CLINICAL AND ECONOMIC IMPACT OF IMMUNOSUPPRESSIVE THERAPY IN THE TREATMENT AND MANAGEMENT OF ADULT RENAL AND LIVER TRANSPLANTATION

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Abstract

World wide the number of people living with renal or liver transplants is growing due to the increase in prevalence of end stage renal disease and end stage liver disease which neccesitate transplantation. Life long immunosuppression is needed for transplant recipients to prevent graft rejection and or death. Whilst the immunosuppression can significantly improve patient and graft survival it comes at a cost to the healthcare services. It is therefore, important that the immunosuppression used in clinical practice is supported by both clinical and cost effectiveness evidence.

The aim of this thesis is to evaluate the clinical and economic impact of immunosuppression therapy in the treatment and management of adult renal and liver transplant recipients based on author's published research. Healthcare systems across the world are now placing greater importance on optimising their finite resources in demonstrating clinical and cost effectiveness of treatments. A number of health authorities such as the United Kingdom(UK), National Institute of Health and Care Excellence (NICE) have implemented methodologies guiding resource allocation decisions through formal health technology assessment (HTA). Clinical and economic evidence generation and synthesis reflecting current clinical practice can help to inform HTA decisions which impacts patients access to medicines.

This thesis presents and critically appraise eight peer reviewed publications to demonstrate the clinical and economic impact of immunosuppression therapy in adult renal and liver transplant recipients. Each publication updated and or contributed to new knowledge in the field. The thesis highlights how the eight publications formed a cohesive body of evidence which can be used by policy makers to inform the development and or updating of clinical and reimbursemsent guidelines which ultimately impact product adoption and patient accesss to immunosuppressive medicines.

The clinical effectiveness of immunosuppression was explored through systematic literature reviews, meta-analysis and indirect treatment comparison to establish the efficacy and safety of the different interventions used in post renal and liver transplant. The outputs from the clinical effectiveness together with relevant data from other sources was used to develop economic models to assess the cost effectiveness of immunosuppression. An assessment of the budget impact of immunosuppression in post renal transplant was also examined.

Based on this research prolonged release tacrolimus was shown to be clinically and economically more effective than immediate release tacrolimus the current standard of care. The thesis concluded that tacrolimus remains the cornerstone of renal and liver post transplant immunosuppression while also highlighting the strengths and limitations of the current research and making recommendations for future studies.

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Contents

Glossary of Terms

Term	Definition
Absolute risk reduction	The difference in event rates between two groups (one subtracted from the other) in a comparative study
Confidence interval	The range within which the 'true' values size of effect of an intervention are expected to lie with a given degree of certainty
Cost-effectiveness analysis	An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental cost-effectiveness ratio.
Cost –utility analysis	is a type of cost-effectiveness analysis in which the (incremental) cost per quality-adjusted life year (**QALY**), is estimated
Generalisability	The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in clinical practice
Heterogeneity	A term used to illustrate the variability or differences between studies in the estimates of effects.
Meta-Analysis	Statistical analysis that integrates results from two or more studies providing a single numerical value of the overall treatment effect for that group of studies
Odds Ratio	The odds of the probabilityof an event occurring compared to the event not occurring in a particular group. The odds ratio is the ratio of the odds between two groups
Probabilistic Sensitivity Analysis (PSA)	Is a technique used in economic modelling that allows the modeler to quantify the level of confidence in the output of the analysis in relation to uncertainty in model inputs
Propensity Score Matching (PSM)	is a statistical technique that attempts to reduce the possible bias associated with confounding variables
Quality-adjusted life year (QALY)	The QALY is a single measure of health related quality of life that takes into account both the quantity and quality of life provided by the intervention.
Random Effects Model	A model that assumes that the treatment effects of all included studies are part of a distribution of treatment effects that fall along a range of values
Relative risk	the ratio of risk in the intervention group to the risk in the control group

Chapter 1: Introduction

1.1 The burden of End Stage Renal Disease and End Stage Liver Disease

End Stage Renal Disease (ESRD) and End Stage Liver Disease (ESLD) are both chronic and irreversible conditions which represent a major public health burden. ESRD is the irreversible final stage of chronic kidney disease (CKD) which can result in death if not treated by either transplantation or dialysis. Worldwide, the number receiving renal replacement therapy (dialysis or renal transplantation) is estimated at more than 1.4 million, with incidence growing by approximately 8% annually [Schieppati and Remuzzi, 2005].

Due to the scarce epidemiological data in RRT. The most recent incidence data could only be sourced at a country and regional level. The Reseau, Epidemiologie, Information, Nephrologie (REIN) report [2010] stated that in terms of incidence of RRT in France in 2010, a total of 9,439 subjects with ESRD started renal replacement therapy corresponding to a crude annual incidence rate of 149 pmp. It should be noted that whilst this data represent the most current data it is nonetheless from a country level and hence cannot be extrapolated to other healthcare systems across the world. Nevertheless, this report provides a more recent reference for incidence of RRT. At a regional level the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry in 2013 reported a total of 72 933 started RRT for ESRD resulting in an overall incidence of 112 pmp [Kramer *et al.*, 2013].This incidence rate is lower than the French data reported in 2010 which could indicate the variation across countries and over time.

On the other hand, ESLD is when the liver has been damaged to the point that it cannot perform its normal functions. Unlike ESRD were patients can have dialysis with ESLD the only hope of long-term survival is transplantation. The global prevalence of ESLD ranges from 4.5% to 9.5% of the general population and it is estimated that more than fifty million people in the world, of the adult population, would be affected with chronic liver disease [Lim and Kim 2008].

Both ESRD and ESLD are serious illnesses with significant health consequences in terms of decreased health related quality of life (HRQoL), increased morbidity and mortality [Mathers *et al.,* 2006; Go *et al.,* 2004; Goicoechea *et al.,* 2005]. In addition, the treatment and management of ESRD and ESLD is associated with significant health resource consumption and high cost

treatment options [Ruhl *et al.*, 2013; Go *et al.,* 2004; Goicoechea *et al.,* 2005]. For example in Canada, less than 0.1% of the population has ESRD; however, the disease generated direct health-care costs of $1.3 billion in the year 2000. The amount of direct spending per person with ESRD was much more than the average spending per person for all health-care conditions [Zelmer, 2007]. Adding indirect morbidity and mortality cost brings the total burden associated with ESRD to $1.9 billion in the Canadian healthcare system [Zelmer, 2007]. In the United States direct costs associated with the management of ESLD in 2004 was estimated to be $2.5 billion [Ruhl *et al.*, 2013]. Therefore, ESRD and ESLD places significant clinical and economic burden on healthcare services and society.

Transplantation is a treatment of choice for both ESRD and ESLD which can lead to improvements in HRQoL, graft and patient survival and lower longer-term costs [Winkelmayer *et al.,* 2002; Wolfe *et al.,* 1999]. However, lifelong regimen of immunosuppressive medication is required for transplant recipients to prevent graft rejection and or death.

The immunosuppressive therapies needed to prevent rejection come at a cost as they account for most of the long-term costs of post transplantation management [Ruhl *et al.*, 2013]. Despite the growing number of people living with renal and liver transplants and economic pressure on healthcare systems. Health economic evaluations in transplantation on immunosuppression are limited. Also clinical and reimbursement guidelines in liver and renal transplant are based on dated clinical evidence. My research has focused on updating the clinical evidence base and generating data on economic evaluations of immunosuppression therapy in adults with renal or liver transplantation.

Morden healthcare is placing great importance on demonstrating clinical and economic effectiveness of treatments. The data and methodology used in such Health Technology Assessments (HTAs) is critically important as it affects whether a treatment is made available to patients. From a period when the choice of immunosuppressive agents was limited, there have now emerged a number of immunosuppressive agents. Consequently, the choice of immunosuppressant to be used in clinical practice should be supported by up to date clinical and economic evidence reflecting current clinical practice.

The growing number of patients living with renal or liver transplants necessitating lifelong immunosuppression and economic pressure on healthcare systems requires efficient allocation of

resources. Evidence based healthcare decision is built on sound clinical and economic evaluations. Given the out dated clinical evidence and limited economic studies in this field. This thesis will focus on evaluating the clinical and economic impact of immunosuppressive therapy in adults with renal or liver transplants based on author's published research.

The thesis presents eight papers, for which the present author was a co-author as is normal practice in health economics and outcomes research which is typically multidisciplinary. In addition to research design and analysis the present author played a critical and leading role in conceiving the research questions and project management of all the research studies and subsequent publications. The eight papers presented as part of this thesis were chosen from fourteen papers co-authored by present author covering period from 2012 to 2017. The thesis presents a critical commentary of the eight papers in the context of the rationale for publication of each paper, highlighting the uniqueness, methodologies, implications and contribution to literature for each paper. In addition, the thesis describes and appraises methodologies used, compare and contrast results from other studies that used clinical and cost effectiveness approaches in renal and liver transplant immunosuppression therapy.

1.2 Aims of the thesis

The overall aim of the thesis is to demonstrate the clinical and economic impact of immunosuppressive therapy in the treatment and management of adult renal and liver transplant recipients based on authors published research.

The specific aims of the thesis are:

1. Describe the methods used in establishing the clinical and economic impact of immunosuppression therapy in adult renal and liver post-transplantation.

2. Evaluate the extent to which the research met requirements in terms of its strengths and limitations.

3. Critically appraise the contribution of each study to knowledge in the field.

1.3 Structure of thesis

The first two chapters introduce the thesis and provide a background on the burden of ESRD and ESLD, treatment and management of post renal and liver transplantation with immunosuppression therapy. The articles included in the thesis are grouped into three different categories and presented in chapters 3 to 5. The thesis provides a critical review of each study and an appraisal of how the studies could have been approached differently. Finally, chapter 6 provides a summary of the thesis, make conclusions and recommendations for future research.

Chapter 1: provided the overall aims and an overview of the topics to be covered in more depth throughout the thesis.

Chapter 2: discusses the background to the burden of ESRD and ESLD, treatment and management of post renal and liver transplantation with immunosuppressive therapy.

Chapter 3: examines the clinical effectiveness of immunosuppression therapy in the modern era of renal and liver transplantation. Systematic literature reviews, indirect treatment comparison and meta-analyses comparing the safety and efficacy of immunosuppressive therapy in renal and liver transplantation are introduced and an explanation of how they add to previous research is provided. Strengths, limitations and potential applications of this research are discussed.

Chapter 4: demonstrates the cost effectiveness of immunosuppressive therapy in renal and liver transplantation from a UK, NHS payer perspective. A critique of health economic modelling in renal and liver transplantation is provided.

Chapter 5: reviews the budget impact analysis of immunosuppressive therapy in renal transplant from a UK, NHS payer perspective. The importance of this research to patients, payers and policy makers is discussed.

Chapter 6: provides a key summary of the research and conclusions highlighting implications for patients, clinical practice, healthcare policy and recommendations for future research.

The next chapter will give a background overview to the burden of ESRD and ESLD, treatment and management of post renal and liver transplantation with immunosuppressive therapy.

Chapter 2: Background

2.1 Introduction

Chapter 1 has outlined the thesis rationale and aims focused on demonstrating the clinical and economic impact of immunosuppresion therapy in adult renal or liver post transplantation. The present chapter aims to provide an overview background in terms of definitions, prevalence, clinical and economic burden of ESRD and ESLD which neccesssitate transplantation. Current treatment and management of post renal and liver transplantation with immunosuppression therapy will be examined including guidelines and challenges to optimising patient outcomes.

