renal unit or to your GP without your permission.**

There are no right or wrong answers
We are interested in your personal views

		ALWAYS	OFTEN	SOMETIMES	RARELY	NEVER
(a1)	I am more than 2 hours late taking my medicines					
(a2)	I forget to take my medicines					
(a3)	I alter the dose of my medicines					
(a4)	I avoid using my medicines if I can					
(a5)	I take less than instructed					
(a6)	I stop taking my medicines for a while					
(a7)	I decide to miss out a dose					

		YES	NO
(M1)	Do you ever forget to take your medicine?		
(M2)	Are you careless at times about taking your medicine?		
(M3)	When you feel better do you sometimes stop taking your medicine?		
(M4)	Sometimes if you feel worse when you take the medicine, do you stop taking it?		

Appendix A4: Significant Others Scale

SIGNIFICANT OTHERS SCALE

Instructions

Please answer the questions below in relation to the person closest to you (eg., spouse, partner, friend). Please circle a number from 1 to 7 to show how well he or she provides the type of help that is listed.

The second part of each question asks you to rate how you would like things to be if they were exactly what you hoped for. As before, please circle around one number between 1 and 7 to show what your rating is.

Please state how this person relates to you eg., partner, spouse, daughter, son, friend

_____

			Never			Sometimes			Always
1a)	Can you trust, talk to frankly and share your feeling with this person	(SS1)	1	2	3	4	5	6	7
b)	What rating would your ideal be	(SS2)	1	2	3	4	5	6	7
2a)	Can you lean on and turn to this person in times of difficulty	(SS3)	1	2	3	4	5	6	7
b)	What rating would your ideal be	(SS4)	1	2	3	4	5	6	7
3a)	Does he/she give you practical help	(SS5)	1	2	3	4	5	6	7
b)	What rating would your ideal be	(SS6)	1	2	3	4	5	6	7
4a)	Can you spend time with him/her socially	(SS7)	1	2	3	4	5	6	7
b)	What rating would your ideal be	(SS8)	1	2	3	4	5	6	7

Appendix A5: Medical Outcome Survey Short Form 36

SHORT FORM 36 HEALTH SURVEY

The following questions ask you for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure how to answer any questions please give the best answer you can.

Please mark by putting a cross in the appropriate box.

1) **In general** would you say your health is:

Please put a cross in one box

Excellent	☐
Very good	☐
Good	☐
Fair	☐
Poor	☐

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

Please put a cross in one box

Much better than one year ago	☐
Somewhat better than one year ago	☐
About the same	☐
Somewhat worse than one year ago	☐
Much worse than one year ago	☐

3) The following questions are about activities you might do in a typical day. Does your health limit you in these activities? If so, how much?

Please put a cross in one box

		Yes, Limited a lot	Yes, Limited a little	No, Not limited at all
3a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
3b)	**Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
3c)	Lifting or carrying groceries	☐	☐	☐
3d)	Climbing **several** flights of stairs	☐	☐	☐
3e)	Climbing **one** flight of stairs	☐	☐	☐
3f)	Bending, kneeling or stooping	☐	☐	☐
3g)	Walking **more than one mile**	☐	☐	☐
3h)	Walking **half a mile**	☐	☐	☐
3i)	Walking **100 yards**	☐	☐	☐
3j)	Bathing and dressing yourself	☐	☐	☐

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

Please answer **yes** or **no** to each question

		Yes	No
4a)	Cut down the **amount of time** you spent on work or other activities		
4b)	**Accomplished less** than you would like		
4c)	Were limited in the **kind** of work or activities		
4d)	Had **difficulty** performing the work or other activities (eg., it took more effort)		

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

Please answer **yes** or **no** to each question

		Yes	No
5a)	Cut down the **amount of time** you spent on work or other activities		
5b)	**Accomplished less** than you would like		
5c)	Were limited in the **kind** of work or other activities		

6) During the past **4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friend, neighbours or groups?

Please put a cross in **one** box

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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

Please put a cross in **one** box

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

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

Please put a cross in **one** box

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9) These questions are about how you feel and how things have been with you **during the past month**. For each question please give one answer that comes closet to the way you have been feeling.

Please put a cross in **one** bow on each line

	How much of the time **during the last month**	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little bit of the time**	**None of the time**
9a)	Did you feel full of life?						
9b)	Have you been a very nervous person?						
9c)	Have you felt so down in the dumps that nothing cheers you up?						
9d)	Have you felt calm and peaceful?						
9e)	Did you have a lot of energy?						
9f)	Have you felt downhearted and low?						
9g)	Did you feel worn out?						
9h)	Have you been a happy person?						
9i)	Did you feel tired?						
9j)	Has your health limited your social activities (like visiting friends or close relatives)?						

10) How true or false is each of the following statements for you?

Please put a cross in **one** bow on each line

		Definitely true	**Mostly true**	**Not sure**	**Mostly false**	**Definitely false**
10a)	I seem to get ill more easily than other people					
10b)	I am as healthy as anybody I know					
10c)	I expect my health to get worse					
10d)	My health is excellent					

Appendix A6: Immunosuppressant Pros and Cons Questionnaire

Benefits and problems you have due to your anti-rejection medicines

Here is a list of things that other patients have said are problems or concerns they have had about their anti-rejection medicines. Please could you rate how much these things have been a problem for you or worried you about your anti-rejection medicines. If you have the problem but think it is related to something else (ie: not due to your anti-rejection medicines) then please mark not applicable.

Please circle the number closest to how much each statement has affected you		***Not applicable***	***Not at all***	***A little***	***Quite a bit***	***A lot***	***Very much***
Memory loss	CM1	0	1	2	3	4	5
Long term risks of the medicines	CM2	0	1	2	3	4	5
Excess hair growth	CM3	0	1	2	3	4	5
Shaking	CM4	0	1	2	3	4	5
Feeling tired	CM5	0	1	2	3	4	5
Increased weight	CM6	0	1	2	3	4	5
Mood changes	CM7	0	1	2	3	4	5
Skin warts	CM8	0	1	2	3	4	5
Catch infections more easily	CM9	0	1	2	3	4	5
High blood pressure	CM10	0	1	2	3	4	5
Risk of kidney damage if there is too much of the drugs in my body	CM11	0	1	2	3	4	5
Oedema (swelling due to excess fluid)	CM12	0	1	2	3	4	5
Bone thinning (osteoporosis)	CM13	0	1	2	3	4	5
Acne	CM14	0	1	2	3	4	5
Stomach irritation or ulcers	CM15	0	1	2	3	4	5
Swelling of my face "moon face" of prednisolone	CM16	0	1	2	3	4	5

Here is a list of things other patients have said are beneficial about taking anti-rejection medicines. Please you rate how much these things make you think your anti-rejection medicines are helpful to you.

Please circle the number closest to how much each statement has affected you		***Not applicable***	***Not at all***	***A little***	***Quite a bit***	***A lot***	***Very much***
Stop my kidney rejecting	PM1	0	1	2	3	4	5
Help keep me well	PM2	0	1	2	3	4	5
Make it less likely my transplant will fail	PM3	0	1	2	3	4	5

Appendix A7: Transplant Pros and Cons Questionnaire

Questions about problems you may have due to your kidney transplant

Here is a list of things other patients have said are problems or concerns they have about their kidney transplant. Please rate how much these things have concerned or worried you about your kidney transplant. If you have the problem but think it is related to something else (ie: not due to your transplant) then please mark not applicable.

Please circle the number closest to how much each statement has affected you	*Not applicable*	*Not at all*	*A little*	*Quite a bit*	*A lot*	*Very much*
Loss of benefits	0	1	2	3	4	5
Worry about the possibility of my kidney rejecting	0	1	2	3	4	5
Aches and pains	0	1	2	3	4	5
Feeling stressed	0	1	2	3	4	5
Other people not making allowances for me still needing medical treatment	0	1	2	3	4	5
Sad thoughts about the donor family's loss	0	1	2	3	4	5
Fear of something bad happening in the future	0	1	2	3	4	5
Feel weird or unusual due to non-functioning kidneys being left in my body	0	1	2	3	4	5
Scar from the operation	0	1	2	3	4	5
Can't play contact sports (eg:rugby)	0	1	2	3	4	5
Sad that someone had to die for me to get a kidney	0	1	2	3	4	5
Miss the people I used to see on dialysis	0	1	2	3	4	5
Need to take tablets every day	0	1	2	3	4	5

Questions about benefits you may have had from your kidney transplant

Here is a list of things other patients have said are better with a kidney transplant than dialysis. Please rate how much these things have been easier or good for you since you had your kidney transplant. If something is good for you but you but think this is related to something else (ie: not due to your transplant) then please mark not applicable.

Please circle the number closest to how much each statement has affected you	*Not applicable*	*Not at all*	*A little*	*Quite a bit*	*A lot*	*Very much*
Able to drink as much fluid as I want to	0	1	2	3	4	5
Able to eat what I want to	0	1	2	3	4	5
Easier to work	0	1	2	3	4	5
Easier to have a social life	0	1	2	3	4	5
Easier to go on holidays	0	1	2	3	4	5
My interest in sex has improved	0	1	2	3	4	5
More fertile (more likely to be able to have a baby)	0	1	2	3	4	5
Can lead a normal life	0	1	2	3	4	5
Better than the alternatives	0	1	2	3	4	5
Feel less tired	0	1	2	3	4	5
Other people can't tell I have kidney disease	0	1	2	3	4	5

Appendix A8: Semi-Structured Interview for subjects without electronic monitors

What it is like to have a kidney transplant.

People who have had a kidney transplant notice good things about a transplant but also usually experience worries, problems or difficulties with the transplant. The good things and worries are different for different people and we are interested in knowing the things that have been important to you.

What have been the things that are good about your transplant (compared to dialysis)?

(listed at the question)	(mentioned elsewhere in interview)

What worries, problems or concerns have you had with your kidney transplant?

(listed at the question)	(mentioned elsewhere in interview)

What are your anti-rejection tablets like to take? (anything that comes to mind. Any changes in your views over the years you've been taking them?)

What are the good things about your anti rejection medicine (that make it worth taking)?

(listed at the question)	(mentioned elsewhere in interview)

What worries, problems or concerns do you have with your anti rejection medicines?
____(listed at the question)_____ _(mentioned elsewhere in interview)_
_____ _____
_____ _____

Give out pros & cons questionnaire!

1)What medication are you on? 2)When do you take your anti-rejection tablets?

NAME	DOSE	NUMBER TABLETS	FREQUENCY
Prednisolone			
Cyclosporin			
Azothiaprine			

(Number of tablets _____ Number of doses per day _____ Number medicines _____)

We know that many people have difficulty remembering to take all their medicines at exactly the right times every day. Do you use anything to help you remember your medicines?
_____

What do you do if you realise that you have missed an anti-rejection tablet?
Misact1

1) take it when remember
2) miss it out
3) miss it only if over 6 hours late otherwise take it when remember
4) never miss

Misact2

1) Take the next later
2) Take the next at the correct time
3) Miss the next tablet
4) Never miss

What sort of things are going through your mind or happening when you miss a tablet? (what makes it more likely that you'll miss a tablet?)
_____ _____
_____ _____

Roughly how often do you take an anti-rejection tablet 2 hours later than the planned time?

1) Very often
2) Quite often
3) Occasionally
4) Very rarely
5) Never

If not never: Could you put a rough frequency on that?

1) More than once a week 2) Once a week 3) Once or twice a month 4) Once or twice every six months 5) Once or twice a year

How often do you miss an anti-rejection tablet completely?

1) Very often
2) Quite often
3) Occasionally
4) Very rarely
5) Never

Do you find that you are more likely to miss one of your anti-rejection tablets than the others?

1) Yes 2) No

1)Which one? 2)Why do you think that is?

People on long term medicines sometimes leave out tablets because of particular concerns or symptoms. What things, worries or other events make you do that?

1) Never misses
2) Misses – reasons below or don't know

Lots of things affect how long a transplant works. Overall, considering all the possible things that keep your kidney working, how important do you think your anti-rejection tablets are in keeping your transplant working? Could you rate that as a percentage from 1-100.

0-100% _____

Are there any other things that you do that you think are important to keep your kidney going? (*list main 3*)

_____ _____ _____

As I said before, we know that if people are taking tablets every day for a long time they miss some, either because they forget or have a particular reason. People with renal transplants aren't likely to be any different. One of the things we are interested in is how many tablets people think it would be possible to miss without it causing harm. This isn't saying that you do it, would think about missing any and isn't saying that we suggest it. There isn't a correct answer and there isn't any medical evidence to indicate a correct answer so please just say what your best guess is.

If you were to miss some tablets for some reason then how many tablets:-

- In a row do you think you could miss without it affecting your transplant _____

If you missed odd tablets, not several in a row , then how many do you think:-

- You could miss in one year without it affecting your transplant _____
- And what about each month _____
- How many do you think you could miss each week without it causing harm _____

Now I'd like to ask you the same questions about your blood pressure
(if not on BP tablets then use alternative) tablets

	% importance in specified function	How many could miss in a row without harm	How many could miss in a year without harm
BP tabs wrt keeping kidney			
BP tabs wrt stable BP			
Other tablet (what pt says it does)			

Now we'll move to some questions about your renal problems in general.
How many transplants have you had_____

What is the problem with your kidneys _____

Age you first saw a nephrologist _____ Age started dialysis _____
Time in between _____ mths

Number rejection episodes in 1st yr _____ or later _____ with current transplant

Time on dialysis prior to first transplant _____ months
Did this affect your view of the benefits of a transplant yes/no
How _____

If not first tx, did your previous transplants affect what you expected from this one? Yes/ No
How _____

How good did you think kidney transplants were overall 0 (terrible) to 10 (brilliant)

Prior to first transplant _____ Now _____

Now just a couple of things about general health issues
Have you ever had (ask relevant direct questions):-

Angina (chest pain on exercise)	Y_1 N_0	Malignacy (incl cured & skin)	Y_1 N_0
MI in last 3mth (ECG,enzyme change)	Y_1 N_0	Claudication (on history)	Y_1 N_0
MI over 3 mth ago but after ESRF	Y_1 N_0	Current ischaemic / neuropathic ulcers	Y_1 N_0
CABG or coronary angioplasty	Y_1 N_0	Non coronary angioplasty	Y_1 N_0
(Diabetes)	Y_1 N_0	Amputation for periph. vasc. Disease	Y_1 N_0
Diabetes not causing ESRF	Y_1 N_0	Smoker (now or last year)	Y_1 N_0
COAD	Y_1 N_0	Abnormal LFT when ESRF (notes)	Y_1 N_0

Number units alcohol per week _____ Number episodes of significantly more (last 6 mths) _____

Height _____ Weight _____ BMI _____

Now there are some questions about your feelings Do CIS-R

In the future when we have the results of this study we may want to do a follow up study looking at how things change over time after a kidney transplant.
Would you be willing to be contacted in the future for a follow up study. Of course the study would be explained and you would decide at that point whether you wanted to take part. **Yes / No**

Now I'd like to ask you a few questions about yourself. We need the descriptions to describe all the patients we have studied to see whether the patients we have studied are similar to other transplant patients in Britain. The information will be described as something like 45% of the sample are female, 60% are working and 75% are living with someone. Of course it won't be possible to identify individuals from the results.