2.2 Definitions of End Stage Renal Disease and End Stage Liver Disease

2.2.1 Definition of End Stage Renal Disease

Chronic kidney disease (CKD) is irreversible and progressive. It is defined as either kidney damage (proteinuria, haematuria or anatomical abnormality) for ≥3 months or a glomerular filtration rate (GFR) <60 ml/min/1.73m^2 measured on at least 2 occasions during ≥3 months [National Collaborating Centre for Chronic Conditions, 2008]. The Renal National Service Framework (NSF) classifies CKD into five stages, defined by evidence of kidney damage and level of renal function as measured by GFR (ml/min/1.73m^2)[Department of Health, 2005]. A patient with stage 5 CKD (kidney failure GFR <15 ml/min/1.73m^2) has a life threatening serious disease and requires renal replacement therapy (RRT) in order to maintain life. RRT refers to either regular dialysis treatment or renal transplantation. Stage 5 disease is also referred to as end stage renal disease (ESRD). End-stage renal disease occurs as the irreversible final stage in chronic kidney disease (CKD) when the kidneys are no longer able to function properly, leading to patient mortality, unless managed by dialysis or renal transplantation [National Collaborating Centre for Chronic Conditions, 2008].

2.2.2 Definition of End Stage Liver Disease

Chronic liver failure, also called end-stage liver disease (ESLD), progresses over months, years, or decades. Most often, chronic liver failure is the result of cirrhosis, a condition in which scar tissue replaces healthy liver tissue until the liver cannot function adequately [Alqahtani, 2012]. Patients with abnormal liver function who develop ascites, variceal hemorrhage, hepatic encephalopathy, or renal impairment are considered to have end-stage liver disease [Mazzaferro *et al.,* 1996]. The main causes of ESLD include persistent alcohol misuse, hepatitis, sclerosing cholongatis and cirrhosis [Alqahtani, 2012].

2.3 Prevalence, clinical and economic burden of ESRD and ESLD

This section presents the prevalence, clinical and economic burden of ESRD and ESLD.

2.3.1 Prevalence, clinical and economic burden of ESRD

ESRD is a global health burden an independent risk factor for cardiovascular disease (CVD) and is associated with increased risks of premature mortality, and decreased quality of life. ESRD is associated with age-related renal function decline accelerated in hypertension, diabetes, obesity and primary renal disorders [Gansevoort *et al.*, 2013].The overlap between ESRD, diabetes and CVD, as well as the increasing risk of ESRD with age, means that the public health impact of ESRD is likely to increase.

Globally the incidence of ESRD is on the increase. Although varying considerably across countries, the annual incident rate of patients starting (RRT) is high, ranging from 150 to 400 per million population (pmp) in the Western world to around 50 pmp in poor countries where access to health care is limited [Jha *et al.,* 2013]. There are nearly 700,000 people with ESRD in the United States corresponding to an annual incidence rate of 355 per million population (pmp) [Collins *et al.,* 2014]. In the United Kingdom (UK) and in Europe, the average annual incidence of ESRD is 120,000 and 135,000, respectively [Steenkamp *et al.,* 2011]. Table 1, below shows the wide variation across regions in the population using and being initiated on RRT.

Table 1.1: Use and annual initiation of renal replacement therapy.

World Bank Region	Use of RRT (pmp)	Initiation of RRT (pmp)
Eastern Europe and Central Asia	332	79
Latin America and Caribbean	441	147
Middle East and North Africa	325	111
East Asia and Pacific	54	29
South Asia	33	10
Sub-Saharan Africa	20	10
High Income	1283	226
All Regions Combined	**316**	**73**

Data are presented according to World Bank Regions, with High Income countries as comparators.

Abbreviations: RRT–renal replacement therapy, pmp–per million population. Source: Anand *et al.,* [2013].

In addition to increased cardiovascular events and overall premature mortality, ESRD is associated with significant healthcare resource use [Go *et al.,* 2004; Goicoechea *et al.,* 2005]. Life expectancy is reduced by as much as 10 to 15 fold in patients who have ESRD [Minino *et al.*, 2009; Bleyer *et al.,* 1996]). Furthermore, patients with ESRD who are on dialysis have lower quality of life in comparison with the general population [Liem *et al.,* 2007; Lumsdaine *et al.,* 2005].

The annual cost per person on RRT is prohibitive ranging from USD $15,000 in Sub Saharan Africa to more than $80,000 in the United States [Collins *et al.*, 2014; Arogundade and Barsoum 2008; Swanepoel *et al.*, 2013]. Over 2% of the total UK, National Health Service (NHS) budget is spent on renal replacement therapy for patients with established renal failure [National Collaborating Centre for Chronic Conditions, 2008].

2.3.2 Prevalence, Clinical and Economic Burden of ESLD

Global prevalence of ESLD ranges from 4.5% to 9.5% of the general population [Melato *et al.,* 1993; Graudal *et al.,* 1991; Lim and Kim 2008]. During 2001, the estimated worldwide mortality from ESLD was 771,000 people, ranking 14th and 10th as the leading cause of death in the

world and in developed countries, respectively [Mathers *et al.,* 2006]. Deaths from ESLD have been estimated to increase and would make it as the 12th leading cause of death in 2020 [Murray and Lopez, 1997]. In Europe ESLD is responsible for 170,000 deaths per year [Blachier *et al.,* 2013].

In addition to increased mortality ESLD also impacts patients' daily activities. Most patients with ESLD report significant impairment of their HRQoL [Afendy *et al.*, 2009; Gutteling *et al.,* 2006]. The degree of HRQoL impairment is dependent on the type of ESLD, patients with viral hepatitis C (HCV), primary biliary cirrhosis (PBC), and nonalcoholic fatty liver disease (NAFLD) seem to have more impairment [van der Plas *et al.,* 2007]. A number of studies have reported that patients with HCV and PBC have significantly reduced HRQoL due to fatigue and depression [Afendy *et al.*, 2009; Gutteling *et al.,* 2006; Sobhonslidsuk *et al.*, 2006].

The clinical and HRQoL burden of ESLD is further compounded by economic impact on healthcare services and societies. The overall cost of ESLD includes direct costs (drug, liver transplantation and hospitalization costs) and indirect costs due to loss of work productivity and reduction in health-related quality of life (HRQOL) [Ruhl *et al.*, 2013]. Direct and indirect financial costs associated with ESLD impose a considerable socioeconomic burden on health services and society [Iacobucci *et al.* 2012; Lee and Kyung-Rae, 2011; Ray *et al.* 2002]. In 2004, the direct costs of chronic liver disease in the United States (US) were estimated to be $2.5 billion, whereas indirect costs were estimated to be $10.6 billion[Ruhl *et al.*, 2013]. Treatment of complications of ESLD including encephalopathy, variceal bleeding and the development of hepatocellular carcinoma (HCC) have all increased in frequency and expense over the past decade [Nathan *et al.,* 2012; Neff *et al.,* 2011; Nguyen *et al.,* 2007]. ESLD due to chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) that are refractory to treatment can progress to decompensated cirrhosis and HCC, resulting in high economic costs for public health services [van der Meer *et al.,* 2012].

The clinical, HRQoL and economic burden together with the increased mortality associated with ESRD and ESLD necessitates transplantation in order to ensure patient survival.

2.4 Renal and Liver Transplantation

Renal transplantation is regarded as the treatment of choice in patients with ESRD whose only alternative is frequent dialysis, a procedure which leads to significant morbidity, impaired quality

of life and greater mortality [Wolfe *et al.*, 1999; UK Renal Registry, 2014]. In the UK, patient survival at ten years after a first renal transplant is 77.0% compared with 28.2% for dialysis [NHSBT 2014; Pruthia *et al.,* 2012].

Equally, liver transplantation is now recognized as the treatment of choice for ESLD [Mazzaferro *et al.,* 1996].The goals of liver transplantation are to improve patient survival and HRQoL since most patients with ESLD typically have poor quality of life due to several factors including fatigue, cachexia, pruritus, ascites, hepatic encephalopathy and variceal bleeding [Alqahtani, 2012]. Liver transplantation continues to mature, with advances in many surgical and medical aspects leading to improved survival rates. In the UK survival rates for liver transplantation are 91% for 1 year, 77% for 5 years and 59% at 10 years, with some patients living for 15–20 years after transplant [NHSBT, 2011]. This indicates that whilst short term survival has increased there is still an unmet need in long term survival.

In addition to patient survival transplantation results in improved patient quality of life, increased independence and lower longer-term costs [Winkelmayer *et al.,* 2002; Wolfe *et al.,* 1999]. However, without lifelong immunosuppression, transplant recipients are at risk of graft rejection or loss, arising from immune processes directed at the transplanted organ. Lifelong regimen of immunosuppressive medication is therefore required for transplant recipients to prevent graft rejection and or loss, death or resumption of dialysis in renal transplantation. It is therefore, imperative that immunosuppression used in clinical practice should be based on its effectiveness in preventing organ rejection, optimisation patient survival and HRQoL afforded by renal or liver transplantation. The use of immunosuppression to optimise graft and patient survival will be explored in Chapter 3, of this thesis.

2.5 Immunosuppression Therapy Current Treatment Options

The ultimate goal of post-transplant immunosuppression is to effectively suppress the immune system, while minimizing post-transplant adverse events and toxicity. The calcineurin inhibitor (CNI) class of immunosuppressive drugs, tacrolimus and ciclosporin, has long been the mainstay of post-transplant immunosuppression. Since the CNIs were first approved for prevention and treatment of graft rejection, a number of new immunosuppressive agents have been developed with the goal of reducing the nephrotoxic effects that have been associated with the CNI class [Goring *et al.,* 2014].

Among these newer agents licensed in the UK for kidney and or liver immunosuppression are the mammalian target of rapamycin (mTOR) inhibitor class, which includes sirolimus and evorolimus; and the selective co-stimulation blocker belatacept. Current treatment with immunosuppression typically constitutes of triple therapy with (1) primary immunosuppression with a CNI, m-TOR inhibitor or selective co-stimulation blocker; (2) an antiproliferative that is Mycophenolic acid or mycophenolate mofetil; and (3) a corticosteroid. This triple therapy is aimed at striking the right balance between effectiveness and toxicity.

Immediate release tacrolimus and ciclosporin form the foundation of modern immunosuppressive therapy in renal and liver transplant recipients with tacrolimus being the standard of care (SoC). These two products have been reformulated specifically, ciclosporin was reformulated into a micro-emulsion (Neoral) and subsequently tacrolimus has been reformulated into a once-daily, prolonged-release (PR) formulation (Advagraf) from the twice-daily, immediate-release (IR)formulation (Prograf) [European FK506, 1994; US FK506, 1994; Otto *et al.*, 1998 ; Loinaz *et al.,* 2001]. The introduction of these new formulations in particular once daily tacrolimus requires literature to reflect on the potential benefits of the once daily formulation in terms of adherence and impact on graft and patient survival. Also the old ciclosporin formulation is no longer used in clinical practice. Therefore, the clinical data in terms of systematic reviews and meta-analysis need to be updated to reflect the changes in formulations and potential implications on relative effectiveness. This thesis addressed this issue in Chapters 3 to 5 through reviewing author's publications based on clinical and cost effectiveness taking into account newer products, formulations and data from recent clinical trials to reflect modern transplant era.

Immediate release tacrolimus is the SoC in the UK [NICE, 2004] and most parts of the world. Tacrolimus is also widely used in the USA for post transplantation immunosuppression see below table 2. As such the focus of this thesis will be predominantly on comparison of other immunosuppressive therapies with immediate release tacrolimus as the SoC in the treatment and management of adult renal or liver transplant recipients.

Table 2.2: Most frequently prescribed maintenance regimens at 1 and 2 years post-transplantation in the US, 2003–2007

	2003	2004	2005	2006	2007
1 year post-transplant					
Tacrolimus + corticosteroids, %	20.9	18.1	15.7	15.1	12.5
Tacrolimus, %	30.1	28.3	28.6	26.5	28.5
Tacrolimus + MMF/MPA, %	13.7	15.2	18.1	22.1	25.0
Tacrolimus + MMF/MPA + corticosteroids, %	14.1	15.5	16.8	17.4	15.2
Cyclosporine + corticosteroids, %	2.0	1.7	1.2	1.2	1.0
2 years post-transplant					
Tacrolimus + corticosteroids, %	13.8	12.1	9.7	9.1	—
Tacrolimus, %	37.9	36.0	35.9	35.6	—
Tacrolimus + MMF/MPA, %	16.0	17.5	21.0	24.5	—
Tacrolimus + MMF/MPA + corticosteroids, %	9.4	10.0	10.9	10.1	—
Cyclosporine + corticosteroids, %	1.4	1.0	0.8	0.7	—

MMF, mycophenolate mofetil; MPA, mycophenolic acid
Source: Wiesner and Fung [2011].

2.5.1 Treatment Guidelines

Published in 2004, currently under review the national guidelines for immunosuppression in adult renal transplant patients in England and Wales reported that tacrolimus should be considered as an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of initial or maintenance immunosuppression in renal transplantation for adults [NICE, 2004]. This guideline has largely been adopted in liver in spite of no official NICE multiple technology appraisal in liver transplantation.

International renal and liver transplantation bodies have developed clinical practice guidelines for the treatment and management of renal and liver transplant recipients. The Kidney Disease

Improving Global Outcomes [KDIGO, 2009] guidelines recommend using a combination of immunosuppressive medications including a CNI and an antiproliferative agent with or without corticosteroids in post renal transplantation. The guideline states that tacrolimus and Mycophenalate should be the first line CNI and antiproliferative respectively. The guideline also recommends that m-TORs should not be started until graft function is established and surgical wounds are healed. No mention is made of belatacept reflecting a need to update the guidelines.

The European Association for the Study of the Liver [EASL, 2015] clinical practice guidelines state that CNI based immunosuppression is still the cornerstone of post liver transplant immunosuppression. The guidelines also state that tacrolimus results in better long term graft and patient survival. However, it does not distinguish between prolonged and immediate release tacrolimus formulations. Emerging data from routine clinical practice appear to indicate that prolonged release tacrolimus is more effective than immediate release tacrolimus in graft survival and hence guidelines should reflect this development [Adam *et al.,* 2015].

It is clear that the reimbursement and clinical guidelines need to be updated to reflect current clinical practice including evidence on new products and formulations. This thesis will review the author's publications on clinical and cost effectiveness of existing products and formulations including those introduced after the publication of the [NICE, 2004] guidelines to ensure the data reflect current clinical practice in both liver and renal transplantation and therefore adding new knowledge to this area.

2.6 Unmet Need

Whilst Immunosuppressants can lead to significant improvements in HRQoL, patient and graft survival they are also associated with side effects such as hypertension, new-onset diabetes after transplantation (NODAT) and renal dysfunction due to nephrotoxicity. Studies have demonstrated that CNIs including tacrolimus the current SoC have a well characterized efficacy and safety profile in patients at risk of post-transplantation graft rejection. However, doses that result in tacrolimus exposure outside of the therapeutic range can result in an increased risk of rejection (with low tacrolimus concentrations) or toxicity (with high tacrolimus concentrations) [Kershner and Fitzsimmons 1996; Borobia et *al.,* 2009; Taatz *et al.,* 2001]. This poses a challenge in optimising graft survival. Adherence to immunosuppression has also been highlighted as a major contributing factor to long-term graft and patient survival.

Whilst the benefits of immunosuppression outweighs the adverse effects. Nephrotoxicity, adherence and within-patient variability are important factors that represent a significant unmet need in post-transplant immunosuppression with current standard of care which need to be explored in terms of their clinical and economic consequences. The next section will briefly evaluate the importance of within-patient variability in immunosuppression therapy.

2.6.1 Within-Patient Variability

Within-patient variability variously referred to as intra-subject, intra-individual or intra-patient variability, the term refers to day-to-day differences in either tacrolimus concentration or tacrolimus clearance in a given patient taking the same daily dose. The high within-patient variability in tacrolimus pharmacokinetics and the relatively narrow therapeutic index (NTI), necessitate the use of regular therapeutic drug monitoring (TDM) of whole-blood tacrolimus trough concentrations (i.e. the concentration immediately before taking another dose) to establish the appropriate dose for a given patient [Scott *et al*., 2003]. Within-patient variability is typically measured using the coefficient of variability (CoV), which is calculated by dividing the standard deviation of the trough concentration by the mean and expressing the result as a percentage [Kahan *et al.,* 2000]. Any reduction in CoV would be likely to reduce the complexity associated with establishing a suitable dose, while potentially also improving patient outcomes by maintaining the whole-blood tacrolimus concentration within the therapeutic range which is critical for NTI drugs because there is little difference between toxic and therapeutic doses.

Published evidence indicates that there is a relationship between high within-patient variability and poor clinical outcomes, specifically graft failure. Notably, Borra *et al.,* [2010] published a retrospective analysis into the relationship between tacrolimus concentration variability and graft loss. The study found that significantly more renal transplant recipients with high within-patient variability had an increased risk of graft loss than those with low within-patient variability.

The impact of within-patient variability will be explored in chapter 5, to evaluate the clinical differences that might exist between formulations and consequent economic effect. This data will provide new knowledge in this area and potentially influence the development of future clinical and reimbursement guidelines. The next section will examine adherence as an unmet need in renal and liver post transplantation.

2.6.2 Adherence

Adherence is the degree to which a patient correctly follows the prescribed dose and interval of dosing [Chisholm *et al.,* 2005]. Given the proven effectiveness of immunosuppressants in preventing post-transplantation graft rejection, patient adherence to the prescribed regimen becomes a critical factor in improving graft survival outcomes. However, adherence to immunosuppression represents a key challenge in renal and liver transplant recipients. The clinical consequences of non-adherence include accelerated renal function decline, increased risk for late acute rejection and increased risk of graft loss. Overall, non-adherence rates in renal transplant recipients are high. A review by Denhaerynck *et al.,* [2005], reported that the weighted mean of self-reported non-adherence was 28%, but the prevalence of non-adherence in individual studies varied from 2% to 67% contributing to 16% of graft losses and 20% of late acute rejections. In liver transplant non-adherence rates are relatively lower compared to renal transplant however, it is still a significant problem increasing the risk of both acute and chronic organ rejection. A study by Burra *et al.,* [2011] reported that the rate of non-adherence to immunosuppression amongst adult liver transplant recipients was 15–40%.

A 2007 meta-analysis reported that the risk of non-adherence to immunosuppressive regimens was highest in renal transplant recipients [Dew *et al.,* 2007]. Several studies have since reported on various factors that can influence adherence in transplant recipients, including a 2012 study which showed that there is a strong inverse association between the number of immunosuppressive medications used by a transplant recipient and the proportion of patients who are adherent to therapy [Dharancy *et al.,* 2012]. Furthermore, dosing frequency and regimen complexity have also been associated with reduced adherence [Weng *et al.*, 2005].

Given that twice-daily, immediate-release formulations still constitute the majority of immunosuppressant prescriptions; there is still a great unmet need in allograft recipients for reduced pill burden [National Health Service Business Services Authority, 2013]. One of the challenging clinical consequences of non-adherence is antibody mediated rejection (AbMR) with approximately 60% of late graft failures thought to be attributable to AbMR [Butler *et al.,* 2004]. Although strict adherence to immunosuppressant medication is essential for the long-term survival of kidney and liver grafts, it has been shown as highlighted above that immunosuppressants are one of the most common groups of prescription drugs to which post-transplant patients are non-adherent [Constantiner and Cukor, 2011] representing an area of unmet need.

Several studies have demonstrated that even minor variations from the prescribed immunosuppression are associated with an increased risk of poor outcomes for transplant recipients [Dharancy *et al.*, 2012; Constantiner and Cukor, 2011; Maclean *et al.,* 2011]. Suboptimal adherence to the immunosuppressive regimen causes a higher risk of late acute rejection and allograft loss [Constantiner and Cukor, 2011; Maclean *et al.,* 2011]. A meta-analysis by [Butler *et al.,* 2004] found that 36% (14%-65%) of graft losses were associated with prior non-adherence. This clearly demonstrates the clinical impact of non-adherence on patient outcomes highlighting this as an area of great unmet need with potential implications for health resource utilisation and cost.

In this thesis data on the relative adherence rates between tacrolimus formulations and how this impacts graft survival and resulting economic consequences is evaluated. This is an area that has up to now never been explored and represents a new body of knowledge from both a clinical and economic perspective which has the potential to change clinical practice and reimbursement guidelines of immunosuppressive therapies.

2.7 Chapter Sumary

This chapter provided an overview of the prevalence and burden of ESRD and ESLD which consequently leads to transplantation. The value of immunosuppression therapy in post renal or liver transplantation was highlighted including improvements in HRQoL, patient and graft survival. Current treatment options, UK and international guidelines were discussed. Adherence and within-patient variability were identified as key unmet needs which have the potential to impact graft survival , increasing the risk of return to dialysis and or re-transplantation which is associated with significant clinical and economic burden on patients and healthcare services. In order to optimise long-term outcomes of patient and graft survival it is important to ensure the adoption of evidence based immunosuppressive therapy in clinical practice.

The next chapter will focus on assessing the relative clinical effectiveness of immunosuppressive therapies in the treatment and management of adult renal or liver transplant recipients based on present author's published research

Chapter 3: Clinical Effectiveness of Immunosuppressive Therapy

3.1 Introduction

The previous chapter discusssed the burden of ESRD and ESLD, management of post renal and liver transplantation with immunosupressive therapies. This chapter will examine the clinical effectiveness of immunosuppressive therapy in adult renal and liver transplantation based on the author's published research with a view to recommending the most effective treatment strategy supported by evidence.

The next section provides an overview of the studies conducted by the researcher Muduma *et al.,* [2016] on the relative effectiveness of immunosuppresive therapy in renal and liver transplantation utilising systematic literature reviews, meta-analysis and indirect treatment comparison. Below a summary and critical commentary of the present author's two studies is presented starting with renal followed by liver clinical effectiveness. For both studies, the research question and study concept was developed by the present author who also had a leading project management role in addition to contributing to the study design, analysis and publication.