Marital status
1)partner or spouse
2)separated or divorced
3)never married or cohabiting
4)widowed

DOB _____
Age _____

Are you currently in full time or part time work? FT_1 PT_2 No work$_3$
What is your job _____ (social class _____)

What was your last full time job before you got kidney failure? _____
(social class _____)

Is your partner currently in full time or part time work? FT_1 PT_2 No work$_3$
What is their job _____ (social class _____)

What age were you when you left Full time education?
1) under 16 2) 16 3) 18 4) 21 5) over 21

What qualifications did you get / did you leave with any qualifications – which ones?
(if over 21: what is the highest qualification you have?)
1) CSE/O level/GCSE
2) A level
2) Undergraduate Degree
3) Postgraduate degree
4) Vocational
5) None

How would you describe your ethnicity
1) White 2) Black carribean 3)Black african 4)Black other 5)Indian
6)Pakistani 7)Bangledeshi 8)Chinese 9)Other

My overall impression of the frequency that anti-rejection medicine is taken more than 2 hours late is:-

1) Very often
2) Quite often
3) Occasionally
4) Very rarely
5) Never

My overall impression of the frequency that anti-rejection medicine is missed completley is:-

1) Very often
2) Quite often
3) Occasionally
4) Very rarely
5) Never

Appendix A9: First and Second Semi-Structured Interview for subjects with an electronic monitor

First Interview

What it is like to have a kidney transplant.

_____

_____

_____

_____

People who have had a kidney transplant notice good things about a transplant but also usually experience worries, problems or difficulties with the transplant. The good things and worries are different for different people and we are interested in knowing the things that have been important to you.

What have been the things that have made a transplant better than dialysis (or CRF if no dialysis)?

____(listed at the question)_____ _(mentioned elsewhere in interview)_

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

What worries, problems or concerns have you had with your kidney transplant?

____(listed at the question)_____ _(mentioned elsewhere in interview)_

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

What about your anti-rejection tablets? What are they like to take (anything that comes to mind. Any changes in your views over the years you've been taking them?)

_____

_____

What are the good things about your anti rejection medicine (that make it worth taking)?

____(listed at the question)_____ _(mentioned elsewhere in interview)_

_____ _____

_____ _____

What worries, problems or concerns do you have with your anti rejection medicines?

____(listed at the question)_____ _(mentioned elsewhere in interview)_

_____ _____

_____ _____

Give out pros & cons questionnaire!

Now we've got some more specific questions about your transplant, kidney problems and current feelings. 1)What medication are you on? 2)When do you take each tablet?

NAME	DOSE	NUMBER OF TABLETS	FREQUENCY
Prednisolone			
Cyclosporin			
Azothiaprine			

(Number of tablets _____ Number of doses per day _____ Number medicines _____)

Now I'd like to ask you some questions about your renal problems in general.
How many transplants have you had_____

What is the problem with your kidneys _____

Age you first saw a nephrologist _____ Age started dialysis _____
Time in between _____ mths

Time on dialysis prior to first transplant _____ months
Did this affect your view of the benefits of a transplant yes/no
How _____

How good did you think kidney transplants were overall 0 (terrible) to 10 (brilliant)

Prior to first transplant _____ Now _____

Now just a couple of things about general health issues Height _____ Weight _____
Have you ever had (ask relevant direct questions):-

Angina (chest pain on exercise)	Y_1 N_0	Malignacy (incl cured & skin)	Y_1 N_0
MI in last 3mth (ECG,enzyme change)	Y_1 N_0	Claudication (on history)	Y_1 N_0
MI over 3 mth ago but after ESRF	Y_1 N_0	Current ischaemic / neuropathic ulcers	Y_1 N_0
CABG or coronary angioplasty	Y_1 N_0	Non coronary angioplasty	Y_1 N_0
(Diabetes)	Y_1 N_0	Amputation for periph. vasc. disease	Y_1 N_0
Diabetes not causing ESRF	Y_1 N_0	Smoker (now or last year)	Y_1 N_0
COAD	Y_1 N_0	Abnormal LFT when ESRF (notes)	Y_1 N_0

Number units alcohol per week _____ Number episodes of significantly more (last 6 mths) _____

Now we've got some questions about your feelings. Do CIS-R

Second Interview

Today I'd like to talk to you in a bit more detail about your medicines and then to ask you a few basic questions about yourself that we use to describe the people in the study.

I know we talked a bit before about your tablets but has anything else come to mind since then about what is it like taking them?

We know that many people have difficulty remembering to take all their medicines at exactly the right times every day. Do you use anything to help you remember your medicines?

What do you do if you realise that you have missed an anti-rejection tablet?

Misact1

5) take it when remember
6) miss it out
7) miss it only if over 6 hours late otherwise take it when remember
8) never miss

Misact2

5) Take the next later
6) Take the next at the correct time
7) Miss the next tablet
8) Never miss

What sort of things are going through your mind or happening when you miss a tablet? (what makes it more likely that you'll miss a tablet?)

Roughly how often do you take an anti-rejection tablet 2 hours later than the planned time?

6) Very often
7) Quite often
8) Occasionally
9) Very rarely
10) Never

If not never: Could you put a rough frequency on that?

2) More than once a week 2) Once a week 3) Once or twice a month 4) Once or twice every six months 5) Once or twice a year

How often do you miss an anti-rejection tablet completely?

6) Very often
7) Quite often
8) Occasionally
9) Very rarely
10) Never

Do you find that you tare more likely to miss one anti-rejection tablet than the others?
6) Yes 2) No

1)Which one? 2)Why do you think that is?

People on long term medicines sometimes leave out tablets because of particular concerns or symptoms. What things, worries or other events make you do that?

3) Never misses
4) Misses – reasons below or don't know

Lots of things affect how long a transplant works. Overall, considering all the possible things that keep your kidney working, how important do you think your anti-rejection tablets are in keeping your transplant working? Could you rate that as a percentage from 1-100.
0-100% _____

Are there any other things that you do that you think are important to keep your kidney going? (list main 3)

_____ _____ _____

As I said before, we know that if people are taking tablets every day for a long time they miss some, either because they forget or have a particular reason. People with renal transplants aren't likely to be any different. One of the things we are interested in is how many tablets people think it would be possible to miss without it causing harm. This isn't saying that you do it, would think about missing any and isn't saying that we suggest it. There isn't a correct answer and there isn't any medical evidence to indicate a correct answer so please just say what your best guess is.

If you were to miss some tablets for some reason then how many tablets:-

- In a row do you think you could miss without it affecting your transplant _____

If you missed odd tablets, not several in a row , then how many do you think:-

- You could miss in one year without it affecting your transplant _____
- And what about each month _____
- How many do you think you could miss each week without it causing harm _____

Now I'd like to ask you the same questions about your blood pressure (if not on BP tablets then use alternative) tablets

	% importance in specified function	How many could miss in a row without harm	How many could miss in a year without harm
BP tabs wrt keeping kidney			
BP tabs wrt stable BP			
Other tablet (what pt says it does)			

In the future when we have the results of this study we may want to do a follow up study looking at how things change over time after a kidney transplant.
Would you be willing to be contacted in the future for a follow up study. Of course the study would be explained and you would decide at that point whether you wanted to take part.
Yes / No

Now I'd like to ask you a few questions about yourself. We need the descriptions to describe all the patients we have studied to see whether the patients we have studied are similar to other transplant patients in Britain. The information will be described as something like 45% of the sample are female, 60% are working and 75% are living with someone. Of course it won't be possible to identify individuals from the results.

Marital status
1)partner or spouse
2)separated or divorced
3)never married or cohabiting
4)widowed

DOB _____
Age _____

Are you currently in full time or part time work? FT_1 PT_2 No work$_3$
What is your job _____ (social class _____)

What was your last full time job before you got kidney failure? _____
(social class _____)

Is your partner currently in full time or part time work? FT_1 PT_2 No work$_3$
What is their job _____ (social class _____)

What age were you when you left Full time education?
1) under 16
2) 16
3) 18
4) 21
5) over 21

What qualifications did you get / did you leave with any qualifications – which ones?
(if over 21: what is the highest qualification you have?)
1) CSE/O level/GCSE
2) A level
7) Undergraduate Degree
8) Postgraduate degree
9) Vocational
10) None

How would you describe your ethnicity
1)White 2)Black carribean 3)Black african 4)Black other
5) Indian 6) Pakistani 7) Bangledeshi 6)Chinese 7)Other

My overall impression of the frequency that anti-rejection medicine is taken more than 2 hours late is:-

6) Very often
7) Quite often
8) Occasionally
9) Very rarely
10) Never

My overall impression of the frequency that anti-rejection medicine is missed completley is:-

6) Very often
7) Quite often
8) Occasionally
9) Very rarely
10) Never

Appendix A10: Clinician rating of adherence

PATIENT VIEWS ABOUT LIVING WITH A RENAL TRANSPLANT

CLINICIAN RATED ADHERENCE

Dear Dr

I would be grateful if you could indicate, on the scales below, your assessment of how well the specified patient has adhered to their immunosuppressant medication and how well they attend clinic. Thank you for your help with this study. Please return these forms to me c/o Dr Mason's secretary at St Mary's Hospital.

Yours sincerely,

Dr Janet Butler.

Patient name _____ Patient DOB _____ Study code ___

Please circle the number corresponding most closely to your assessment of the specified patient's adherence to their immunosuppressant medication as indicated by the question. (NB: **This is a clinician rating so**, although you may wish to complete this in clinic when you see the patient, **please do not ask the patient their views of their adherence,** we are doing that in another part of the study).

My overall impression of the frequency that **anti-rejection medicine is taken more than 2 hours late** in to 1999/20002001 is:-

11) Very often
12) Quite often
13) Occasionally
14) Very rarely
15) Never

My overall impression of the frequency that **anti-rejection medicine is missed completely** in to 1999/2000/2001 is:-

11) Very often
12) Quite often
13) Occasionally
14) Very rarely
15) Never

This patient **misses clinic appointments**:-

1) Very often
2) Quite often
3) Occasionally
4) Very rarely
5) Never

Appendix A11: Variables compared to adherence using bivariate tests

Group of variables	Measured variable
Socio-demographic factors	age
	sex
	living alone
	[1]working (full-time or part-time); exclude retired
	[1]social class I or II
	[1]left full-time education aged over 18 years old
Medical factors	type of first transplant
	type of current transplant
	re-graft
	duration of current transplant
	[1]one or more rejection episodes with current transplant a) in total from the subject b) in total from the notes
	[1] 'other' HLA mis-match
	pre-emptive transplantation
	total duration of time with a transplant
	total duration of time on dialysis
	duration of time on dialysis prior to first transplant
	prescribed prednisolone
	dosing frequency of prednisolone
	last creatinine
	[1]score of 1 or more on renal registry comorbidity scale
	diabetic
	units of alcohol each week
	body mass index
	total number of medicines taken each day
	total number of doses of medicine taken each day
	uses a reminder for medication
Functional health status	SF36 physical functioning scale total
	SF36 role limitation due to physical problems scale total
	SF36 role limitation due to emotional problems scale total
	SF36 social functioning scale total
	SF36 mental health scale total
	SF36 energy/vitality scale total
	SF36 pain scale total
	SF36 general health perception scale total
Beliefs about the transplant	[2]IPQ identity scale: total number of symptoms endorsed
	IPQ identity scale: percentage of endorsed symptoms attributed to the transplant
	IPQ identity scale: percentage of endorsed symptoms attributed to immunosuppressants
	IPQ time-line scale total
	[3]IPQ consequences scale total minus one item with the 3 items added for the current study
	IPQ control-cure scale total

Group of variables	Measured variable
Beliefs about the transplant continued	[4]IPQ emotional scale total (from the revised version of the IPQ)
	total score on the pros of a transplant questionnaire
	total score on the cons of a transplant questionnaire
	total number of spontaneously reported benefits of a transplant compared to dialysis given in the interview
	view of the worth of a transplant prior to transplantation
	view of the worth of a transplant post transplantation
	change in view of the worth of a transplant
	total number of spontaneously reported disadvantages of a transplant compared to dialysis given in the interview
Beliefs about medication	BMQ overuse sub-scale total
	BMQ harm sub-scale total
	[4]BMQ benefit sub-scale total (from the revised BMQ)
	BMQ necessity scale total for prednisolone
	BMQ necessity scale total for immunosuppressants
	[5]BMQ concerns scale total with 2 added items for prednisolone
	[5]BMQ concerns scale total with 2 added items for immunosuppressants
	BMQ necessity minus modified concerns scale total for prednisolone
	BMQ necessity minus modified concerns scale total for immunosuppressants
	total score on the cons of immunosuppressants questionnaire
	total number of spontaneously reported benefits of immunosuppressants given in the interview
	total number of spontaneously reported problems with immunosuppressants given in the interview
	estimated importance of immunosuppressants as a percentage of all things maintaining the transplant
	estimated number of days immunosuppressants could be missed in a year without harming the transplant
	estimated number of consecutive days immunosuppressants could be missed without harming the transplant
Other psychosocial factors	CIS-R total score
	score of 12 or more on the CIS-R
	self-report of binge eating in the last month
	ICD10 diagnosis of mild depression
	ICD10 diagnosis of moderate depression
	ICD10 diagnosis of severe depression
	ICD10 diagnosis of moderate or severe depression
	ICD10 diagnosis of depression (any severity)
	Significant others scale total for actual practical support
	Significant others scale total for ideal practical support
	Significant others scale total for actual emotional support
	Significant others scale total for ideal emotional support
	Ideal more than actual practical support on significant others scale
	Ideal more than actual emotional support on significant others scale