3.2 Muduma G, Hart W, Patel S. Indirect treatment comparison of belatacept versus tacrolimus from a systematic review of immunosuppressive therapies for kidney transplant patients. ***Current Research and Medical Opinion.*** 2016; 30:1-8 **(Publication 1).**

3.2.1 Description of the Study

This research on indirect treatment comparison (ITC) of belatacept versus tacrolimus was developed in order to address the lack of clinical effectiveness data comparing tacrolimus formulations with belatacept in renal post-transplant immunosuppression. Immediate release tacrolimus (Prograf) has long been the mainstay therapy in renal transplant and is the recommended immunosuppressive treatment of choice within the current National Institute of Clinical Excellence [NICE, 2004] technology appraisal (TA) 85 which is currently under review. Since publication of NICE TA85 in 2004, newer therapies such as prolonged release tacrolimus (Advagraf) a newer formulation of tacrolimus and belatacept a selective co-stimulation were developed. However, there are no direct head to head trials comparing tacrolimus with belatacept. The aim of this study was to compare the clinical effectiveness of tacrolimus (Prograf

and Advagraf) and belatacept through a systematic review of immunosuppressive therapies in order to determine the most effective treatment strategy for renal transplant recipients using an indirect treatment comparison (ITC) approach.

A systematic literature review was conducted comparing all formulations of tacrolimus, belatacept and ciclosporin in renal transplant recipients. Both more intense (MI) and less intense (LI) dosing regimens of belatacept were included in the study. The key endpoints captured in the review included glomerular filtration rate (GFR), acute rejection (AR), graft and patient survival. Searches of randomized controlled trials (RCTs) were carried out from EMBASE, Medline and Cochrane Library databases for publications covering period from 2002 to June 2013. It was assumed that the [NICE, 2004] technology appraisal (TA85) would have captured relevant data up to 2002. The relevant data prior to 2002 were combined with data from this systematic literature review for the meta-analysis. Utilising results from the meta-analysis an indirect treatment comparison was conducted between tacrolimus formulations and belatacept using ciclosporin as a common comparator. The Bucher *et al.*, [1997] adjusted ITC model was used to calculate the relative risks of tacrolimus versus belatacept for graft failure, AR, patient mortality and mean difference of GFR.

The literature search in line with the study protocol yielded a total of twenty one studies (21), nineteen (19) comparing tacrolimus formulations with ciclosporin and two (2) comparing belatacept MI and LI regimens with ciclosporin. Random effects modeling assuming that the true effect size varies among studies was selected over fixed effects model, taking into account both within and between studies heterogeneity [Borenstein *et al.*, 2009].

The results of this ITC analysis showed no statistically significant difference in the GFR weighted mean difference between tacrolimus formulations and belatacept regimens. Similarly, there was no statistically significant difference between tacrolimus formulations and belatacept regimes for patient mortality and graft loss. However, the acute rejection rate was statistically significant lower with immediate and prolonged release tacrolimus relative to belatacept regimens 0.22(0.13, 0.39) and 0.44(0.20, 0.99) respectively.

3.2.2 Evaluation of the Study

The study results indicate that tacrolimus is associated with fewer acute rejections compared with belatacept and results are consistent with a manufacturer's report from All Wales Medicines Strategy Group [AWMSG, 2012] and a recently published study [Goring *et al.,* 2014]. The study also showed no statistically significant difference in GFR between tacrolimus and belatacept. However, a restricted analysis of belatacept versus tacrolimus using only one of the belatacept studies, Belatacept Evaluation of Nephroprotection and Efficacy as First line Immunosuppression Trial (BENEFIT) showed a statistically significant GFR weighted mean difference in favour of belatacept. There is need for this endpoint to be explored further in a direct head to head study. This is imperative because GFR is a predictor of long term graft survival.

A key strength of this publication is that it is the first ITC comparing tacrolimus formulations with both belatacept MI and LI dosing regimens to be published in a peer reviewed journal adding knowledge to this field. The findings can be used to inform decision making in clinical practice, as well as in health policy for example in updating clinical and reimbursement guidelines. Although this analysis focused on clinical outcomes, the study results provided part of the clinical data that was utilised in the renal cost utility analysis Publication 3, which included an economic evaluation comparing tacrolimus against a number of alternatives including belatacept in adult renal transplant recipients in the United Kingdom.

The major strength of this study is that it utilised current and widely accepted methodology in ITC. The Bucher adjusted ITC method used in this study has been the foundation for indirect treatment comparisons in meta-analyses of RCTs [Wells *et al.,* 2009]. More important the Bucher ITC method is widely accepted by drug reimbursement agencies such as the Australian Pharmaceutical Benefits Advisory Committee [PBAC, 2008], the UK National Institute of Clinical Excellence [NICE, 2008] and the Canadian Agency for Drug and Technologies in Health (CADTH) [Wells *et al.,* 2009].

Furthermore, the Bucher ITC method uses a statistical technique for making indirect comparisons of treatment effects that preserves the randomization of the originally assigned patient groups [Bucher *et al.,* 1997]. This reduces confounding and bias of results. Unlike with a naive ITC where comparisons of results across different trials break the original randomisation

and as such are subject to significant confounding and bias because of systematic differences between or among the trials being compared [Kim *et al.,* 2014].

However, there are shortcomings of this study which need to be acknowledged including limitations of the systematic review and meta-analysis in terms of variations in clinical and study design differences among the trials included in the analysis. These include varying uses of primary immunosuppression and concomitant medication, such as varied uses of the antiproliferative agents across trial arms, some using combinations of tacrolimus or ciclosporin with either mycophenolate mofetil or azathioprine. There were also varying administrative patterns for the drugs used in terms of dosages all of which could have a confounding impact on the outcomes affecting the accuracy of the results.

Relatedly, variability in study outcomes was not investigated. Any heterogeneity in this study could have been assessed by an I^2 test that describes the percentage of the variability that is due to heterogeneity rather than chance [Higgins and Green, 2008; Higgins *et al.,* 2003]. Whilst the heterogeneity in this study was described and addressed by using random effects model the I^2 test was not perfomed. This could have provided more detail quantifying the magnitude of the heterogeneity. Depending on the extent of the heterogeneity a sensitivity analysis of the outcomes with substantial heterogeneity could have been done using fixed effects to assess the impact on the outcomes and robusness of results. In addition meta-regression analysis could have been performed to further investigate the heterogeneity.

The analysis was further limited by the relatively short-term outcomes on which it was based, namely 12-month RCTs. Findings based on these relatively short-term outcomes may not be indicative of longer-term clinical outcomes. The 12-month duration of clinical trials included in this analysis on which the meta-analysis outcomes are based on can be argued to be inadequate given the chronic nature of immunosuppression therapy. The response seen in the RCT follow up period might not necessarily indicate how the patients might do over a long-term period in routine clinical practice as the disease evolves. Therefore, the external validity of the treatment outcomes based on limited treatment or follow up period such as in this study should be treated with caution. Basically, the veracity of this RCT based meta-analysis and ITC need to be complemented with routine clinical practice data covering long term follow up.

It is acknowledged that ITCs should be performed and can provide policy makers with useful information for clinical and economic decision-making. However, direct clinical evidence comparing two relevant treatments, through a randomized controlled trial with a long term follow up to establish the impact of the interventions as the disease evolves represents a strong evidence base. When RCTs are not available or cannot be conducted, researchers may resort to ITCs and interpret results carefully based on such analyses as in the case of this study.

3.3 Conclusions

This sudy presented the clinical effectiveness of tacrolimus formulations relative to belatacept. The results of this ITC suggests that tacrolimus is significantly superior to belatacept in terms of acute rejection outcomes but comparable for GFR, graft and patient survival. The key implication of this study is that belatacept is a newer drug, which has been suggested as a potential replacement for CNIs. This analysis fails to support the premise of replacing tacrolimus with belatacept in clinical practice. However, there is need for future research to include a properly designed clinical trial comparing tacrolimus versus belatacept directly with a long follow up period to determine the short and long-term outcomes of these therapies on renal transplant patients' including GFR, AR, patient and graft survival. Whilst this study focused on clinical effectiveness in renal transplant. The next section will examine a study on clinical effectiveness of immunosuppressive therapies in adult liver post-transplant recipients.

3.4 Muduma G, Saunders R, Odeyemi I, Pollock RF. Systematic Review and Meta-Analysis of Tacrolimus versus Ciclosporin as Primary Immunosuppression after Liver Transplant. *Public Library of Science (PLOS One) Journal*, **November 3, 2016 (Publication 2)**

3.4.1 Description of the Study

Several meta-analyses comparing ciclosporin with tacrolimus have been conducted since the 1994 publication of the tacrolimus registration trials, but most captured data from randomized controlled trials (RCTs) predating recent improvements in waiting list prioritization, induction protocols and concomitant medications. In the interest of evidence-based medicine, the established understanding from these meta-analyses should be periodically reviewed to ensure that it remains grounded in fact, particularly in cases where other complementary aspects of treatment are evolving alongside the primary therapies comprising the standard of care which is

the case in liver transplantation. This study was designed to address the need for an up-to-date meta-analysis of RCTs of ciclosporin and tacrolimus. This meta-analysis was the first analysis of post-transplant immunosuppression in liver transplant recipients conducted based exclusively on RCTs published since 2000, representing the most recent available data and therefore reflecting current clinical practice.

A systematic literature review was conducted based on searches from PubMed, Cochrane Library and EMBASE databases covering publications between January 2000 and August 6, 2014. The search strategy was designed to identify RCTs comparing all formulations of tacrolimus with ciclosporin used as primary immunosuppression therapy in adult patients receiving their first liver transplant.

The literature searches yielded forty nine (49) studies which were reviewed and identified eleven (11) relevant RCTs for inclusion in the meta-analysis. No studies were identified comparing prolonged release tacrolimus with ciclosporin. Only one RCT was identified comparing immediate release with prolonged release tacrolimus. The key study endpoints extracted for analysis included; acute rejection (AR), patient mortality, graft loss, new onset of diabetes (NODAT) and hypertension at 12 months.

Based on the extracted endpoints data a meta-analysis was undertaken to calculate the relative treatment effects of interventions using a random effects model for the base case analysis. In order to assess the robustness of the results, a number of sensitivity analyses were undertaken in which the outcomes were reported as odds ratios and risk differences. Fixed effects model was used instead of the random effects model adopted in the base case analysis.

This study results are based on endpoints which had sufficient data for analysis that is AR, hypertension, graft loss, mortality and NODAT. Relative to ciclosporin, tacrolimus was associated with significantly improved outcomes in terms of patient mortality (risk ratio [RR] with ciclosporin of 1.26; 95% confidence interval [95%CI] 1.01-1.58). Tacrolimus was superior to ciclosporin in terms of hypertension (RR with ciclosporin 1.26; 95%CI 1.07-1.47), but inferior in terms of NODAT (RR with ciclosporin 0.60; 95%CI 0.47-0.77). There were no significant differences between ciclosporin and tacrolimus in terms of graft loss or AR.

3.4.2 Evaluation of the Study

This systematic literature review and meta-analysis showed that tacrolimus is significantly more effective than ciclosporin in terms of patient survival and hypertension. Conversely, patients on ciclosporin had a lower risk of developing NODAT than those on tacrolimus. No other investigated outcomes significantly differed between ciclosporin and tacrolimus. However, analyses of patient survival and graft loss in Hepatitis C Virus (HCV) subgroups were opposite to those in the whole population.

The finding that patient mortality was significantly reduced in patients using tacrolimus relative to ciclosporin is consistent with previous meta-analyses. For instance, in 2006, Haddad and colleagues reported a relative risk of mortality of 0.85 (95% CI 0.73, 0.99) with tacrolimus relative to ciclosporin [Haddad *et al.*, 2006]. Similarly, Haddad *et al.*, [2006] reported a significantly higher risk of NODAT with tacrolimus relative to ciclosporin with a risk ratio of 1.27, compared to the RR of 0.59 with ciclosporin relative to tacrolimus in the present study. However, the meta-analysis by Haddad *et al.*, [2006] also reported an 18% reduction in the risk of acute rejection with tacrolimus versus ciclosporin, an endpoint around which this study identified no significant difference. This is probably due to the fact that with newer CNI formulations there has been a drastic reduction in patients experiencing acute rejections. Given this analysis focused on recent data these results might just be explaining what is happening in current clinical practice.

Outcomes in the HCV subgroup analysis of graft loss were also in line with a meta-analysis by Liu *et al.*, [2014]. Liu and colleagues reported a graft loss risk ratio of 1.05 (95% CI: 0.83–1.33) with tacrolimus relative to ciclosporin, which matches the present study directionally the risk ratio for graft loss in the HCV subgroup was 0.52 (95% CI 0.28, 0.98; $p = 0.04$) with ciclosporin relative to tacrolimus. This difference in outcomes in the HCV sub group which is opposite to the whole population is believed to be due to the way the CNIs work. While both tacrolimus and ciclosporin are CNI inhibitors, the mechanism of inhibition is distinct, with ciclosporin blocking efficient HCV replication in vitro by binding to regulators of the HCV ribonucleic acid (RNA) polymerase, independently of its immunosuppressive effect. Tacrolimus, conversely, binds to FK506 binding proteins, which are not required for HCV replication [Watashi *et al.,* 2005].

While hypertension was not investigated in the meta-analysis by Haddad *et al.*, [2006], the present study showed that tacrolimus would be expected to result in reduced incidence of hypertension relative to ciclosporin, a finding that is in line with the results of a meta-analysis comparing tacrolimus with ciclosporin in recipients of other solid organ grafts [Penninga *et al.,* 2010]. However, it should be noted that the results of the hypertension analysis from the present study was informed by a small number of studies that is four of the eleven included in the review. Therefore, further research is needed to validate these results.

Similar, to previous study Publication 1, this analysis main strength lies in its use of widely accepted evidence synthesis methodology. In addition, a specific strength of this publication is that the study analysis and reporting was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Furthermore, the Cochrane collaborations risk of bias tool was used to assess risk of bias including selection and reporting bias hence the study was conducted following good research practice.

Another key strength of this study is that unlike the previous study Publication 1, in this analysis study heterogeneity was ascertained by the I^2 statistic for each outcome. Furthermore, comprehensive sensitivity analyses were performed to assess the robustness of the results. For example the high heterogeneity in the graft loss analysis (I^2 of 53%) indicated a high variability. This was addressed by the use of random effects analysis model for the base case and fixed effects as a sensitivity analysis. The graft loss analysis was affected by the switch to a fixed effects analysis, with a fixed effects model yielding a RR of 1.02 (95% CI: 0.67–1.56), reduced from a RR of 1.20 (95% CI: 0.57–2.53) in the random effects analysis. The difference between random and fixed effects model outcomes may suggest that the random effects estimate, while likely more appropriate than a fixed effects model given the heterogeneity across studies, is not reflective of the true difference between treatments. Changes to the model and the reported outcome measure made no difference to the AR analysis, which remained non-significant across all analyses.

Finally, the analysis focused on RCTs published since 2000. This ensured that the data was more reflective of the present immunosuppression era and therefore representing current clinical practice. In addition, the analysis also validated previous studies and meta-analyses to ensure evidence is still relevant.

However, there are some limitations associated with the study which need to be acknowledged including publication bias and heterogeneity. A potential source of publication bias, in this analysis is the omission of studies that have not been published or have only been published in abstract form. Nevertheless, this was mitigated by the study protocol that only included fully published studies because of peer review rigour they would have undergone.

This study also did not compare prolonged release tacrolimus formulation with Ciclosporin. Only one RCT of once-daily tacrolimus was identified in the literature. The study, published by Trunečka *et al.*, [2010], compared twice-daily tacrolimus with once-daily tacrolimus in liver transplant recipients. The study was excluded from the meta-analysis as there was no comparison with ciclosporin and an indirect treatment comparison was not performed on the grounds that only this single non-inferiority study was identified. On reflection this analysis could have benefited from an ITC of prolonged release tacrolimus and ciclosporin based on this one identified RCT to get an indication of direction of the outcomes at the same time acknowledging the limitations of basing such analysis on one trial.

Finally, similar to previous study Publication 1, (section 3.2.2) these study outcomes were based on RCT data which has a stringent inclusion and exclusion criteria. The results of this meta-analysis are therefore, applicable to specific group of patients in line with the RCT study protocols. These strict eligibility criteria can effectively limit the generalisability of the results by limiting the group of patients which the results could be applied on in routine clinical practice. Consequently, this could potentially limit the patient population eligible for reimbursement in some healthcare systems based on these RCT data.

3.5 Conclusion

This study showed that, despite numerous changes in other aspects of routine care for liver transplant recipients, tacrolimus remains superior to ciclosporin in liver transplant recipients with respect to mortality and hypertension. While ciclosporin resulted in significantly lower incidence of NODAT than tacrolimus. Further research is required to establish the efficacy of prolonged-release tacrolimus relative to immediate-release tacrolimus and ciclosporin in liver transplant recipients.

3.6 Chapter Summary

This chapter examined the relative effectiveness of immunosuppressive therapy used in adult renal and liver transplant. The two articles included in this chapter described an update on immunosuppressive clinical effectiveness evidence in adult post renal and liver transplantation which added new knowledge to the field. The studies were developed to address a gap in literature and the research was conducted using well established evidence synthesis methodologies. Both strengths and limitations of the research were highlighted. The findings of the research provide further evidence supporting the use of tacrolimus as the cornerstone of immunosuppressive therapy in both liver and kidney transplant recipients. However, further research is needed to establish the long-term effectiveness of immunosuppression therapy in post renal and liver transplantation in routine clinical practice. Whilst it is important to establish the clinical effectiveness of therapies. In mordern day resource constrained healthcare systems it is even more imperative to demonstrate the economic consequences of the different therapies used in clinical practice.

The next chapter will look at the cost-effectiveness of immusuppressive therapy in renal and liver transplant.

Chapter 4: Cost effectiveness analysis of immunosuppressive therapy

4.1 Introduction

The thesis so far has discussed the burden of ESRD and ESLD and the clinical effectiveness of immunosuppressive therapy in this area. This chapter, will focus on how the findings from the clinical effectiveness and other relevant data sources were used to develop cost-effectiveness analyses of immunosuppressive therapy in adult renal and liver transplant recipients from a UK, NHS payer perspective.

This chapter will examine the health economic evaluation of immunosuppressive therapy in adult renal and liver transplant recipients based on author's research with a view to recommend the most cost effective treatment strategy. Three publications are presented covering three economic evaluation models; a renal transplant cost utility analysis based in part on clinical data from the indirect treatment comparson (ITC) publication 1 discussed in chapter 3, cost utility analysis in post liver transplantation immunosuppression based on outputs from a network meta-analysis (NMA), and a cost-effectiveness analysis in post liver transplant immunosuppression based on routine clinical practice data.

4.2 Muduma G, Shaw J, Hart W, Odeyemi A, Odeyemi I. Cost utility analysis of immunosuppressive regimens in adult renal transplant recipients in England and Wales. ***Patient Preference and Adherence.*** 2014; 8:1537-46. **(Publication 3)**

4.2.1 Description of the Study

Tacrolimus is the Standard of Care (SoC) in renal post-transplant immunosuppression in the United Kingdom (UK) and is currently recommended by National Institute of Health and Clinical Excellence (NICE) guidelines technology assessment (TA) 85 [NICE, 2004]. Prior to 2013, no health economic analysis had been conducted comparing immediate-release tacrolimus to newer immunosuppressive agents introduced on the market post NICE TA 85 [NICE, 2004] review.

The renal cost utility analysis was developed to address this lack of economic evaluations of renal post-transplant immunosuppression regimens in the UK since the publication of an economic

evaluation by [Woodroffe *et al.,* 2005] based on the NICE review. The aim of this study was to carry out a cost utility analysis of immunosuppression, including more recent agents such as a once daily prolonged-release formulation of tacrolimus (Advagraf) and Belatacept a first in-class co-stimulation blocker, relative to a twice-daily immediate-release formulation of tacrolimus (Prograf) from a UK National Health Service (NHS) payer perspective.

A Markov model was constructed to represent the patient flow following successful kidney transplantation. The model comprised six health states: onset of biopsy confirmed acute rejection (BCAR), functioning graft with or without a biopsy-confirmed acute rejection, non-functioning graft (dialysis), re-transplantation, and death. Patients could be in only one of the finite health states at any given time point in the simulation. The health states were developed in consultation with clinicians and validated by Key Opinion Leaders (KOLs) at an advisory board. The model used a 1-year cycle length and was designed to support time horizons of between 5 and 25 years. The model used underlying rates of graft failure from the National Health Service Blood and Transplant (NHSBT). Data on clinical effectiveness were derived from a systematic literature review. The model captured the effects of patient adherence to immunosuppressant therapy on graft survival using relative risk of graft survival based on published data on odds of graft failure and adherence to once and twice daily tacrolimus from [Butler *et al.,* 2004, Kuypers *et al.,* 2013]. Health related quality of life utility values for functioning renal transplant, hemodialysis, and peritoneal dialysis were also derived from the literature [Lee *et al.,* 2005]. Comparator drugs in the analysis included Advagraf, Prograf, belatacept, sirolimus and ciclosporin. In the base case, the time horizon was 25 years, one way and probabilistic sensitivity analyses were conducted. One way sensitivity analyses indicated that Incremental Cost Effectiveness Ratios (ICERs) were affected by the time horizon and effect of adherence. However, overall the results were not sensitive to changes from other variables such as discount rate, costs and utilities associated with dialysis suggesting the model is robust.

The results showed that in the base case immediate release tacrolimus was cost-effective when compared with ciclosporin and belatacept and was more effective than sirolimus, but would not be considered cost effective against sirolimus. Prolonged release tacrolimus dominated immediate release tacrolimus.

Advisory Boards were utlised in this study and in publications 4 and 7 as a methodological tool to elicit information and validate data to ensure that economic modelling assumptions were in

line with clinical practice. The Advisory Boards were composed of multi-disciplinary experts in the field of transplantation including Physicians, Nurses, Payers/Commissioners and Pharmacist. The advisory boards provided expert opinions which were taken into account in order to ensure that the outputs from the economic analysis were aligned with what happens in the clinical environment.

4.2.2 Evaluation of the study

The study showed that Advagraf is the most cost effective option compared to Prograf the current SoC. This result was driven to a large extent by the high adherence rates of Advagraf relative to Prograf which impacts graft survival rates and consequent costs associated with treating graft loss that is dialysis and or re-transplantation. Advagraf and Prograf were seen to be more effective and less costly relative to belatacept a new agent which was developed with the intention to replace CNIs. The cost and significantly higher acute rejection rate associated with belatacept compared with CNIs in the first 3 months of therapy as detailed in a recent report of the All Wales Medicines Strategy Group could act as a barrier to the wider use of belatacept in England and Wales [AWMSG, 2014].