[1]categorized after inspecting distribution of the data
[2]IPQ cause scale not included in bivariate analyses because total scale score not derivable
[3]modified scale after seeing the internal reliability, tables 8.5.3 and 12.5.2c
[4]see table 8.5.3
[5]see tables 8.5.3 and 12.5.1b

Appendix B1: Definition of terms relating to psychometric properties

Validity	the extent that a tool measures what it is meant to measure[1]
Face validity	the measure looks as if it is measuring what it is meant to[2]
Content validity	whether all relevant topics are sampled by the measure[2]
Construct validity	the extent to which the tool tests the theory it is measuring[3]
Convergent validity	requires that the tool correlates with related variables[3]
Discriminant validity	requires that the tool does not correlate with dissimilar variables[3]
Criterion validity	covers correlations of the tool with another measure that is recognised as standard, usually termed the 'gold standard' measure[3] and is often thought of as being made up of concurrent and predictive validity[2]
Concurrent validity	the measure correlates with a 'gold standard' or criterion measure.
Predictive validity	whether the tool can predict future changes in key variables in expected directions[3]
Reliability	the extent to which a measure will produce the same outcome when used in an identical setting. It is reflected in the reproducibility of test scores and the internal consistency of the items[2]
Test-retest reliability	is a test of the stability of the measure over a period of time in which it is not expected to change[3]. It is described by the size of a correlation coefficient. A highly reliable test has a correlation coefficient approaching +1.
Inter-rater reliability	the extent to which results obtained by two or more raters or interviewers agree between independent observers. It is usually measured by Cohen's kappa statistic with results in excess of +0.60 indicating reasonable reliability[2]
Internal consistency	reflects the homogeneity of items and is often described by internal consistency coefficients such as Cronbach's alpha. Cronbach's alpha can vary from 0 to +1, with higher values reflecting greater internal consistency[2]. A value of 0.70, for example, implies that 70% of the measured variance is reliable and 30% is owing to random error[3]
Sensitivity	the chance of correctly identifying 'true' cases[3] (few false negatives).
Specificity	the probability of correctly identifying a non-affected individual[3] (few false positives).
Bias	a systematic error in recording results
Selection bias	if the all members of the population do not have an equal chance of being sampled. It results in the characteristics of the sample differ from those of the wider population

Sampling bias	occurs when not all members of the population have a calculable chance of being selected in the sample. It results in the characteristics of the sample differ from those of the wider population
Non-response bias	if there are differences in the characteristics between responders and non-responders to the study[3].
Response style bias	is particularly relevant to questionnaire studies and refers to a subject's manner of responding to items regardless of their content[3] such as always tending to agree with statements
Social desirability bias	when people want to present themselves at their best[3].
Interviewer bias	when the interviewer, consciously or subconsciously, biases respondents answers: for example, by appearing to hold certain values which lead to a social desirability bias, or by asking leading questions[3]
Hawthorne effect	when a subject is aware their behaviour is being measured such that the effect of being studied changes their behaviour[3]

1 Vitolins et al 2000
2 Todd & Bradley 1994
3 Bowling 1997.

Appendix B2 : Illustration of the calculation of dosing and daily adherence

a) For subjects prescribed prednisolone once each day

Table representing the openings of the electronic monitoring container for a subject who had the monitor for 26 days

Opening	+	-	-	-	-	-	-	-	+	+	+	+	-
Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Opening	+	++	-	-	+	++	+	-	-	-	+	+	+
Day	14	15	16	17	18	19	20	21	22	23	24	25	26

The first opening occurs on day one but then there is a week's gap before another opening occurs on day 9. Therefore the monitored period is assumed to be from day 9 to 26 (17 days).

Two openings occur on day 15 and 19, the dose closest to the usual time of openings on other days will be taken to be the dose used to calculate the inter-dose interval for these days

Prednisolone is prescribed for 17 monitored days
Openings occurred on 12 of these days and did not occur on 6 days

- Therefore the percentage missed doses are 6/17 *100 = 35.3%

The longest period without an opening is between day 20 and day 24
A dose of prednisolone should have been taken within 24 hours of the dose taken on day 20

- Therefore the longest delay in dosing is the number of hours between the doses on day 20 and day 24 minus 24 hours

There was no opening of the monitor on days 13, 16, 17 and 21-23
An opening should (according to the prescription) occur within 24 hours of the previous opening
If one dose is missed, an opening should occur within 48 hours of the previous opening
If an opening occurs after more than 48 hours then more than one dose (reflected by an opening) has been missed
Therefore inter-dose intervals of less than 48 hours reflect days when medication is taken or when only one dose is missed
Therefore only inter-dose intervals of under 48 hours are used to calculate variability in dose timing

- Variability in dose timing is calculated using the standard deviation of inter-dose intervals under 48 hours

b) For subjects prescribed prednisolone once on alternate days

Table representing the openings of the electronic monitoring container for a subject who had the monitor for 26 days

Opening	+	-	-	-	-	-	-	-	+	-	+		+
Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Opening	-	++	-	-	-	+	-	+	-	-	-	+	+
Day	14	15	16	17	18	19	20	21	22	23	24	25	26

The first opening occurs on day one but then there is a week's gap before another opening occurs on day 9. Therefore the monitored period is assumed to be from day 9 to 26 (17 days).

Two openings occur on day 15 and 19, the dose closest to the usual time of openings on other days will be taken to be the dose used to calculate the inter-dose interval for these days

An extra opening occurs on day 26. This will not be counted as a dose.

Prednisolone is prescribed for 9 monitored days (days 9, 11, 13, 15, 17, 19, 21, 23 and 25)
The expected opening occurred on day 9 (the first day used in the calculations) and then openings occurred as expected two days after the last opening on days 13, 15 and 21.
Day 17 and day 23 should have had an opening, so counted as days with missed medication.
The day before did not have an opening so an opening was expected on days 18 and 24.
Therefore these days also counted as days with missed medication.

- Therefore the percentage missed doses are 4/9 *100 = 44.4%

The longest periods without expected opening are days 17 and 18 and days 23- 24
A dose of prednisolone should have been taken within 48 hours of the doses taken on days 15 and 21

- Therefore the longest delay in dosing is the longest number of hours between the openings between days 15 and 19 and days 21 and 25 minus 48 hours

There was no opening of the monitor on days when this was expected on days 17, 18, 23 and 24
An opening should (according to the prescription) occur within 48 hours of the previous opening
If one dose is missed, an opening should occur within 72 hours of the previous opening
If an opening occurs after more than 72 hours then more than one dose (reflected by an opening) has been missed
Therefore inter-dose intervals of less than 72 hours reflect days when medication is taken or when only one dose is missed
Therefore only inter-dose intervals of under 72 hours are used to calculate variability in dose timing

- Variability in dose timing is calculated using the standard deviation of inter-dose intervals under 72 hours

Appendix B3: Summary of psychometric properties given in the original description of questionnaires used in the study

	Illness Perception Questionnaire[1]	Beliefs About Medicines Questionnaire[2]	Morisky Questionnaire[3]	Revised Clinical Interview Schedule[4]	Short Form 36[5]	Social Support Questionnaire[6]
Illness group(s) in which the questionnaire was designed	On haemodialysis, post heart attack, asthma, insulin dependant diabetes, juvenile rheumatoid arthritis, idiopathic chronic pain	On haemodialysis, diabetes mellitus, asthma, attending psychiatry out-patients, general medical & cardiac in-patients	Hypertension	General practice attenders in London	American general population	Female university students
Number of items	38	18	4	Variable depending on answers to prompt questions	36	8
Number of sub-scales	5 (identity, cause, time-line, consequences, control-cure)	4 (general-overuse, general-harm, specific-concern, specific-necessity)	Nil	14 (somatic symptoms, fatigue, concentration & memory, sleep, irritability, worry about physical health, worry, anxiety, phobias, compulsions, obsessions depression, depressive ideas)	8 (physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, general health perceptions)	4 (actual-practical, actual-emotional, ideal-practical, ideal-emotional)
How items are rated	5 point scale: strongly agree-strongly disagree	5 point scale: strongly agree-strongly disagree always-never	Binary: yes or no	Score of 0-4 on each sub-scale (except 0-5 for depressive ideas)	Varies from a choice of 1 from 3 responses to a 6 point scale: all of the time-none of the time	7 point scale: always-never
Internal consistency of sub-scales (Cronbach's alpha)	0.73-0.82	0.47-0.86 (0.55-0.83 in renal group)	0.61	0.82	Not given	0.42-0.76
Indicators of convergent validity	Different sub-scale distributions in different illness groups, Sub-scales correlate as predicted with other measures	Sub-scale distributions in different illness groups, sub-scale scores correlated in predicted manner with illness perception sub-scale scores	Adherence to anti-hypertensives correlated with blood pressure at 2 years (R^2=0.33)	Not given	Not given	Not given

	Illness Perception Questionnaire[1]	Beliefs About Medicines Questionnaire[2]	Morisky Questionnaire[3]	Revised Clinical Interview Schedule[4]	Short Form 36[5]	Social Support Questionnaire[6]
Indicators of criterion validity	Not given	Sub-scale scores correlated in predicted direction with single statements about problems and adherence with medication	Score of adherence to anti-hypertensives correlated with blood pressure at baseline	Total score correlates with psychiatrists diagnoses (r=0.77)	Not given	Subjects with high scores on the general health Questionnaire-28 had high discrepancies between actual and ideal support
Test-retest reliability	0.49-0.84 at 1 month & 0.34-0.54 at 3 months	0.60-0.78 at 2 weeks	Not given	0.41-0.82 at 'a few minutes'	Not given	0.73-0.83 at 6 months
Changes to questionnaire for this study	Reworded for renal transplant recipients, added 3 consequence items	Reworded for immunosuppressant medication, added emotional sub-scale (4 items), 2 concern items & 1 information item	None	None	None	None

1 Weinman et al. 1996 (see section 7.5.1)
2 Horne et al. 1999 (see section 7.5.2)
3 Morisky, Green & Levine 1986 (see section 7.3.5)
4 Lewis et al. 1992 (see section 7.5.6)
5 Ware & Sherbourne 1992 (see section 7.2.1)
6 Power, Champion & Aris 1988 (see section 7.5.7)

The Medication Adherence Rating Scale (MARS; Horne, Personal communication 1999) that was also used in this study (see section7.3.5) is not included in the table since validation data is not available

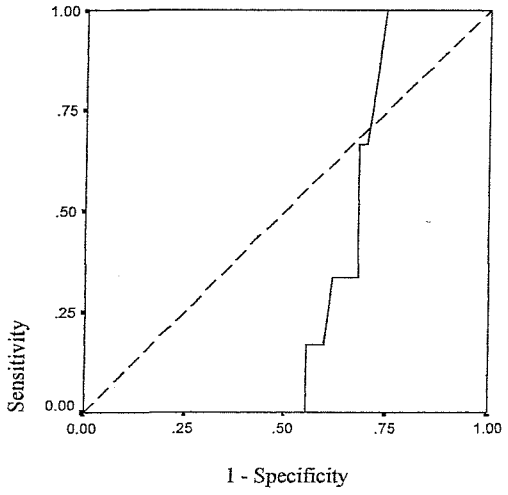
APPENDIX B4: Sensitivity and specificity of measures of adherence to detect subjects missing 20% or more days medication

Range of the last 6 cyclosporin levels

Table: Range of cyclosporin levels to detect subjects missing 20% or more days medication

Range to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
≥ 60	100.0	23.4	14.3	100.0	1.3	67.9
≥ 65	83.3	27.7	12.8	92.9	1.2	66.0
≥ 75	66.7	29.8	10.8	87.5	1.0	66.0
≥ 85	33.3	32.0	6.1	80.0	0.5	66.0
≥ 110	16.7	40.0	3.6	80.0	0.3	60.4
≥ 120	0.0	46.8	0.0	78.6	0.0	58.5

Figure: ROC curve of the range of the last six cyclosporin levels compared to missing 20% or more days medication assessed by electronic monitoring



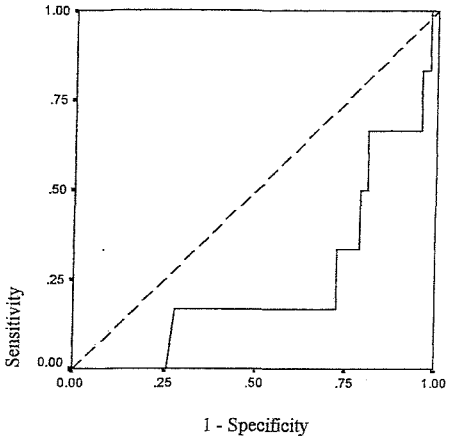
area under the curve (95% CI)
0.34 (0.20 - 0.47)

Lowest of the last 6 cyclosporin levels

Table: Low levels of the lowest cyclosporin level used to detect subjects missing 20% or more days medication

Level to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
≤ 90	0.0	76.6	0.0	86.0	n/a	30.2
≤ 100	16.7	66.0	6.7	86.8	0.5	35.8
≤ 130	16.7	29.8	2.9	73.7	0.1	71.7
≤ 140	50.0	21.3	7.5	76.	0.3	75.5
≤ 150	66.7	17.0	9.1	77.8	0.4	79.2
≤ 170	66.7	6.1	8.3	60.0	0.2	86.8
≤ 190	100.0	0.0	11.3	0.0	n/a	88.7

Figure: ROC curve of lowest of the last six cyclosporin levels compared to missing 20% or more days medication assessed by electronic monitoring



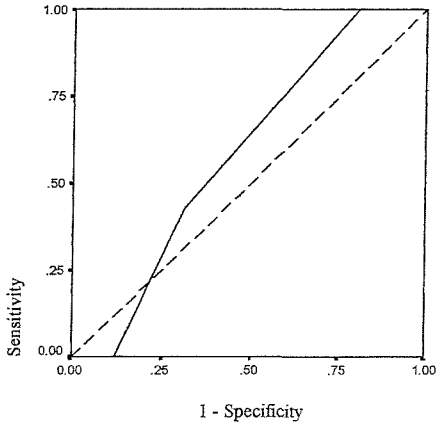
area under the curve (95% CI)
0.25 (0.00 - 0.45)

Single item self-report by questionnaire

Table: Single questionnaire item to detect subjects missing 20% or more days medication

Responses to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
Rarely, sometimes, often or always	100.0	19.6	14.6	100.0	1.2	70.7
Sometimes, often or always	42.9	68.6	15.8	89.7	1.4	34.5
Often or always	0.0	88.2	0.0	86.5	0.0	22.4

Figure: ROC curve of the single questionnaire item compared to missing 20% or more days medication



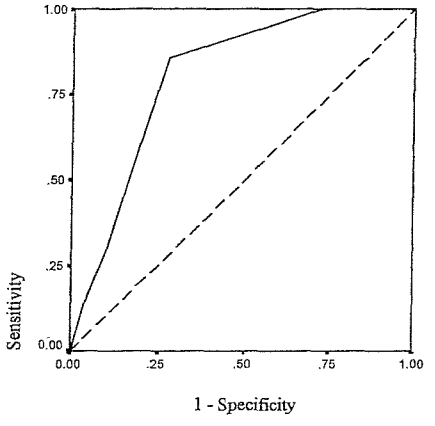
area under the curve (95% CI)
0.59 (0.41 – 0.77)

Self report in Interview

Table: Self report in Interview of late doses to detect subjects missing 20% or more days medication

Responses to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
at least very rarely	100.0	27.5	15.9	100.0	1.4	63.8
occasionally, quite often or very often	85.7	72.5	30.0	97.4	3.1	25.9
quite often or very often	28.6	90.2	28.6	90.2	2.9	17.2
very often	14.3	96.1	33.3	89.1	3.7	13.8

Figure: ROC curve of the self-report in interview of late doses compared to missing 20% or more days medication



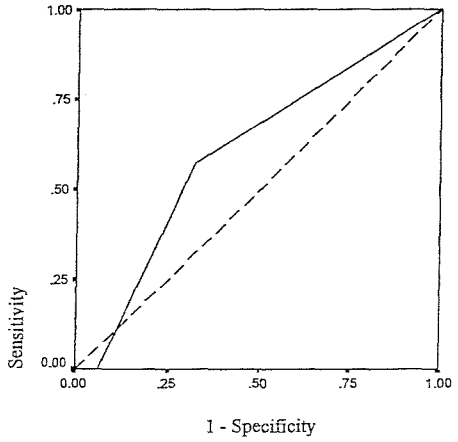
area under the curve (95% CI)
0.81 (0.67 – 0.95)

Morisky Self report questionnaires

Table: Morisky questionnaire used to detect subjects missing 20% or more days medication

Cut-off to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
1/2 or ≥ 1	57.1	68.0	20.0	91.9	1.8	33.3
2/3 or ≥ 2	0.0	94.0	0.0	87.0	0.0	20.0

Figure: ROC curve of the Morisky questionnaire compared to missing 20% or more days medication assessed by electronic monitoring



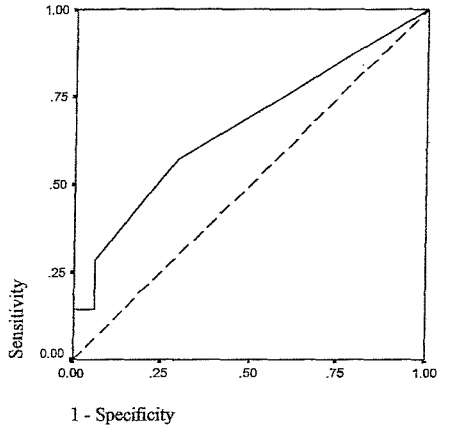
area under the curve (95% CI)
0.61 (0.39–0.83)

MARS Self report questionnaire

Table: MARS questionnaire used to detect subjects missing 20% or more days medication

Value to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
25/24 or ≤ 24	57.1	70.6	21.1	92.3	1.9	31.0
24/23 or ≤ 23	28.6	94.1	40.0	90.6	4.8	13.8
23/22 or ≤ 22	14.3	94.1	25.0	88.9	2.4	15.5
22/21 or ≤ 21	14.3	98.0	50.0	89.2	7.1	12.1
21/20 or ≤ 20	14.3	98.0	50.0	89.2	7.1	12.1
20/19 or ≤ 19	14.3	100.0	100.0	89.5	n/a	10.3
19/18 or ≤ 18	0.0	100.0	100.0	87.9	n/a	12.1

Figure: ROC curve of the MARS questionnaire compared to missing 20% or more days medication assessed by electronic monitoring



area under the curve (95% CI)
0.66 (0.43–0.90)

Clinician rating

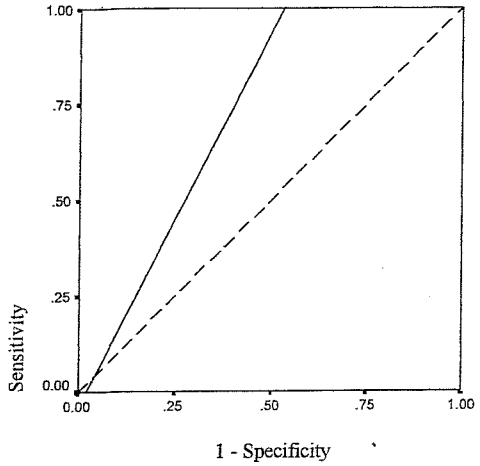
Table: Clinician rating of late doses to detect subjects missing 20% or more days medication

Responses used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
Occasionally, quite often or very often	100.0	47.1	20.6	100.0	1.9	46.6
quite often or very often	0.0	98.0	0.0	87.7	0.0	13.8

Table: Clinician rating of missed doses to detect subjects missing 20% or more days medication

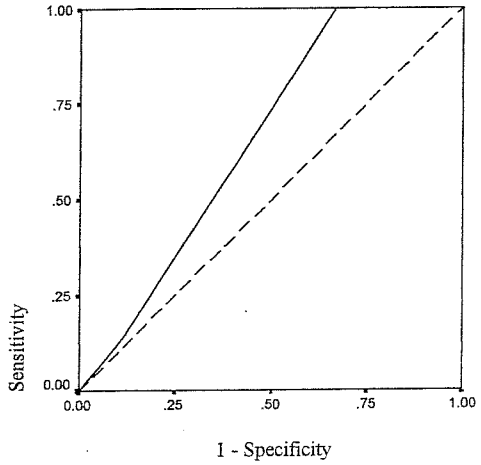
Responses used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	100.0	33.3	17.1	100.0	1.5	58.6
occasionally, quite often or very often	14.3	88.2	14.4	88.2	1.2	20.7
quite often or very often	0.0	100.0	0.0	87.9	n/a	12.1

Figure: ROC curve of the clinician rating of late doses compared to missing 20% or more days medication



area under the curve (95% CI)
0.73 (0.58–0.87)

Figure: ROC curve of the clinician rating of missed doses compared to missing 20% or more days medication



area under the curve (95% CI)
0.66 (0.49–0.83)

Interviewer rating

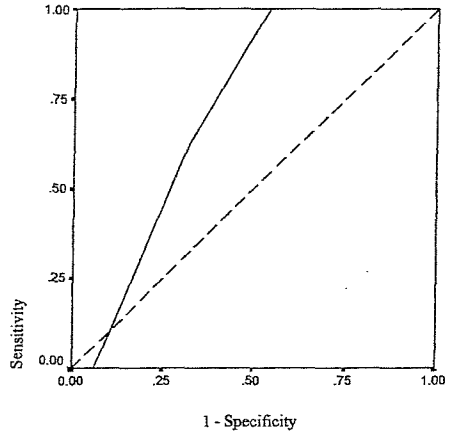
Table: Interviewer rating of late doses to detect subjects missing 20% or more days medication

Responses used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	100.0	3.9	12.5	100.0	n/a	84.5
occasionally, quite often or very often	100.0	45.1	20.0	100.0	n/a	48.3
quite often or very often	71.4	68.6	23.8	94.6	4.4	31.0
very often	0.0	94.1	n/a	87.3	n/a	17.2

Table: Interviewer rating of missed doses to detect subjects missing 20% or more days medication

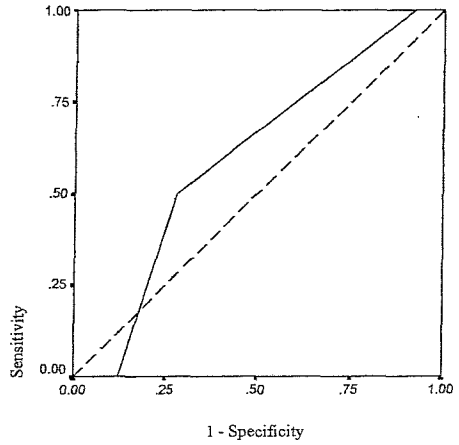
Responses used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	100.0	7.8	13.0	100.0	n/a	81.0
occasionally, quite often or very often	57.1	72.5	22.2	92.5	3.0	29.3
quite often or very often	0.0	88.2	n/a	86.5	n/a	12.1

Figure: ROC curve of the interviewer rating of late doses compared to missing 20% or more days medication



area under the curve (95% CI)
0.72 (0.58-0.86)

Figure: ROC curve of the interviewer rating of missed doses compared to missing 20% or more days medication assessed by electronic monitoring



area under the curve (95% CI)
0.60 (0.41–0.79)

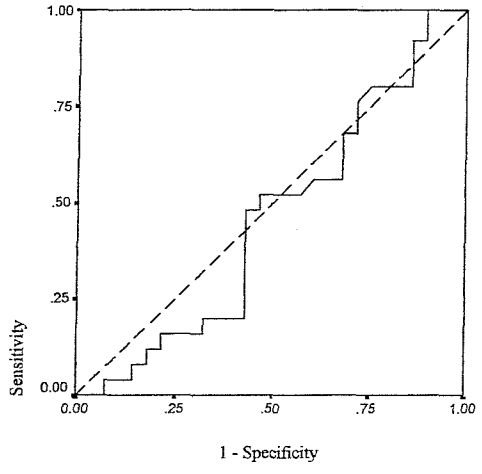
APPENDIX B5: Ability of adherence measures to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Range of the last 6 cyclosporin levels

Table: Range of cyclosporin levels to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Range to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
≥ 20	100.0	10.7	49.0	100.0	1.1	49.1
≥ 40	92.0	14.3	47.8	57.1	1.0	50.9
≥ 60	80.0	21.4	476	54.5	1.0	50.9
≥ 80	64.0	32.1	45.7	50.0	0.9	52.8
≥ 108	52.0	42.9	44.8	50.0	0.9	52.8
≥ 120	48.0	54.0	48.0	53.6	1.0	49.1
≥ 160	20.0	60.7	29.4	61.5	0.5	60.4
≥ 300	12.0	82.1	28.6	50.0	0.7	52.8
≥ 470	0.0	92.9	n/a	50.9	0.0	509

Figure: Range of cyclosporin levels to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours



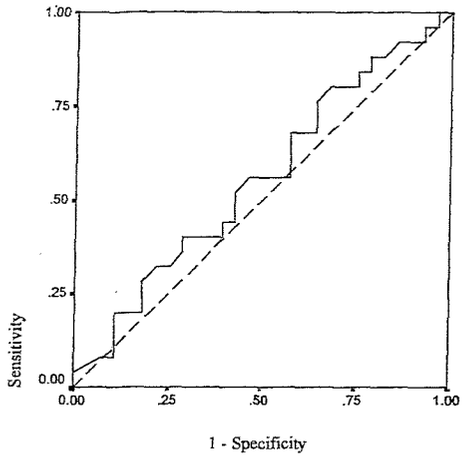
area under the curve (95% CI)
0.46 (0.30-0.62)

Lowest of the last 6 cyclosporin levels (lower level to indicate non-adherence)

Table: Lowest of the last 6 cyclosporin levels to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Range used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
≤ 190	100.0	0.0	47.2	n/a	1.0	52.8
≤ 160	88.0	17.9	50.0	66.7	1.1	47.2
≤ 130	68.0	39.3	50.0	57.8	1.1	47.2
≤ 100	36.0	71.4	53.3	55.2	1.3	45.3
≤ 90	20.0	82.1	50.0	53.5	1.1	47.2
≤ 80	16.0	89.3	57.1	54.3	1.5	45.3
≤ 70	8.0	89.3	50.0	53.0	0.7	47.2
≤ 50	4.0	100.0	n/a	87.5	0.0	45.3

Figure: Lowest of the last 6 cyclosporin levels to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours



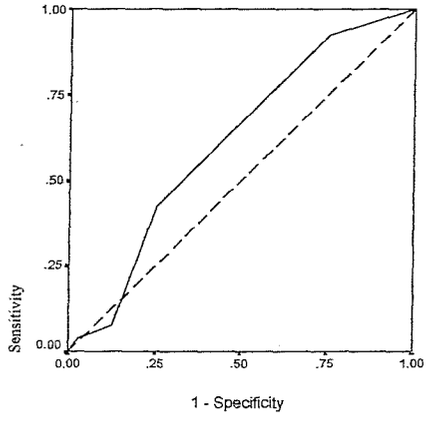
area under the curve (95% CI)
0.56 (0.40-0.71)

Single questionnaire item

Table: Single questionnaire item to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
Rarely, sometimes, often or always	92.3	25.0	50.0	80.0	1.2	44.8
Sometimes, often or always	42.3	75.0	57.9	61.5	1.7	39.7
Often or always	7.7	81.8	33.3	42.9	0.4	48.3
Always	3.8	96.9	50.0	55.4	1.2	44.8

Figure: Single questionnaire item to detect subjects with a standard deviation of inter-dose intervals of 6 hours or more



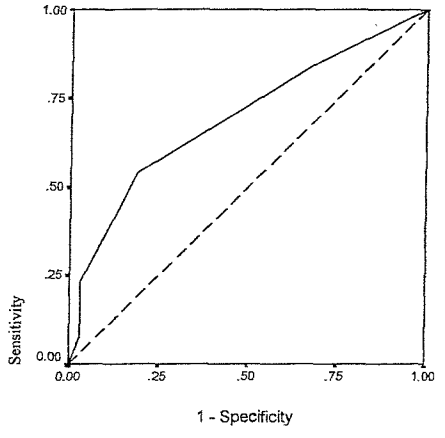
area under the curve (95% CI)
061 (0.47-0.76)

Self-report of late taking at interview

Table: Self report in Interview of late doses to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
at least very rarely	84.6	31.3	50.0	71.4	1.2	44.8
occasionally, quite often or very often	53.8	81.3	70.0	68.4	2.9	31.0
quite often or very often	23.1	96.9	85.7	60.8	7.5	36.2