In terms of contribution to knowledge this study represented the first cost-utility analysis to be published on post-renal transplant immunosuppression that captured the effects of patient adherence specifically to tacrolimus formulations. There is evidence suggesting a link between graft survival and adherence to immunosuppressive therapy in renal transplant as discussed in Chapter 2 (section 2.6.2). However, up to now the potential economic impact of adherence on graft survival had never been assessed in health economic models for post renal transplantation.

The key strength of this study is therefore its ability to model adherence data to graft survival and resulting economic consequences. This modeling approach is innovative in post renal transplant area and could be used as a basis for further adherence data based economic models in post liver transplantation and other therapeutic areas.

The second strength of this study is that the analysis compared the current SoC immediate release tacrolimus with all relevant interventions for primary immunosuppression in post renal transplant. In addition to established products the analysis included new products and formulations in the model reflecting current clinical practice. Furthermore, the model represents a significant update to the health economic evidence base in renal post-transplant

immunosuppression in the UK since the publication by [Woodroffe *et al.,* 2005]. Therefore, this study contributed to knowledge in this area which could help payers make informed decisions for their reimbursement guidelines on post renal transplant immunosuppression.

Finally, the health states and economic model were validated by a panel of experts at an advisory board which was multidisciplinary including health economics, renal transplant physicians and healthcare professionals. Therefore, another key strength of this study is that the economic model was developed following good practice incorporating what KOLs would expect to be in a credible model. Consulting with subject experts assured that the model addressed the research question and disease processes adequately.

However, like most studies there are limitations which need to be acknowledged. The first limitation of this study which is inherent in most health economic analyses is that of multiple data sources used to derive the model inputs. A number of data sources were used in the model, underlying graft failure rates from NHSBT, mortality data from the Office for National Statistics, adherence data from [Kuypers *et al.,* 2013], graft failure odds from [Butler *et al.,* 2004], dosing data from [Silva *et al.,* 2007], and drug prices from the British National Formulary. Whilst the use of heterogeneous data sources is common practice in modeling it nevertheless needs to be highlighted as a potential limitation since the different data sources have varying degrees of quality which could affect the accuracy of the results. To mitigate the impact of heterogeneity of the data sources one way and probabilistic sensitivity analyses were conducted. The analyses suggest that the results are robust. However, the ICERs were impacted by changes in time horizon and effect of adherence.

The second limitation was the lack of patient adherence data for belatacept, sirolimus and ciclosporin. Whilst this study represented the first time adherence data was used in a health economic evaluation of immunosuppressants the data was only used for Advagraf and Prograf arms. It is recommended that future studies capture long-term adherence data for all the competing interventions and model them accordingly. This is would result in a more comprehensive comparison of all relevant interventions using the same approach for effectiveness data. This is important since in renal transplantation adherence with immunosuppresants is linked to improved graft survival which impacts patient HRQoL, return to dialysis and or re-transplantation and the resulting costs.

Finally, the study adopted a payer perspective which meant that the analysis did not include indirect costs such as productivity which might affect a proportion of this patient population as renal transplantation is associated with significant loss of productivity. In this regard the analysis could be considered to be an underestimation of the total burden of renal transplantation on the UK society.

4.2.3 Conclusion

Prograf appears to maintain its status as the SoC for the immunosuppression of renal transplant recipients against relevant comparators in the UK. National recommendations should consider Advagraf as a viable alternative to Prograf as the SoC due to the improvement in graft survival attributable to the improvement in adherence observed in patients taking the once daily formulation. In addition based on this analysis Advagraf was the only drug found to be more effective and less costly relative to Prograf the current SoC. This could have implications for the UK, national reimbursement guidelines which are currently under review with NICE. The next paper will review the cost utility analysis in post liver transplantation based on NMA data.

4.3.1 Muduma G, Odeyemi I, Pollock RF. A Cost-Utility Analysis of Prolonged-Release Tacrolimus Relative to Immediate-Release Tacrolimus and Ciclosporin in Liver Transplant Recipients in the UK**.** ***Journal of Medical Economics 2016; 19(10): 995-1002.*** **(Publication 4)**

4.3.2 Description of the study

This cost utility analysis of prolonged-release tacrolimus relative to immediate-release tacrolimus and ciclosporin was designed to address the lack of economic studies of immunosuppressive therapies in post liver transplantation in the UK. Prior to this study no health economic analysis had been conducted ever comparing immunosuppressive agents in post liver transplantation in the UK. The present author conceived the research question in order to address this gap in literature. In addition to the study design and analysis the present author led the project management of the research and publication. Calcineurin inhibitors (CNIs) represent the cornerstone of immunosuppressive therapy after liver transplantation. This indicates that CNIs are clinically effective. However, it is important to have estimates of the cost effectiveness of immunosuppressive therapies, in order to ensure that limited healthcare resources are being allocated efficiently into a product(s) that optimises HRQoL, patient and graft survival. This

study evaluated the cost utility of prolonged-release tacrolimus relative to ciclosporin or immediate-release tacrolimus in liver transplant recipients from a UK, NHS payer perspective.

A three health states Markov model was developed to evaluate the cost-utility of immunosuppressive regimens in liver transplant recipients, capturing costs associated with immunosuppression, re-transplantation, acute rejection (AR), and cytomegalovirus infection. The three health states were alive with first transplant, alive after retransplantation, and dead. No states were included to capture recurrence of conditions for which liver transplant was indicated, such as hepatocellular carcinoma (HCC) and hepatitis C virus (HCV). Mortality, graft loss, and AR odds ratios were derived from a network meta-analysis (NMA). Transitions between states were based on underlying rates of mortality from the NHSBT, while rates of re-transplantation were derived from [Marudanayagam *et al.,* 2010]. Differential rates were then calculated based on the odds ratios reported in the NMA. The model also captured rates of acute rejection in year 1 of the analysis and supported time horizons of up to 25 years, extrapolating from the 10-year NHSBT mortality data using a rational model fit to the Kaplan-Meier curves. Costs were taken from the British National Formulary and the NHS National Tariff and expressed in 2016 pounds sterling. Future costs and effects were discounted at 3.5% annually in line with NICE guidelines on discounting [NICE, 2008]. All simulations were conducted using probabilistic sensitivity analysis in which key model parameters were sampled to capture the uncertainty around model inputs. Additionally, a series of one-way sensitivity analyses were conducted. The base case analysis was performed over a 25-year time horizon. This approach was taken to capture the full effectiveness differences between the respective treatments and for consistency with another recent cost-utility analysis of immunosuppressive regimens after solid organ transplantation [Muduma *et al.,* 2014].

The base case analysis, showed prolonged release tacrolimus resulted in increased life expectancy and quality-adjusted life expectancy (QALE) relative to immediate release tacrolimus and ciclosporin. Relative to ciclosporin, QALE increased by 1.17 quality adjusted life years (QALYs) with prolonged release tacrolimus while costs increased by GBP £4645, yielding an incremental cost-effectiveness ratio (ICER) of £3962 per QALY gained. Relative to immediate release tacrolimus, QALE increased by 0.78 QALYs and costs by £1474, resulting in an ICER of £1889 per QALY gained. Deterministic sensitivity analysis showed the model to be most sensitive to dosing assumptions of tacrolimus.

4.3.3 Evaluation of the study

The study analysis suggests PR tacrolimus is highly cost effective and should be considered as the first line treatment in post liver transplant immunosuppression. Similar to previous publication 3, a key strength of this study is the wide consultation with clinical experts that informed the model structure and choice of health states. This ensured that the model adequately addressed the research question.

Also a critical strength of this study is the fact that the clinical outcomes data driving the model were derived from a NMA which combined data from RCTs and large observational studies using a Bayesian confounder controlled hierarchical model. This data set is more robust than RCT only data since it brings in a component of routine clinical practice into the analysis. An approach and data source which is likely to be well received by payers [Stegenga *et al.,* 2017]

Another key strength of the study is the targeted nature of the model which focused on patient population with non-recurrent conditions for which liver transplant is indicated. This allowed for a more transparent evaluation of the impact of immunosuppression which would be lost if for instance patients with recurrent HCV and HCC were to be included in the analysis. In addition the model structure and assumptions were validated by clinical experts.

However, the study has limitations that should be acknowledged when interpreting the findings. Similar to the previous paper publication 3 (section 4.2.2), the main limitations of this analysis was the adoption of a payer perspective and the use of heterogeneous data sources for the clinical efficacy parameters, health utilities, body weight and the dosing assumptions. As in publication 3, the impact of the heterogeneous data sources was mitigated to a great extent because all simulations of ICERs were conducted using probabilistic sensitivity analysis in which key model parameters were sampled to capture the uncertainty around model inputs. Nevertheless, the model was sensitive to the long term dosing assumption based on RCT data which was then extrapolated for the 25 year time horizon of the analysis. Until long-term data on immunosuppressive dosing become available, long-term dose modeling will continue to be a challenge in health economic analyses of immunosuppressive products. This indicates the need for collection of longitudinal dosing data to address the uncertainty associated with this variable.

This study was designed specifically for the purposes of modeling cost-utility in non-recurrent indications for liver transplant which is strength in terms of transparent modeling. However, given that the highest indication for liver transplant is Hepatitis C Virus (HCV). The results of this analysis are unlikely to be applicable to patients with HCV. Nonetheless, limitations around the exclusion of HCV should be alleviated by the approval of the second generation direct-acting antivirals (DAAs) with HCV cure rates up to 100% [Afdhal *et al.*, 2014]. This should mean the number of people indicated for liver transplantation due to HCV should go down and any recurrence of HCV after liver transplantation could be successfully treated. Therefore, the current model exclusion of HCV population might not be a huge limitation as HCV treatments evolve in clinical practice.

Finally, the cost estimate for liver re-transplantation was based on costs from a single center study. Whilst the cost of retransplantation is being derived from a single data source. It has to be highlighted that the single centre study as good as it might be it might not reflect clinical practice of other centres. The specific center protocols and practices, may have affected the cost estimates presented, and the final cost estimate may not be applicable to other centers affecting the generalisability of this study. Therefore, there is need to gather re-transplantation cost data from multiple centers to take into account the potential clinical diversity and hence varying costs. This data can be used to update the analysis assessing the impact on the results relevant to clinical practice and reimbursement requirements.

4.3.4 Conclusions

Based on this UK, specific analysis of the projected cost-utility of PR tacrolimus relative to IR tacrolimus and ciclosporin, PR tacrolimus was cost effective, improving life expectancy and QALE relative to both IR tacrolimus and ciclosporin, yielding ICERs below £20 000 per QALY gained. The main limitations of the study were the cost estimate for liver re-transplantation and lack of long-term routine clinical practice data on immunosuppression dosing.

Whilst this publication was based on data from a NMA the next study will present the first within trial liver cost effectiveness analysis based on routine clinical practice data which represents a significant advance in immunosuppression therapy economic modeling.