Figure: ROC curve of the self-report in interview of late doses compared to a standard deviation of inter-dose intervals of at least 6 hours



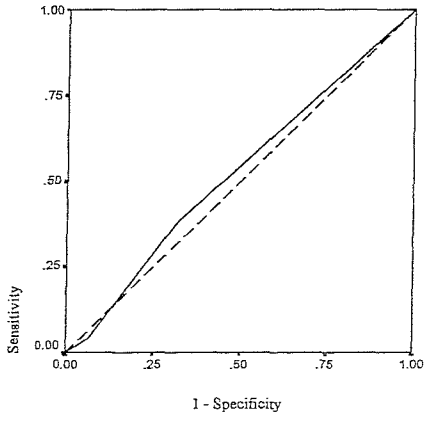
area under the curve (95% CI)
0.70 (0.56-0.84)

Morisky self-reported adherence questionnaire

Table: Morisky questionnaire used to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Cut-off to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
1/2 or ≥ 1	38.5	67.7	50.0	56.8	1.2	45.6
2/3 or ≥ 2	3.8	93.5	33.3	53.7	0.6	77.7
3/4 or ≥ 3	0.0	100.0	n/a	54.4	0.0	45.6

Figure: Morisky questionnaire used to detect subjects with a standard deviation of inter-dose intervals of 6 hours or more



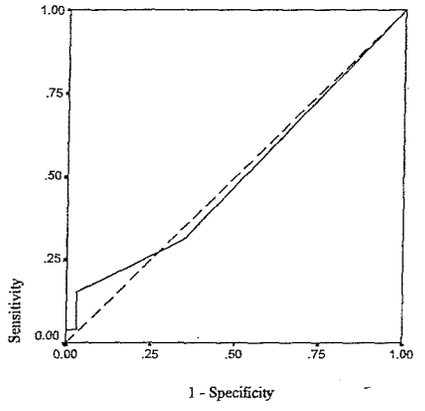
area under the curve (95% CI)
0.53 (0.37-0.68)

MARS self-reported adherence questionnaire

Table: MARS questionnaire used to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Value used to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
25/24 or ≤ 24	30.8	65.6	42.1	53.8	0.9	50.0
24/23 or ≤ 23	15.4	96.9	80.0	58.5	5.0	39.7
23/22 or ≤ 22	11.5	96.9	75.0	57.4	3.7	41.4
22/21 or ≤ 21	11.5	96.9	75.0	57.4	3.7	41.4
21/20 or ≤ 20	3.8	96.9	50.0	55.4	1.2	44.8
20/19 or ≤ 19	3.8	100.0	100.0	56.1	0.0	43.1

Figure: MARS questionnaire used to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours



area under the curve (95% CI)
0.50 (0.35-0.66)

Clinician rating

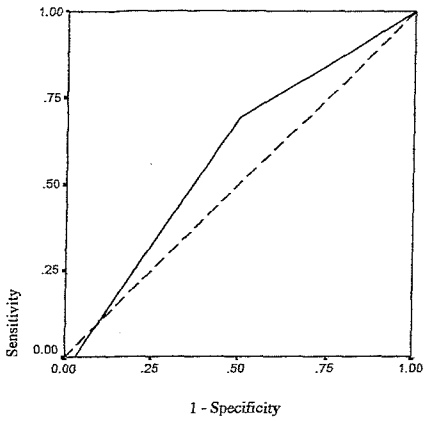
Table: Clinician rating of late doses to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	100.0	0.0	100.0	0.0	1.0	55.1
occasionally, quite often or very often	69.2	50.0	52.9	50.0	1.4	55.2
quite often or very often	0.0	96.9	0.0	54.4	0.0	46.6

Table: Clinician rating of missed doses to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

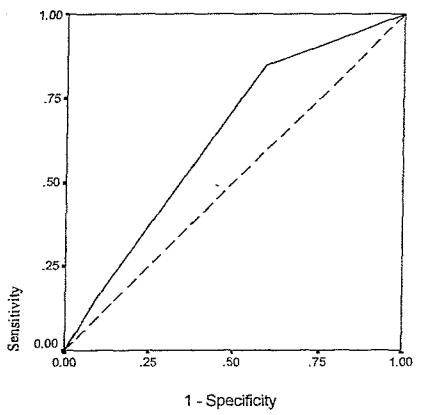
Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	84.6	40..6	53.7	76.5	1.4	39.7
occasionally, quite often or very often	15.4	90.6	57.1	56.9	1.6	43.1
quite often or very often	0.0	100.0	0.0	55.2	1.0	44.8

Figure: ROC curve of the clinician rating of late doses compared to a standard deviation of inter-dose intervals of at least 6 hours



area under the curve (95% CI)
0.59 (0.44-0.73)

Figure: ROC curve of the clinician rating of missed doses compared to a standard deviation of inter-dose intervals of at least 6 hours



area under the curve (95% CI)
0.63 (0.49-0.78)

Interviewer rating

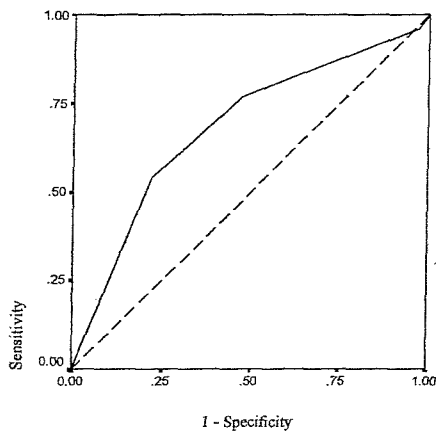
Table: Interviewer rating of late doses to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	96.0	3.1	44.6	50.0	13.9	55.2
occasionally, quite often or very often	76.9	53.1	57.1	73.9	1.6	36.2
quite often or very often	53.8	78.1	66.7	67.6	2.5	32.8

Table: Interviewer rating of missed doses to detect subjects with a standard deviation of inter-dose intervals of at least 6 hours

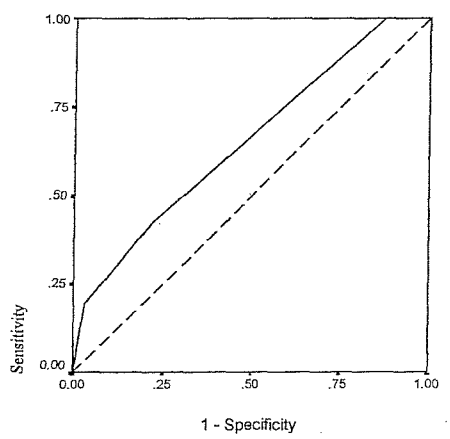
Response to define non-adherence	sensitivity	specificity	positive predictive value	negative predictive value	positive likelihood ratio	misclassification rate
very rarely, occasionally, quite often or very often	100.0	12.5	48.1	100.0	1.1	48.3
occasionally, quite often or very often	19.2	96.4	61.1	62.5	5.3	37.9
quite often or very often	19.2	96.9	83.3	59.6	5.3	37.9

Figure: ROC curve of the interviewer rating of late doses compared to a standard deviation of inter-dose intervals of at least 6 hours



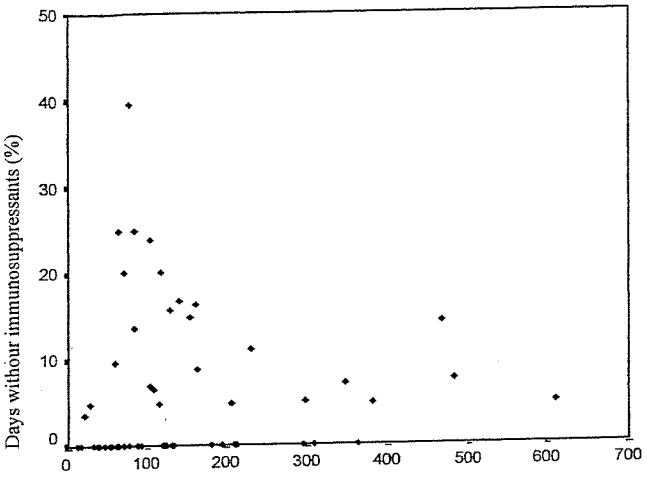
area under the curve (95% CI)
0.69 (0.55-0.83)

Figure 10.6.5a ROC curve of the interviewer rating of missed doses compared to a standard deviation of inter-dose intervals of at least 6 hours

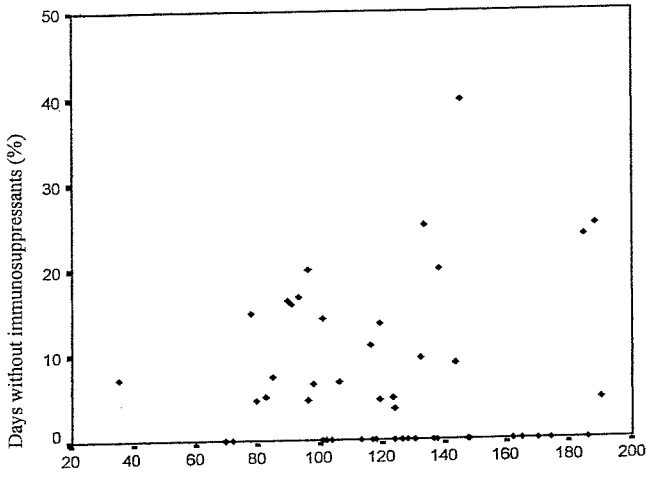


area under the curve (95% CI)
0.65 (0.51-0.79)

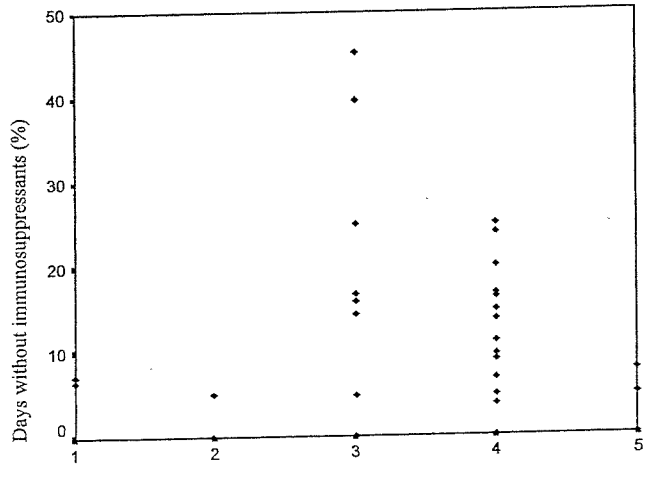
APPENDIX B6: Scatter plots of the other adherence measures compared to the percentage of days that immunosuppressants were missed



Spearman's r = 0.16

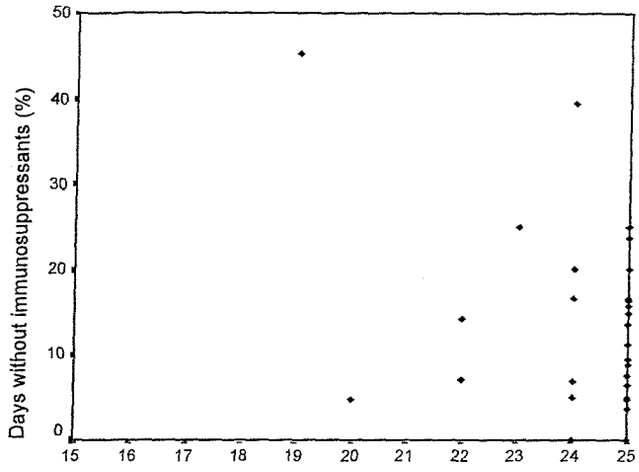


Spearman's r = -0.11

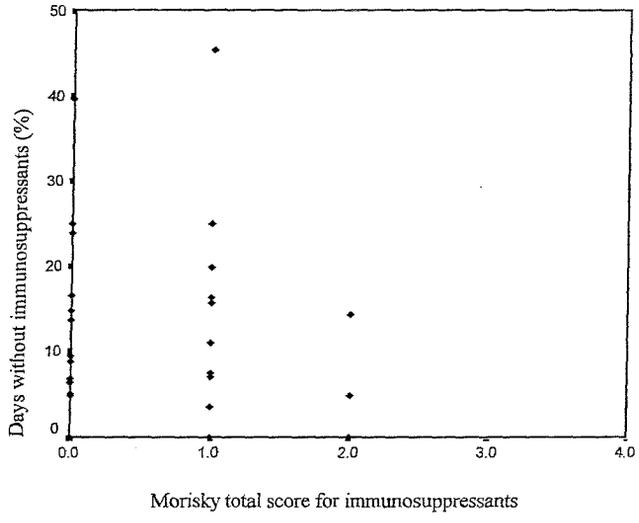


Spearman's r = -0.19

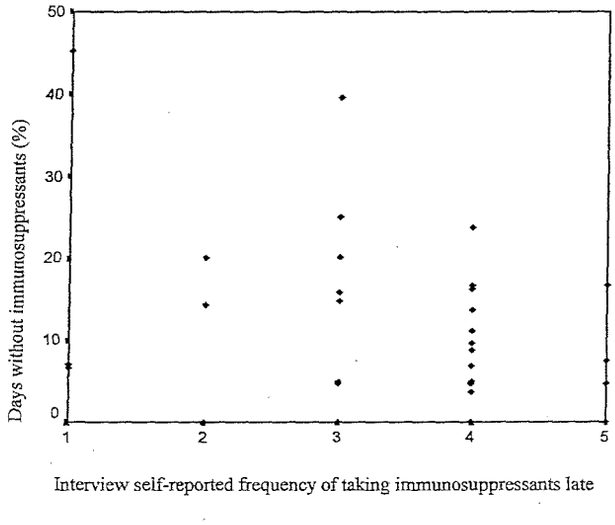
1 = 'always'
2 = 'often'
3 = 'sometimes'
4 = 'rarely'
5 = 'never'



Spearman's r = -0.17

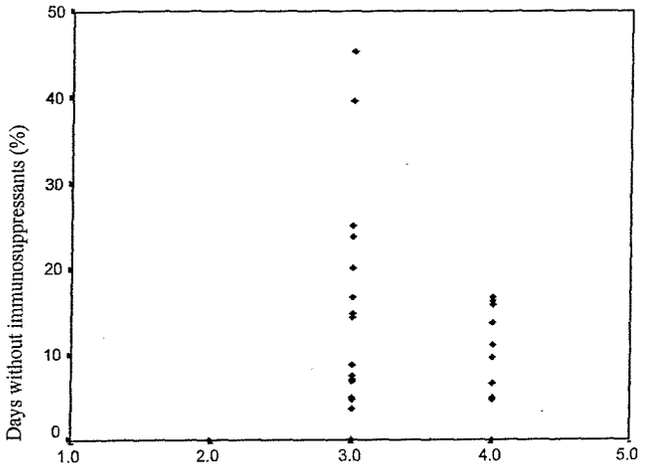


Spearman's r = 0.18



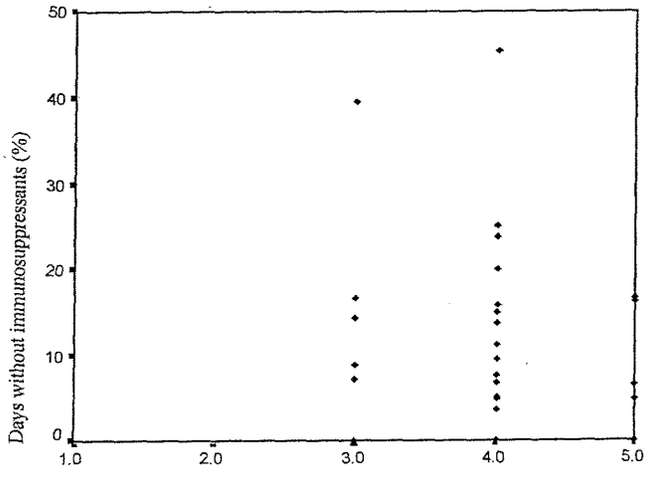
Spearman's r = -0.38

1 = 'very often'
2 = 'quite often'
3 = 'occasionally'
4 = very rarely'
5 = 'never'



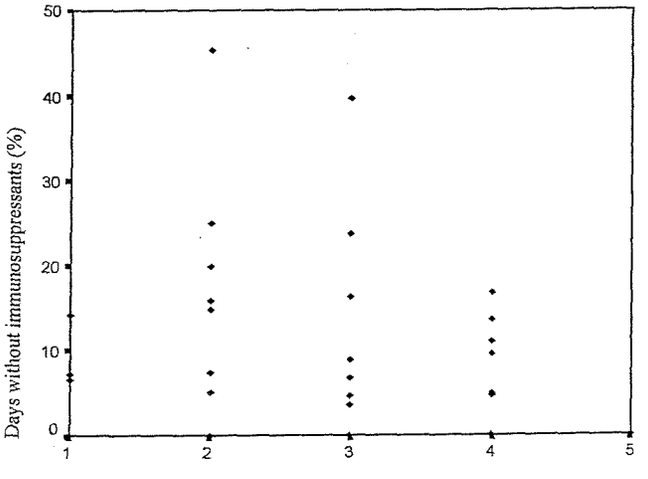
Spearman's r = -0.18

1 = 'very often'
2 = 'quite often'
3 = 'occasionally'
4 = very rarely'
5 = 'never'



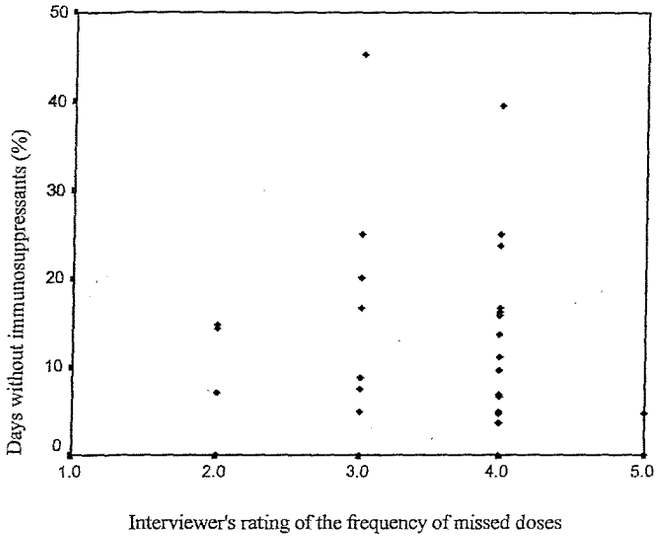
Spearman's r = -0.27

1 = 'very often'
2 = 'quite often'
3 = 'occasionally'
4 = very rarely'
5 = 'never'



Spearman's r = -0.26

1 = 'very often'
2 = 'quite often'
3 = 'occasionally'
4 = very rarely'
5 = 'never'



Spearman's r = -0.24

1 = 'very often'
2 = 'quite often'
3 = 'occasionally'
4 = very rarely'
5 = 'never'

Appendix B7: graft function at the end of the study

Two subjects who had been eligible for the study (and who both consented and received electronic monitoring) had moved out of the area and so been transferred to another renal unit by the end of the study. Graft function for all other eligible subjects (n=170) was assessed at a mean (standard deviation) of 22.9 (3.7) months since the subjects were interviewed and 57.1 (16.3) months since their transplant. Nineteen (13%) subjects who participated in the study (n=151) had experienced transplant failure at follow up. The occurrence of transplant failure did not differ in the group who refused to participate.

From the subjects who had consented to the study, 12 (8%) grafts had failed and 7 (5%) subjects had died with a functioning graft (table 16.0). From the 56 available subjects who had received electronic monitoring only 4 (7%) grafts had failed and 3 (5%) subjects had died with a functioning graft. These numbers were too small for analysis of the effect of adherence, or other variables, on graft function.

Table: Graft function at the end of the study

	Subjects who consented to the study (n=151)*	**Subjects who refused to take part (n=19)**
Graft still functioning	132	18
Graft failed – returned to dialysis	12	0
Subject died with functioning graft	7	1

* 2 subjects who consented to the study had moved out of the area and so transferred renal units so their current renal function was not available

References

1992, *The ICD-10 Classification of Mental and Behavioural Disorders: clinical descriptions and diagnostic guidelines.*

1992, *Renal Transplant Audit 1981-1991* United Kingdom Transplant Support Service Authority.

1992, *Renal Transplant Audit 1981-1991*. United Kingdom Transplant Support Service Authority.

1997, *Transplant Activity 1996*. United Kingdom Transplant Support Service Authority.

1999, *British National Formulary* British Medical Association and the Royal Pharmaceutical Society of Great Britain.

Transplantation Proceedings 1999, vol. 31[4A].

Ajzen, I. & Fishbein, M. 1980, *Understanding and predicting social behaviour* Prentice-Hall, Englewood Cliffs, NJ.

Ansell, D. & Feest, T. 1999, *The Second Annual Report of the UK Renal Registry,* The Renal Association.

Bachmann, L. H., Stephens, J., Richey, C. M., & Hook, E. W., III 1999, "Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance", *Sexually Transmitted Diseases*, vol. 26, no. 5, pp. 272-278.

Becker, M. H. 1974, "The health belief model and personal health behaviour", *Health Education Monographs*, vol. 2, pp. 324-508.

Bergmann, L., Roper, L., Bow, L. M., Hull, D., Bartus, S. A., & Schweizer, R. T. 1992, "Late graft loss in cadaveric renal transplantation", *Transplantation Proceedings*, vol. 24, no. 6, pp. 2718-2719.

Bergmann, L. S., Roper, L., Bow, L. M., Hull, D., Bartus, S. A., & Schweizer, R. T. 1993, "Causes of late graft failure in cadaveric renal transplantation", *Transplantation Proceedings*, vol. 25, pp. 1340-1341.

Birkeland, S. A. 2001, "Steroid-free immunosuppression in renal transplantation", *Transplantation*, vol. 71, no. 8, pp. 1089-1090.

Bittar, A. E., Keitel, E., Garcia, C. D., Bruno, R. M., Silveira, A. E., Messias, A., & Garcia, V. D. 1992, "Patient noncompliance as a cause of late kidney graft failure", *Transplantation Proceedings*, vol. 24, no. 6, pp. 2720-2721.

Blackwell, B. 1989, "Compliance - measurement and intervention", *Current Opinion in Psychiatry*, vol. 2, no. 6, pp. 787-789.

Bradley, C. 1994, "Measures of perceived control of diabetes," in *Handbook of Psychology and Diabetes*, C. Bradley, ed., Harwood Academic Publishers, pp. 291-331.

Brickman, A. L. & Yount, S. E. 1996, "Non-compliance in end-stage renal disease: a threat to quality of care and cost containment", *Journal of Clinical Psychology in Medical Settings*, vol. 3, no. 4, pp. 399-412.

British Transplantation Society 1998, *Towards Standards for Organ and Tissue Transplantation in the United Kingdom.*

Bunzel, B. & Laederach-Hofmann K. 2000, "Solid organ transplantation: Are there predictors for posttransplant noncompliance? A literature overview", *Transplantation*, vol. 70, no. 5, pp. 711-716.

Burnier, M. 2000, "Long-term compliance with antihypertensive therapy: Another facet of chronotherapeutics in hypertension", *Blood Pressure Monitor*, vol. 5, no. Supp. 1, p. S31-S34.

Butkus, D. E., Meydrech, E. F., & Raju, S. S. 1992, "Racial differences in the survival of cadaveric renal allografts. Overriding effects of HLA matching and socioeconomic factors", *New England Journal of Medicine*, vol. 327, no. 12, pp. 840-845.

Butkus, D. E., Dottes, A. L., Meydrech, E. F., & Barber, W. H. 2001, "Effect of poverty and other socioeconomic variables on renal allograft survival", *Transplantation*, vol. 72, no. 2, pp. 261-266.

Butler, J. A., Chalder, T., & Wessely, S. 2001, "Causal attributions for somatic sensations in patients with chronic fatigue syndrome and their partners", *Psychological Medicine*, vol. 31, pp. 97-105.

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A.-L., Sandercock, P., Spiegelhalter, D., & Tyrer, P. 2000, "Framework for design and evaluation of complex interventions to improve health", *British Medical Journal*, vol. 321, pp. 694-696.

Chisholm, M. A., Vollenweider, L. J., Mulloy, L. L., Jagadeesan, M., Wynn, J. J., Rogers, H. E., Wade, W. E., & DiPiro, J. T. 2000, "Renal transplant patient compliance with free immunosuppressive medications", *Transplantation*, vol. 70, no. 8, pp. 1240-1244.

Chmelik, F. & Doughty, A. 1994, "Objective measurements of compliance in asthma treatment", *Annals of Allergy*, vol. 73, pp. 527-532.

Choo, P. W., Rand, C. S., Inui, T. S., Lee, M. L., Cain, E., Cordeiro, B. M., Canning, C., & Platt, R. 1999, "Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy", *Medical Care*, vol. 37, no. 9, pp. 846-857.

Cluss, P. & Epstein, L. H. 1985, "The measurement of medical compliance in the treatment of disease," in *Measurement Strategies in Health Psychology*, P. Karoly, ed., John Wiley and Sons, pp. 403-432.

Cochrane, G. M., Horne, R., & Chanez, P. 1999, "Compliance in asthma", *Respiratory Medicine*, vol. 93, no. 11, pp. 763-769.

Cochrane, G. M., Bala, M. V., Downs, K. E., Mauskopf, J., & Ben-Joseph, R. H. 2000, "Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique", *Chest*, vol. 117, no. 2, pp. 542-550.

Cramer, J. A., Mattson, R. H., Prevey, M. L., Scheyer, R. D., & Ouellette, V. L. 1989, "How often is medication taken as prescribed? A novel assessment technique", *Journal of the American Medical Association*, vol. 261, no. 22, pp. 3273-3277.

Cramer, J. A., Scheyer, R. D., & Mattson, R. H. 1990, "Compliance declines between clinic visits", *Archives of Internal Medicine*, vol. 150, pp. 1509-1510.

De Geest, S., Borgermans, L., Gemoets, H., Abraham, I., Vlaminck, H., Evers, G., & Vanrenterghem, Y. 1995, "Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients", *Transplantation*, vol. 59, no. 3, pp. 340-347.

De Geest, S., Abraham, I., Moons, P., Vandeputte, M., Van Cleemput, J., Evers, G., Daenen, W., & Vanhaecke, J. 1998, "Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients", *Journal of Heart and Lung Transplantation*, vol. 17, no. 9, pp. 854-863.

De Geest, S. & Vanhaecke, J. 1999, "Methodological issues in transplant compliance research", *Transplantation Proceedings*, vol. 31, no. 4A, pp. 81S-83S.

De Geest, S., Abraham, I., Dunbar-Jacob J., & Vanhaecke, J. 1999, "Behavioural strategies for long-term survival of transplant recipients," in *Drug Regime Compliance: issues in clinical trials and patient management*, J.-M. Metry & U. A. Meyer, eds., John Wiley and Sons, pp. 163-180.

Denton, M. D., Magee, C. C., & Sayegh, M. H. 1999, "Immunosuppressive strategies in transplantion", *The Lancet*, vol. 353, pp. 1083-1091.

Dew, M. A., Roth, L. H., Thompson, M. E., Kormos, R. L., & Griffith, B. P. 1996, "Medical compliance and its predictors in the first year after heart transplantation", *Journal of Heart and Lung Transplantation*, vol. 15, no. 6, pp. 631-645.

Dew, M. A., Kormos, R. L., Roth, L. H., Murali, S., DiMartini, A., & Griffith, B. P. 1999, "Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation", *Journal of Heart and Lung Transplantation*, vol. 18, no. 6, pp. 549-562.

Didlake, R. H., Dreyfus, K., Kerman, R. H., Van Buren, C. T., & Kahan, B. D. 1988, "Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants", *Transplantation Proceedings*, vol. 20, no. 3 Suppl 3, pp. 63-69.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. 2000, "Depression is a risk factor for noncompliance with medical treatment: a meta-analysis of the effects of anxiety and depression on patient adherence", *Archives of Internal Medicine*, vol. 160, pp. 2101-2107.

Douglas, S., Blixen, C., & Bartucci, M. R. 1996, "Relationship between pretransplant noncompliance and posttransplant outcomes in renal transplant recipients", *Journal of Transplant Coordinators*, vol. 6, no. 2, pp. 53-58.

Dunbar-Jacob J., Erlen, J. A., Schlenk, E. A., Ryan, C. M., Sereika, S. M., & Doswell, W. M. 2000, "Adherence in chronic disease," in *Annual Review of Nursing Research*, pp. 48-90.