4.4.1 Muduma G, Odeyemi I, Pollok RF. Evaluating The Cost-Effectiveness of Prolonged-Release Tacrolimus Relative To Immediate-Release Tacrolimus in Liver Transplant Patients Based on Data From Routine Clinical Practice. *Drugs - Real World Outcomes Journal.* 2016;3:61-68 **(Publication 5)**

4.4.2 Description of the study

Data from RCTs alone do not always provide the information that HTAs and reimbursement agencies require to make their decisions on adoption of a technology. As a consequence, increasingly reimbursement and market access decisions require evidence of relative effectiveness of an intervention compared to the SoC when used in routine clinical practice [Stegenga *et al.,* 2017]. This economic analysis is based on clinical outcomes from routine clinical practice. The present author conceived this study to address the lack of economic models in post liver transplant immunosuppression in the UK, based on routine clinical practice data. Immediate release tacrolimus is currently the cornerstone of post-transplant immunosuppression in liver transplant recipients. However, a recent propensity-score matched analysis of data from the European Liver Transplant Registry (ELTR) has demonstrated a significant improvement in graft survival in patients on prolonged-release, once-daily versus immediate-release, twice-daily tacrolimus [Adam *et al.,* 2015]. These emerging data appear to corroborate the findings of previous studies that have demonstrated improved adherence with reduced pill burden, and improved graft outcomes with improved adherence [Eberlin *et al.*, 2013; Kuypers *et al.,* 2013; Florman *et al.,* 2005]. Given the substantial effect that these findings may have on incidence of graft loss in liver transplant recipients. The objective of this study was to evaluate the cost-effectiveness of prolonged-release tacrolimus (PRT) versus immediate-release tacrolimus (IRT), the current SoC in liver post-transplant immunosuppression. The analysis was conducted using routine clinical practice data from the ELTR focusing on both the monetary and epidemiological implications of using PRT relative to IRT. As with the previous study in addition to contributing to the study design and data analysis the present author led the project management of this research.

A cost effectiveness model was developed in Microsoft Excel. The model was a Kaplan-Meier based analysis of patient and graft survival data from the ELTR, capturing costs of primary immunosuppressive medications and re-transplantation over the three-year time horizon of the ELTR data analysis.

Over a 3 year time horizon, the numbers needed to treat with PRT relative to IRT were 14 to avoid one graft loss and 18 to avoid one death. The base case demonstrated that PR tacrolimus was less costly and more effective than IR tacrolimus meaning IR tacrolimus was dominated. However, the model was sensitive to dosing assumptions, with incremental cost estimates varying between a saving of GBP 1,642 (standard deviation GBP 885) per patient, assuming the same dosing of PRT and IRT (per kilogram bodyweight) and an increase of GBP 1,350 (GBP 964) using RCT dose data.

4.4.3 Evaluation of the study

The study showed that, based on a recent retrospective analysis of routine clinical practice data from the ELTR, PR tacrolimus would be expected to be associated with higher gains in life expectancy and graft survival relative to IR tacrolimus. In addition PR tacrolimus would reduce costs incurred by the healthcare payer.

This study had significant contributions in a number of areas. The study represented the first within-trial analysis of cost effectiveness in liver transplant recipients and the first attempt to estimate the pharmacy and re-transplantation costs based on the findings of a long-term study in routine clinical practice. Furthermore, this cost-effectiveness analysis represented the first health economic model of post liver transplant immunosuppression to report outcomes in natural units such as cost per graft month gained and numbers needed to treat to avoid graft failure. While the cost analysis presented is UK specific, the epidemiological results derived from the ELTR data are likely to be applicable to many countries.

In addition to the contribution to knowledge this study's key strength is that the economic analysis was based on clinical outcomes data derived from a retrospective analysis of routine clinical practice data without the need to extrapolate the data beyond the duration of the study. This had the benefit of reducing the uncertainty associated with the extrapolation of data beyond that observed in the study. Furthermore, the clinical outcomes used in the analysis were derived from a single source without the need to model surrogate markers to hard outcomes of graft and patient survival.

Another key strength of this publication is the new dimension it brought to the cost effectiveness analysis of immunosuppression in post liver transplantation. Whilst the previous cost utility analysis studies (Publications 3 and 4) were modelled on clinical data from ITC and

NMA. This study used the ELTR real world data to model the cost effectiveness of immunosuppression in post liver transplant. Since key clinical outcomes of patient and graft survival used in the model were derived from a real world experience which reflects what happens in routine clinical practice. It can therefore, be argued that this study presents clinical and economic effectiveness of tacrolimus formulations in post liver transplantation recipients based on real world evidence. This is in line with payers' expectations in terms of using RWE in economic evaluations [Stegenga *et al.,* 2017]. This study is a significant advance in modelling of post liver transplant immunosuppression which could be used as a template in post renal transplantation where so far no economic model has been developed based on real world data.

As with any cost effectiveness analysis, this study has a number of limitations that should be acknowledged. Similar to the previous study, publication 4 (section 4.3.3), the most significant limitations of this analysis include the use of a single center costs to inform the re-transplantation costs, payer perspective and the lack of longitudinal immunosuppression dosing. In fact dosing data were not recorded in the ELTR and as such did not form part of the retrospective analysis by [Adam *et al.,* 2015] that underpinned the clinical aspects of this analysis. A series of probabilistic and one way sensitivity analyses were employed to address these concerns.

Finally, this study provides a great platform from where routine clinical practice data can be further extended to collect a number of variables not currently captured in the ELTR data such as long term dosing. This is needed in economic modelling of immunosuppression therapy since current models are sensitive to dosing assumptions based on short-term RCT data.

4.4.4 Conclusion

Based on this analysis, PR tacrolimus is superior in graft and patient survival relative to IR tacrolimus. Moreover, PR tacrolimus was less costly and more effective than IR tacrolimus. This provides a strong rationale for the adoption of PR tacrolimus over IR tacrolimus in adult liver transplant recipients in the UK healthcare system.

4.6 Chapter Summary

Three articles included in this chapter each summarised and critiqued the approach taken in the development of cost utility and effectiveness analyses in renal and liver post–transplant

immunosuppression. The studies provided new knowledge and significant update on economic analyses of post liver and renal transplant immunosuppression therapy. The analyses confirmed that tacrolimus maintains its position as the cornerstone of post-transplant immunosuppression therapy. The prolonged-release tacrolimus (Advagraf) appears to be the most cost effective option in the UK setting. The routine clinical practice based cost effectiveness analysis provided a template of how real world data could be used in economic modeling in immunosuppression therapy. However, further work is required to address the heterogeneity of data sources used in the economic modelling in particular the linking of adherence rates with graft survival from different trials with different study design and patient populations. In addition, collection of longitudinal dosing data would go a long way in addressing the uncertainty surrounding this key variable in long term economic modeling of immunosuppression therapy in post-transplantation. These analyses provide much needed evidence in this area to inform clinical and reimbursement guidelines in the UK and after adaptation in other countries.

Whilst CEAs help with priority setting there is also need to assess affordability and sustainability of funding at a local, regional and national level. The next chapter will focus on the budget impact analysis of tacrolimus formulations in post-renal transplant immunosuppression and how this might influence local decisions on product adoption.

Chapter 5: Budget impact analysis of immunosuppression therapy

5.1 Introduction

The previous chapter examined the cost-effectiveness of post-transplant immunosuppression. Whilst cost effectiveness and cost utility analyses help healthcare decision makers in assigning priority to efficient interventions. Budget Impact Analysis (BIA) is useful in assessing affordability of interventions and hence sustainability of their funding. Therefore, BIA is key to product adoption and patient access to medicines [Orlewska and Gula´csi, 2009]. This chapter will focus on BIA of renal post-transplant immunosuppression specifically tacrolimus formulations.

Prior to 2013, no tacrolimus formulations BIAs had been conducted in renal transplant and hence a significant gap in literature. The within-patient variability (Publication 6) and patient adherence (Publication 7) budget impact analyses were developed to address this gap. Similarly, the antibody-mediated rejection (AbMR) based budget impact analysis (Publication 8) was subsequently developed to conduct a health economic analysis of data from a retrospective study showing an association between non-adherence to immunosuppression, AbMR and graft loss. Similar to the previous papers in addition to taking a lead role in the project management of the studies the present author also contributed to the research design and analysis of the three articles to be critically evaluated in this chapter.

5.2 Muduma G , Odeyemi I , Pollock R .A UK Analysis of the cost of switching Renal Transplant Patients from an Immediate-release to a Prolonged-release formulation of tacrolimus Based on differences in Trough Concentration Variability**.** ***Journal of Medical Economics 2014; 17(7): 520-6*** **(Publication 6)**

5.2.1 Description of the Study

Randomised controlled trials have shown that a once-daily prolonged-release (PR) tacrolimus formulation (Advagraf) is non-inferior to a twice-daily immediate-release (IR) tacrolimus formulation (Prograf) in terms of biopsy-confirmed acute rejection, graft failure and mortality in renal transplant recipients [European FK506, 1994; US FK506, 1994]. While studies have

demonstrated that tacrolimus has a well-characterised efficacy and safety profile in patients at risk of post-transplantation graft rejection, doses that result in tacrolimus exposure outside of the therapeutic range can result in an increased risk of rejection (with low tacrolimus concentrations) or toxicity (with high tacrolimus concentrations). However, relative to IR tacrolimus, PR tacrolimus exhibits reduced tacrolimus trough concentration variability, which has been associated with reduced graft failure. Based on these data, this study evaluated the cost of switching UK renal transplant patients from IR tacrolimus to PR tacrolimus.

An Excel based cohort model was developed to model rates of renal graft failure in patients prescribed Prograf versus Advagraf as the primary immunosuppressive therapy. The model was able to estimate the effects of different proportions of patients with high or low within patient tacrolimus variability on longer-term graft loss outcomes based on two studies [Wu *et al.,* 2011; Borra *et al*., 2010]. The underlying rate of graft failure was based on NHSBT data on renal transplant recipients in the UK. Cost data were taken from the British National Formulary and 2012–2013 NHS tariff information. Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of the model results.

The results of the analysis showed a mean per-patient cost (including tacrolimus, concomitant immunosuppressive medications, dialysis after graft failure, and treatment for acute rejection) was GBP 26,941 (standard deviation [SD] = GBP 2765) with PR tacrolimus vs. GBP 30,356 (SD = GBP 3085) for IR tacrolimus over a 5-year period, corresponding to a saving of GBP 3415 (SD = GBP 516) per patient.

5.2.2 Evaluation of the Study

This study demonstrated that over a 5-year time horizon, using Advagraf, a prolonged-release tacrolimus formulation in renal transplant recipients could result in substantial cost savings in the UK healthcare system relative to immediate-release tacrolimus. Cost savings were driven primarily by a reduction in the incidence of graft failure in patients with lower within-patient variability, of which there were more in the prolonged-release arm than the immediate-release arm , 96.9% of patients in the prolonged- release arm vs. 82.6% in the immediate-release arm [Wu *et al.,* 2011].

This study has a number of strengths and limitations. Key strengths include the use of simple and transparent modelling approach together with UK specific data for underlying graft loss and up to date UK cost data at time of publication.

Another strength of the study is that this analysis was the first to factor within-patient variability data into an evaluation of the budgetary implications of post-renal transplant immunosuppression, and was the first UK, budget impact analysis of immunosuppressive agents ever to be published in peer-reviewed journals. The modelling approach used to link pharmacokinetic data to outcomes is a unique and great development which provides a framework for other therapeutic areas to utilise in their economic analysis. Furthermore, the analysis has contributed to knowledge in this field and addressed the gaps that existed in literature.