Dunn, J., Golden, D., Van Buren, C. T., Lewis, R. M., Lawen, J., & Kahan, B. D. 1990, "Causes of graft loss beyond two years in the cyclosporine era", *Transplantation*, vol. 49, no. 2, pp. 349-353.

Epstein, L. H. & Cluss, P. 1982, "A behavioural medicine perspective on adherence to long-term medical regimes", *Journal of Consulting and Clinical Psychology*, vol. 50, no. 6, pp. 950-971.

Fallab-Stubi, C. L., Zellweger, J. P., Sauty, A., Uldry, C., Iorillo, D., & Burnier, M. 1998, "Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis", *International Journal of Tuberculosis and Lung Disease*, vol. 2, no. 7, pp. 525-530.

Farmer, K. C. 1999, "Methods for measuring and monitoring medication regime adherence in clinical trials and clinical practice", *Clinical Therapeutics*, vol. 21, no. 6, pp. 1074-1090.

Feldman, H. I., Hackett, M., Bilker, W., & Strom, B. L. 1999, "Potential utility of electronic drug compliance monitoring in measures of adverse outcomes associated with immunosuppressive agents", *Pharmacoepidemiology and Drug Safety*, vol. 8, pp. 1-14.

Fernandez-Lucas M., Lopez, S. J., Miranda, B., & Matesanz, R. 1998, "Adhesion to treatment in renal transplant recipients: a Spanish multicentre trial", *Nefrologia*, vol. 18, no. 4, pp. 316-325.

Frazier, P. A., Davis-Ali, S. H., & Dahl, K. E. 1994, "Correlates of noncompliance among renal transplant recipients", *Clinical Transplantation*, vol. 8, no. 6, pp. 550-557.

Fujisawa, M., Ichikawa, Y., Yoshiya, K., Isotani, S., Higuchi, A., Nagano, S., Arakawa, S., Hamami, G., Matsumoto, O., & Kamidono, S. 2000, "Assessment of health-related quality of life in renal transplant and haemodialysis patients using the SF36 health survey", *Urology*, vol. 56, no. 2, pp. 201-206.

Garcia, V., Bittar, A., Keitel, E., Goldani, J., Minozzo, M., Pontremoli, M., Garcia, C., & Neumann, J. 1997, "Patient noncompliance as a major cause of kidney graft failure", *Transplantation Proceedings*, vol. 29, pp. 252-254.

Gaston, R. S., Hudson, S. L., Ward, M., Jones, P., & Macon, R. 1999, "Late renal allograft loss: noncompliance masquerading as chronic rejection", *Transplantation Proceedings*, vol. 31, no. supp. 4, pp. 21S-23S.

Geletko, S. M., Segarra, M., Ravin, D. S., & Babich, M. P. 1996, "Zidovudine compliance as measured by different methods in an HIV ambulatory clinic", *Journal of Pharmacy Technology*, vol. 12, no. 3, pp. 105-108.

George, C., Peveler, R., Heliger, S., & Thompson, C. 2000, "Compliance with tricyclic antidepressants: the value of four different methods of assessment", *British Journal of Clinical Pharmacology*, vol. 50, pp. 166-171.

Green, K., Tapson, J., Gerstenkorn, C., Manas, D., & Talbot, D. 1999, "Determining non compliance by nurse practitioner", *Abstract for the First European Conference on Non-compliance in Transplantation* Salzburg.

Greenstein, S. M. & Siegal, B. 1997, "Postrenal transplant health beliefs and ethnicity. The Compliance Study Group", *Transplantation Proceedings*, vol. 29, no. 8, pp. 3741-3742.

Greenstein, S. & Siegal, B. 1998, "Compliance and noncompliance in patients with a functioning renal transplant: a multicenter study", *Transplantation*, vol. 66, no. 12, pp. 1718-1726.

Greenstein, S. & Siegal, B. 1999, "Odds probabilities of compliance and noncompliance in patients with a functioning renal transplant: a multicenter study", *Transplantation Proceedings*, vol. 31, pp. 280-281.

Greenstein, S. & Siegal, B. 2000, "Evaluation of a multivariate model predicting noncompliance with medication regimens among renal transplant patients", *Transplantation*, vol. 69, no. 10, pp. 2226-2228.

Hand, C. 1998, "Adherence and asthma," in *Adherence to Treatment in Medical Conditions*, L. B. Myers & K. Midence, eds., Harwood Academic Publishers, pp. 383-421.

Hathaway, D. K., Combs, C., De Geest, S., Stergachis, A., & Moore, L. W. 1999, "Patient compliance in transplantation: a report on the perceptions of transplant clinicians", *Transplantation Proceedings*, vol. 31, no. 4A, pp. 10S-13S.

Haynes, R. B. 1979, "Introduction," in *Compliance in Health Care*, R. B. Haynes, D. W. Taylor, & D. L. Sackett, eds., Johns Hopkins University Press, Baltimore.

Haynes, R. B., McKibbon, K. A., & Kanani, R. 1996, "Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications", *The Lancet*, vol. 348, no. 9024, pp. 383-386.

Haynes, R. B., Montague, P., Oliver, T., McKibbon, K. A., Brouwers, M. C., & Kanani, R. 2000, "Interventions for helping patients to follow prescriptions for medications", *Cochrane Database of Systematic Reviews* no. 2.

Hilbrands, L. B., Hoitsma, A. J., & Koene, R. A. 1995, "Medication compliance after renal transplantation", *Transplantation*, vol. 60, no. 9, pp. 914-920.

Hong, J. H., Sumrani, N., Delaney, V., Davis, R., Dibenedetto, A., & Butt, K. M. 1992, "Causes of late renal allograft failure in the ciclosporin era", *Nephron*, vol. 62, no. 3, pp. 272-279.

Horne, R. & Weinman, J. 1994, "Illness cognitions: implications for the treatment of renal disease," in *Quality of Life Following Renal Failure*, McGee & C. Bradley, eds., Harwood Academic Publishers, pp. 113-132.

Horne, R. 1997, "Representations of medication and treatment: advances in theory and measurement," in *Perception of Health and Illness*, K. Petrie & J. Weinman, eds., Harwood Academic Publishers, pp. 155-188.

Horne, R. 1998, "Adherence to medication: a review of existing research," in *Adherence to Treatment in Medical Conditions* , L. B. Myers & K. Midence, eds., Harwood Academic Publishers, pp. 285-310.

Horne, R. & Weinman, J. 1998, "Predicting treatment adherence: an overview of theoretical models," in *Adherence to Treatment in Medical Conditions*, L. B. Myers & K. Midence, eds., Harwood Academic Publishers, pp. 25-50.

Horne, R. & Weinman, J. 1999, "Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness", *Journal of Psychosomatic Research*, vol. 47, no. 6, pp. 555-567.

Horne, R., Weinman, J., & Hankins, M. 1999, "The Beliefs about Medicines Questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication", *Psychology and Health*, vol. 14, no. 1, pp. 1-24.

Horwitz, R. I., Viscoli, C. M., Berkman, L., Donaldson, R. M., Horowitz, S. M., Murray, C. J., Ransohoff, D. F., & Sindelar, J. 1990, "Treatment adherence and risk of death after a myocardial infarction", *The Lancet*, vol. 336, no. 542, p. 545.

Horwitz, R. I. & Horwitz, S. M. 1993, "Adherence to treatment and health outcomes", *Archives of Internal Medicine*, vol. 153, pp. 1863-1868.

House, A. 1989, "Psychiatric referrals from a renal unit: a study of clinical practice in a British hospital", *Journal of Psychosomatic Research*, vol. 33, no. 3, pp. 373-372.

Howard, R. J., Patton, P. R., Reed, A. I., Hemming, A. W., Van der Werf, W. J., Pfaff, W. W., Srinvas, T. R., & Scornik, J. C. 2002, "The changing causes of graft loss and death after kidney transplantation", *Transplantation*, vol. 73, no. 12, pp. 1923-1928.

Isaacs, R. B., Conners, A., Nock, S., Spencer, C., & Lobo, P. 1999, "Noncompliance in living-related donor renal transplantation: the United Network of Organ Sharing experience", *Transplant.Proceedings*, vol. 31, no. 4A, pp. 19S-20S.

Isaacs, R. B. 2001, "Optimal transplant immunosuppression: a case of the haves and have nots?", *American Journal of Kidney Diseases*, vol. 37, no. 1, pp. 160-163.

Jeffery, J. R., Downs, A., Fong, H., Hosking, D., McKenna, R., McKenzie, J. K., Ramsey, E., Rush, D. N., Thomson, A. E., & Walker, R. 1988, "Transplantation in Manitoba," in *Clinical Transplants*, P. Terasaki, ed., pp. 159-166.

Jenkinson, C., Coulter, A., & Wright, L. 1993, "Short form 36 (SF36) health survey questionnaire: normative data for adults of working age", *British Medical Journal*, vol. 306, pp. 1437-1440.

Jha, V., Muthukumar, T., Kohli, H. S., Sud, K., Gupta, K. L., & Sakhuja, V. 2001, "Impact of cyclosporin withdrawal on living related transplants: a single-centre experience", *American Journal of Kidney Diseases*, vol. 37, pp. 119-124.

Kahan, B. D., Welsh, M., Urbauer, D. L., Mosheim, M. B., Beusterien, K. M., Wood, M. R., Schoenberg, L. P., Dicesare, J., Katz, S. M., & Van Buren, C. T. 2000, "Low intraindividual variability of cyclosporin A exposure reduces chronic rejection incidence and health care costs", *Journal of the American Society of Nephrology*, vol. 11, pp. 1122-1131.

Kalil, R. S., Heim-Duthoy, K. L., & Kasiske, B. L. 1992, "Patients with a low income have reduced renal allograft survival", *American Journal of Kidney Diseases*, vol. 20, no. 1, pp. 63-69.

Kasiske, B. L., Harini, A., Louis, T. A., & Ma, J. Z. 2000, "A meta-analysis of immunosuppression withdrawal trials in renal transplantation", *Journal of the American Society of Nephrologists*, vol. 11, pp. 1910-1917.

Kaul, V., Khurana, S., & Munoz, S. 2000, "Management of medication noncompliance in solid-organ transplant recipients", *Biodrugs*, vol. 13, pp. 313-326.

Kiley, D. J., Lam, C. S., & Pollak, R. 1993, "A study of treatment compliance following kidney transplantation", *Transplantation*, vol. 55, no. 1, pp. 51-56.

Kim, Y. S., Oh, C. K., & Park, K. 1994, "Causes of early and late renal allograft failure in the cyclosporine era", *Transplantation Proceedings*, vol. 26, no. 4, pp. 2021-2022.

Kory, L. 1999, "Nonadherence to immunosuppressive medications: a pilot survey of members of the transplant recipients international organization", *Transplantation Proceedings*, vol. 31, no. 4A, pp. 14S-15S.

Kruse, W. & Weber, E. 1990, "Dynamics of drug regimen compliance - its assessment by microprocessor-based monitoring", *European Journal of Clinical Pharmacology*, vol. 38, no. 6, pp. 561-565.

Laederach-Hofmann, K. & Bunzel, B. 2000, "Noncompliance in organ transplant recipients: a literature review", *General Hospital Psychiatry*, vol. 22, no. 6, pp. 412-424.

Lai, M. K., Huang, C. C., Chu, S. H., Chuang, C. K., Huang, J. Y., & Chen, H. W. 1992, "Noncompliance in renal transplant recipients: Experience in Taiwan", *Clinical Transplantation*, vol. 6, pp. 291-293.

Lee, J. Y., Kusek, J. W., Greene, P. G., Bernhard, S., Norris, K., Smith, D., Wilkening, B., & Wright-JT, J. 1996, "Assessing medication adherence by pill count and electronic monitoring in the African American study of kidney disease and hypertension (AASK) pilot study", *American Journal of Hypertension*, vol. 9, pp. 719-725.

Leventhal, H. 1970, "Findings and theory in the study of fear communications", *Advances in Experimental and Social Psychology*, vol. 5, pp. 119-186.

Leventhal, H., Diefenbach, M., & Leventhal, E. A. 1992, "Illness cognition: using common sense to understand treatment adherence and affect cognition interactions", *Cognitive Therapy and Research*, vol. 16, no. 2, pp. 143-163.

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. 1992, "Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers", *Psychological Medicine*, vol. 22, pp. 465-486.

Manu, M. A., Radulescu, S., Harza, M., Manu, R., Capsa, D., & Sinescu, I. 2001, "Quality of life assessed by SF-36 health survey in renal transplant patients", *Transplantation Proceedings*, vol. 33, pp. 1927-1928.

Mason, B. J., Matsuyama, J. R., & Jue, S. G. 1995, "Assessment of sulfonylurea adherence and metabolic control", *The Diabetes Educator*, vol. 21, no. 1, pp. 52-57.

Matas, A. J., Gillingham, K. J., Payne, W. D., & Najarian, J. S. 1994, "The impact of an acute rejection episode on long-term renal allograft survival (t1/2)", *Transplantation*, vol. 57, pp. 6-859.

McGavock, H. 1996, *A Review of the Literature on Drug Adherence*, Royal Pharmaceutical Society of Great Britain & Merck Sharp & Dohme.

McHorney, C. A., Ware, J. E., & Raczek, A. 1993, "The MOS 36-item short-form health survey (SF36): 2 psychometric and clinical tests of validity in measuring physical and mental health constructs", *Medical Care*, vol. 31, no. 3, pp. 247-263.

Melbourne, K. M., Geletko, S. M., Brown, S. L., Willey, L. C., Chase, S., & Fisher, A. 1999, "Medication adherence in patients with HIV infection: A comparison of two measurement methods", *AIDS Reader*, vol. 9, no. 5, pp. 329-338.

Meltzer, H., Gill, B., Petticrew, M., & Hinds, K. 1995, *The Prevalence of Psychiatric Morbidity Among Adults Living in Private Households* 1.

Mengden, T., Binswanger, B., Spuhler, T., Weisser, B., & Vetter, W. 1993, "The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening", *Journal of Hypertension*, vol. 11, no. 12, pp. 1403-1411.

Michelon, T., Dominguez, V., Losekan, A., Messias, A., Bruno, R., Bittar, A., Keitel, E., Santos, A., Goldani, J., Bianchinni, J., Garcia, C., Neumann, J., & Garcia, V. 1999, "Kidney graft failure due to noncompliance", *Transplantation Proceedings*, vol. 31, no. 7, pp. 3031-3032.

Monaco, A. P., Burke-JF, J., Ferguson, R. M., Halloran, P. F., Kahan, B. D., Light, J. A., Matas, A. J., & Solez, K. 1999, "Current thinking on chronic renal allograft rejection: issues, concerns, and recommendations from a 1997 roundtable discussion", *American Journal of Kidney Diseases*, vol. 33, no. 1, pp. 150-160.

Moon, J. I., Kim, Y. S., Chung, S. Y., Kim, M. S., Kim, S. I., & Park, K. 2001, "Long-term results of kidney transplantation between HLA-identical siblings", *Surgery Today*, vol. 31, no. 2, pp. 123-128.

Moons, P., De Geest, S., Abraham, I., Cleemput, J. V., & Van Vanhaecke, J. 1998, "Symptom experience associated with maintenance immunosuppression after heart transplantation: patients' appraisal of side effects", *Heart and Lung*, vol. 27, no. 5, pp. 315-325.

Moosa, M. R., Grobbelaar, C., Swanevelder, S. A., & Edelstein, C. L. 1992, "The influence of race and the impact of socioeconomic and clinical factors on primary renal allograft survival", *Transplant.Proc.*, vol. 24, no. 5, pp. 1754-1756.

Morisky, D. E., Green, L. W., & Levine, D. M. 1986, "Concurrent and predictive validity of a self-reported measure of medication adherence", *Medical Care*, vol. 24, no. 1, pp. 67-74.

Mulleners, W. M., Whitmarsh, T. E., & Steiner, T. J. 1998, "Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better", *Cephalalgia*, vol. 18, no. 1, pp. 52-56.

Myers, L. B. & Midence, K. 1998, "Methodological and conceptual issues in adherence," in *Adherence to Treatment in Medical Conditions*, L. B. Myers & K. Midence, eds., Harwood Academic Publishers, pp. 1-24.

Nagasawa, M., Smith, M. C., Barnes, J. H., & Fincham, J. E. 1990, "Meta-analysis of correlates of diabetes patients' compliance with prescribed medications", *The Diabetes Educator*, vol. 16, no. 3, pp. 192-200.

Namkoong, K., Farren, C. K., O'Connor, P. G., & O'Malley, S. S. 1999, "Measurement of compliance with naltrexone in the treatment of alcohol dependence: research and clinical implications", *Journal of Clinical Psychiatry*, vol. 60, no. 7, pp. 449-453.

Nevins, T. E., Kruse, L., Skeans, M. A., & Thomas, W. 2001, "The natural history of azathioprine compliance after renal transplantation", *Kidney International*, vol. 60, pp. 4-1570.

Nichol, M. B., Venturini, F., & Sung, J. C. Y. 1999, "A critical evaluation of the methodology of the literature on medication compliance", *Annals of Pharmacotherapy*, vol. 33, no. 5, pp. 531-540.

Office of Population Censuses and Surveys (OPCS) 1991, *Standard Occupational Classification* Her Majesty's Stationary Office (HMSO), London.

Orofino, L., Marcen, R., Quereda, C., Burgos, J., & Ortuno, J. 1994, "Patient compliance in renal transplant recipients", *Nefrologia*, vol. 14, pp. 3-332.

Papajcik, D., Mastroianni, B., Goormastic, M., & Flechner, S. M. 1999, "A tool to identify risk factors for noncompliance in the adult renal transplant recipient", *Transplantation Proceedings*, vol. 31, no. 4A, pp. 84S-86S.

Petrie, K. 1989, "Psychological well-being and psychiatric disturbance in dialysis and renal transplant patients", *British Journal of Medical Psychology*, vol. 62, pp. 91-96.

Petrie, K. & Weinman, J. 1997, "Illness representations and recovery from myocardial infarction," in *Perceptions of Health and Illness*, K. Petrie, ed., Harwood Academic Publishers, pp. 441-461.

Power, M. J., Champion, L. A., & Aris, S. J. 1988, "The development of a measure of social support: The Significant Others (SOS) Scale", *British Journal of Clinical Psychology*, vol. 27, no. 4, pp. 349-358.

Pruna, A. & Fornairon, S. 2000, "European multicenter survey on noncompliance after solid organ transplantation", *Transplantation Proceedings*, vol. 32, no. 2, pp. 393-395.

Raiz, L. R., Kilty, K. M., Henry, M. L., & Ferguson, R. M. 1999, "Medication compliance following renal transplantation", *Transplantation*, vol. 68, no. 1, pp. 51-55.

Rand, C. S., Wise, R. A., Nides, M., Simmons, M. S., Bleeker, E. R., Kusek, J. W., Li, V. C., & Tashkin, D. P. 1992, "Metered-dose inhaler in a clinical trial", *American Reviews of Respiratory Disease*, vol. 146, pp. 1559-1564.

Renal Standards Subcommittee of the Renal Association 2002, *Treatment of Adults and Children with Renal Failure: standards and audit measures*, 3rd edn, Royal College of Physicians, London.

Roderick, P. J., Ferris, G., & Feest, T. G. 1998, "The provision of renal replacement therapy for adults in England and Wales: recent trends and future directions", *Quarterly Journal of Medicine*, vol. 91, pp. 581-587.

Rodriguez, A., Diaz, M., Colon, A., & Santiago-Delpin, E. A. 1991, "Psychosocial profile of noncompliant transplant patients", *Transplantation Proceedings*, vol. 23, no. 2, pp. 1807-1809.

Rogers, K. R. 1987, "Nature of spousal supportive behaviors that influence heart transplant patient compliance", *Journal of Heart Transplantation*, vol. 6, no. 2, pp. 90-95.

Rollnick, S., Mason, P., & Butler, C. 1999, *Health Behaviour Change: a guide for practitioners* Churchill Livingstone, Harcourt Publishers Limited.

Rovelli, M., Palmeri, D., Vossler, E., Bartus, S., Hull, D., & Schweizer, R. 1989a, "Noncompliance in organ transplant recipients", *Transplantation Proceedings*, vol. 21, no. 1, pp. 833-834.

Rovelli, M., Palmeri, D., Vossler, E., Bartus, S., Hull, D., & Schweizer, R. 1989b, "Noncompliance in renal transplant recipients: evaluation by socioeconomic groups", *Transplantation Proceedings*, vol. 21, no. 6, pp. 3979-3981.

Royal College of Surgeons 1999, *The Report of the Working Party to Review Organ Transplantation*, The Royal College of Surgeons of England.

Royal Pharmaceutical Society 1997, *From Compliance to Concordance: achieving shared goals in medicine taking* Royal Pharmaceutical Society of Great Britain & Merck Sharp & Dohme, London.

Rustomjee, S. & Smith, G. 1996, "Consultation-liaison psychiatry to renal medicine: work with an in-patient unit", *Australian and New Zealand Journal of Psychiatry*, vol. 30, pp. 229-237.

Sackett, D. L. & Haynes, R. B. 1976, *Compliance with Therapeutic Regimes* London.

Salovey, P. & Birnbaum, D. 1989, "Influence of mood on health-relevant cognitions", *Journal of Personality and Social Psychology*, vol. 57, no. 3, pp. 539-551.

Scharloo, M. & Kaptein, A. 1997, "Measurement of illness perceptions in patients with chronic somatic illness: a review," in *Perceptions of Health and Illness*, K. Petrie, ed., Harwood Academic Publishers, pp. 103-154.

Schwed, A., Fallab, C. L., Burnier, M., Waeber, B., Kappenberger, L., Burnand, B., & Darioli, R. 1999, "Electronic monitoring of compliance to lipid-lowering therapy in clinical practice", *Journal of Clinical Pharmacotherpy*, vol. 39, no. 4, pp. 402-409.

Schweizer, R. T., Rovelli, M., Palmeri, D., Vossler, E., Hull, D., & Bartus, S. 1990, "Noncompliance in organ transplant recipients", *Transplantation*, vol. 49, no. 2, pp. 374-377.

Shapiro, P. A., Williams, D. L., Foray, A. T., Gelman, I. S., Wukich, N., & Sciacca, R. 1995, "Psychosocial evaluation and prediction of compliance problems and morbidity after heart transplantation", *Transplantation*, vol. 60, no. 12, pp. 1462-1466.

Sharma, A. K., Gupta, R., Tolani, S. L., Rathi, G. L., & Gupta, H. P. 2000, "Evaluation of socioeconomic factors in noncompliance in renal transplantation", *Transplantation Proceedings*, vol. 32, p. 1864.

Sharpe, L. A. 1999, "A medical anthropologist's view on posttransplant compliance: the underground economy of medical survival", *Transplantation Proceedings*, vol. 31, no. Supp.4A, p. S31-S33.

Shoskes, D. A., Avelino, L., Barba, L., & Sender, M. 1997, "Patient death or renal graft loss within 3 yr of transplantation in a county hospital: importance of poor initial graft function", *Clinical Transplantation*, vol. 11, pp. 618-622.

Siegal, B. & Greenstein, S. M. 1998, "Differences between compliers and partial compliers: a multicenter study", *Transplantation Proceedings*, vol. 30, pp. 1310-1311.

Siegal, B. & Greenstein, S. M. 1999, "Profiles of noncompliance in patients with a functioning renal transplant: a multicenter study. Compliance Study Group", *Transplantation Proceedings*, vol. 31, pp. 1326-1327.

Siegal, B. & Greenstein, S. 1999, "Compliance and noncompliance in kidney transplant patients: cues for transplant coordinators", *Journal of Transplant Coordinators*, vol. 9, pp. 104-108.

Siegal, B. R., Hanson, P., Viswanathan, R., Margolis, R., & Butt, K. M. 1989, "Renal transplant patients' health beliefs", *Transplantation Proceedings*, vol. 21, pp. 3977-3978.

Siegal, B. R. 1993, "Postrenal transplant compliance: report of 519 responses to a self-report questionnaire", *Transplantation Proceedings*, vol. 25, no. 4, p. 2502.

Siegal, B. R. & Greenstein, S. M. 1997, "Postrenal transplant compliance from the perspective of African-Americans, Hispanic-Americans, and Anglo-Americans", *Advances in Renal Replacement Therapy*, vol. 4, pp. 46-54.

Sketris, I., Waite, N., Grobler, K., West, M., & Gerus, S. 1994, "Factors affecting compliance with cyclosporine in adult renal transplant patients", *Transplantation Proceedings*, vol. 26, pp. 2538-2541.

Straka, R. J., Fish, J. T., Benson, S. R., & Suh, J. T. 1997, "Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug", *Pharmacotherapy*, vol. 17, pp. 126-132.

Svarstad, B., Chewning, B. A., Sleath, B. L., & Claesson, C. 1999, "The brief medication questionnaire: a tool for screening patient adherence and barriers to adherence", *Patient Education and Counselling*, vol. 37, pp. 113-124.

Teixeira-de-Barros, C. & Cabrita, J. 2000, "Noncompliance with immunosuppressive therapy: prevalence and determinants", *Transplantation Proceedings*, vol. 32, p. 2633.

Teixeira, d. B. & Cabrita, J. 1999, "Self-report of symptom frequency and symptom distress in kidney transplant recipients", *Pharmacoepidemiology and Drug Safety*, vol. 8, pp. 395-403.

The Coronary Drug Project Research Group 1980, "Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project", *New England Journal of Medicine*, vol. 303, no. 18, pp. 1038-1041.

Touchard, G., Hauet, T., Cogny-Van-Weydevelt, F., Hurault-de-Ligny, B., Peyronnet, P., Lebranchu, Y., Toupance, O., N'Doye, P., & Busson, M. 1997, "Maintenance cyclosporin monotherapy after renal transplantation--clinical predictors of long-term outcome", *Nephrology, Dialysis and Transplantation*, vol. 12, pp. 1956-1960.

Valentine, A. 2000, "Is it surprising they omit their tablets?", *EDTNA.ERCA.Journal*, vol. 26, pp. 2-38.

Vitolins, M. Z., Rand, C. S., Rapp, S. R., Ribisl, P. M., & Sevick, M. A. 2000, "Measuring adherence to behavioral and medical interventions", *Controlled Clinical Trials*, vol. Controlled-Clinical-Trials. 2000; 21, no. 5 Suppl. 1, pp. 188S-194S.

Waeber, B., Burnier, M., & Brunner, H. R. 1999, "Rational prescribing in sub-optimal compliance," in *Drug Regime Compliance: Issues in Clinical Trials and Patient Management*, J-M. Metry & U. A. Meyer, eds., John Wiley & Sons Ltd., pp. 147-154.

Waiser, J., Slowinski, T., Brinker-Paschke, A., Budde, K., Schreiber, M., Bohler, T., Hauser, I., & Neumayer, H. 2002, "Impact of the variability of cyclosporin A trough levels on long-term renal allograft function", *Nephrology, Dialysis and Transplantation*, vol. 17, pp. 1310-1317.

Wallston, B. S., Wallston, K. A., Kaplan, G. D., & Maides, S. A. 1976, "Development and validation of the health locus of control (HLC) scales", *Journal of Consulting and Clinical Psychology*, vol. 44, pp. 580-585.

Wallston, K. A., Wallston, B. S., & Devellis, R. 1978, "Development of the multidimensional health locus of control (MHLC) scales", *Health Education Monographs*, vol. 6, pp. 160-170.

Ware, J. E. & Sherbourne, C. D. 1992, "The MOS 36-item short-form health survey (SF36): 1 conceptual framework and item selection", *Medical Care*, vol. 30, no. 6, pp. 473-483.

Waterhouse, D. M., Calzone, K. A., Mele, C., & Brenner, D. E. 1993, "Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring", *Journal of Clinical Oncology*, vol. 11, pp. 1189-1197.

Weinman, J., Petrie, K. J., Moss-Morris, R., & Horne, R. 1996, "The Illness Perception Questionnaire: A new method for assessing the cognitive representation of illness", *Psychology and Health*, vol. 11, pp. 431-445.

Winsett, R. P., Stratta, R. J., Alloway, R., Wicks, M. N., & Hathaway, D. K. 2001, "Immunosuppressive side effect profiles does not differ between organ transplant types", *Clinical Transplantation*, vol. 15 (supp. 6), pp. 46-50.

Yeung, M., O'Connor, S. A., Parry, D. T., & Cochrane, G. M. 1994, "Compliance with prescribed drug therapy in asthma", *Respiratory Medicine*, vol. 88, pp. 31-35.