The main limitation of this study is that no long-term data were available to directly demonstrate differences in graft loss between patients on Advagraf relative to Prograf. The modeling analysis therefore utilised two data sources one on the proportions of patients on Advagraf and Prograf with high within patient variability [Wu *et al.,* 2011], and modeled these data with previously-published evidence on the increased risks of graft loss associated with high within patient variability [Borra *et al.,* 2010]. The use of two different studies with different patient populations to model outcomes could impact the certainty of the results. To mitigate for this heterogeneity of data sources, probabilistic sensitivity analysis was conducted in the base case sampling from distributions of key model parameters including graft failure risk, body weight, tacrolimus and concomitant medicines dosing. In addition, a number of one way sensitivity analyses were conducted. The results confirmed the model was robust whilst the magnitude of the savings changed the direction of the savings remained the same in favour of Advagraf.

5.2.3 Conclusion

This study demonstrated that, relative to IR tacrolimus, PR tacrolimus is cost-saving in renal transplant recipients in the UK. Savings were driven primarily by the lower costs associated with dialysis after graft failure which is lower with PR tacrolimus relative IR tacrolimus. PR tacrolimus therefore, offers both clinical (reduced graft failure) and economic (cost savings) benefits to renal transplant recipients and payers in the UK. Based on the results of this study PR tacrolimus should be considered as an alternative to the IR tacrolimus the current SoC in the UK. This

study presented a BIA based on within patient variability the next study will examine a budget impact analysis based on adherence to immunosuppression therapy.

5.3 Muduma G, Odeyemi I, Smith-Palmer J, Pollock R. Budget Impact of switching from an Immediate-Release to a Prolonged-Release formulation of tacrolimus in Renal Transplant Recipients in the UK based on differences in Adherence. ***Patient Preference and Adherence. 2014; 8: 391-9.*** **(Publication 7)**

5.3.1 Description of the study

Similar to the previous paper the development of this study was driven primarily by lack of budget impact analyses to inform payer decision making and the availability of data on the improvements in patient adherence observed with prolonged-release tacrolimus (Advagraf) relative to immediate-release tacrolimus (Prograf). Advagraf is associated with improved adherence compared with Prograf [Kuypers et *al.*, 2013], which may ultimately improve long-term graft survival outcomes. This study evaluated the budget impact of switching patients from Prograf to Advagraf in the UK based on patient adherence rates to immunosuppression.

An Excel-based cohort model was developed to model rates of renal graft failure in patients prescribed Prograf versus Advagraf as the primary immunosuppressive therapy. The model was able to estimate the effects of different rates of patient adherence on longer-term graft loss outcomes using published data. Different proportions of adherent patients in the Prograf and Advagraf arms were taken from a randomised controlled trial by Kuypers et *al.,* [2013] and risk of graft failure from an earlier study [Butler *et al.*, 2004]. Similar to previous publication 6 (section 5.2.2) study utilised the same methodology in terms of underlying rate of graft failure, cost data, time horizon, discounting and sensitivity analyses.

The results of the analysis over a 5-year time horizon, showed the mean cost per patient (including tacrolimus, concomitant immunosuppressive medications, dialysis after graft failure, and treatment for acute rejection) was £29,328 (standard deviation [SD] £2,844) for Advagraf versus £33,061 (SD £3,178) for Prograf. The total cost saving of £3,733 (SD £530) was driven primarily by reduced dialysis costs arising from the lower incidence of graft failure (21.6% with

Prograf versus 18.3% with Advagraf) in the larger proportion of adherent patients in the Advagraf arm.

5.3.2 Evaluation of the study

This study showed that, relative to immediate-release tacrolimus, using prolonged-release formulation in renal transplant patients could result in substantial cost savings in the UK healthcare system over 5 years. This analysis has the same strengths as the previous study highlighted in (section 5.2.2). In addition, the specific strength of this study is that these analyses were the first to factor patient adherence data into an evaluation of the budgetary implications of post-renal transplant immunosuppression, and were the first adherence budget impact analysis of immunosuppressive agents ever to be published in peer-reviewed journals.

The proportion of patients' adherent to treatment with immediate-release versus prolonged-release tacrolimus formulations was a key driver of the modelling analysis. The Kuypers *et al.,* [2013] study adherence data used in this analysis was recently corroborated by a prospective observational study reported by [Sabbatini *et al.,* 2014]. This gives credibility to the data supporting the economic analysis strengthening the findings of the model. However, there is a need to design a study with long-term follow up to assess the impact of adherence on graft loss in the same patient population to validate these results.

As with the previous study publication 6 highlighted in section (5.2.2), the most notable limitation of this analysis was the lack of long term graft survival data from a single source. No long-term data were available to directly demonstrate differences in graft loss between patients immunosuppressed with Advagraf versus Prograf. The modeling analysis therefore utilised data on the different rates of patient adherence on Advagraf and Prograf [Kuypers *et al.,* 2013] and modeled these data with previously published evidence on the increased risks of graft loss associated with non-adherence [Butler *et al.,* 2004]. These two studies are different in terms of the primary immunosuppressant used for instance in Butler *et al.,* [2004] the majority of patients were taking either ciclosporin or azathioprine unlike the Kuypers *et al.,* [2013] study in which all patients were on Advagraf or Prograf. The linking of outcomes from these two studies could therefore, be challenged. Acknowledging this limitation probabilistic sensitivity analysis was conducted in the base case. In addition, a series of one way sensitivity analyses were conducted

including varying the rates of adherence between Advagraf and Progaf arms and altering the relative risk of graft failure. None of these analyses changed the direction of cost-saving of Advagraf relative to Prograf. However, the size of the cost savings was reduced.

Another potential shortcoming of this study is around the limited outcomes captured. For example, Pinsky *et al.,* [2009] reported significant variations in the incidence of mortality up to 3 years after transplant, across patients divided into quartiles by first-year adherence to their immunosuppressive regimen. In the study, patient mortality in the "excellent" adherence group was 3.0% compared with 5.4% in the "fair" compliance group ($p = 0.0001$) [Pinsky *et al.,* 2009] Despite this evidence, this study assumed no difference in mortality either between Prograf and Advagraf or between adherent and non-adherent patients. The primary justification for this was the implication of capturing mortality in a budget impact model, namely that a comparator associated with an increased risk of mortality would appear to be cheaper, while the reduction in life expectancy would not be captured in the model. Cost-effectiveness analyses, in which incremental costs are balanced with incremental effectiveness outcomes such as life expectancy, are better suited to capturing differences in mortality as discussed in chapter 4.

5.3.4 Conclusion

This study demonstrated that conversion of renal transplant recipients from Prograf to Advagraf was associated with lower pharmacy and dialysis costs, with the reduction in dialysis costs being driven by improved adherence to Advagraf regimen and the consequent improvement in graft survival. This analysis suggests that Advagraf is a clinically and economically prudent choice for immunosuppression in renal transplant recipients in the UK. These findings could influence the development and or review of post-renal transplant immunosuppression local formularies, clinical and reimbursement guidelines at a national level.

This study evaluated budget impact due to adherence. The next study will present a budget impact analysis based on AbMR due to non-adherence in post renal transplant.

5.4 Muduma G, Odeyemi I, Pollock RF. Evaluating the Economic Implications of Non Adherence and Antibody -Mediated Rejection in Renal Transplant Recipients: The Role of Once-Daily, Prolonged-Release Tacrolimus in the UK setting. ***Journal of Medical Economics 2015; 18(12): 1010-20.*** **(Publication 8)**

5.4.1 Description of the Study

The development of the antibody-mediated rejection (AbMR) budget impact model was started to address the lack of data on the economic implications of non-adherence and the resulting increase in AbMR and graft loss, as reported in [Sellarés *et al.,* 2012]. This analysis builds on the previous study (Publication 7) by including data linking non adherence with AbMR. While short-term kidney graft survival has gradually improved over time, improvements in long-term graft survival have been more modest. One key clinical factor limiting improved longer-term outcomes is AbMR, the incidence of which appears to be higher in patients who are non-adherent to immunosuppressants. The aim of this study was to model the incidence and economic consequences of graft loss and AbMR in patients taking prolonged-release (PR) tacrolimus (Advagraf) compared to immediate-release (IR) tacrolimus (Prograf) from a UK, NHS payer perspective.

A combined decision tree and four-state Markov model was developed which included the following health states: functioning graft, functioning graft with AbMR, dialysis after failed graft, and death. The model estimated the incidence of graft failure, AbMR and mortality in renal transplant recipients taking PR vs. IR tacrolimus. The underlying rates of graft failure were based on data from the NHSBT, while differential rates between Advagraf and Prograf were driven by the proportion of patients adherent to each regimen [Kuypers *et al.,* 2013] and the increased risk of AbMR and graft failure in non-adherent patients reported by [Sellarés *et al.,* 2012]. Cost data were taken from the British National Formulary and National Health Service reference costs and reported in 2014 pounds sterling.

Modelling results showed that improved adherence would be associated with reduced incidence of AbMR, graft failure and health resource utilisation in renal transplant recipients. Based on improvements in adherence resulting from switching from IR to PR tacrolimus, the modelling analysis projected cost savings of GBP 4862 per patient over 5 years with Advagraf relative to Prograf, on absolute costs of GBP 40,974 and GBP 45,836, respectively.

5.4.2 Evaluation of the study

This study demonstrated that using Advagraf, a prolonged-release tacrolimus formulation in renal transplant recipients could result in substantial cost savings in the UK healthcare system

relative to immediate-release tacrolimus. In terms of contribution to knowledge this analysis was the first to evaluate the economic implications of non-adherence and AbMR in renal transplant recipients and the role of once-daily PR tacrolimus in the UK healthcare system.

This analysis has the same strengths as Publication 6 (highlighted in section 5.2.2). In addition the specific strength of this study is that this analysis was the first to establish the costs associated with various AbMR treatment regimens in the UK setting, including treatment based on the Edinburgh Renal Unit (ERU) AbMR treatment protocol, and the ERU treatment protocol in combination with rituximab, eculizumab and botezomib infusions. The study highlighted that the lack of recognition of AbMR as a treatable indication had led to a lack of data on the efficacy of different treatment options.

Similar to the previous BIA Publications 6 and 7 the key limitation of this analysis was the lack of long-term clinical outcomes data and use of different data sets to bridge this gap. This included using data from an RCT for the proportion of patients' adherent to once-daily versus twice-daily tacrolimus formulations by Kuypers *et al.,* [2013], and data from Sellares *et al.,* [2012] for the relative risk of graft failure and AbMR in non-adherent patients relative to adherent patients. Similar to previous publications 6 and 7 both probabilistic and deterministic analyses were conducted to mitigate uncertainty that may arise from use of heterogeneous data sets. A number of one way sensitivity analyses were performed around graft failure risk, AbMR treatment modality, patient mortality and time horizon. The results confirmed the model to be robust. However, the sensitivity analyses showed that the incidence of AbMR had significant impact on absolute cost savings indicating that therapies with lower incidence of AbMR would yield greater cost savings suggesting Advagraf should be the tacrolimus formulation of choice.

5.4.3 Conclusion

This study has demonstrated that Advagraf would be cost-saving relative to Prograf in renal transplant recipients in the UK setting, with cost savings driven by reduced costs associated with dialysis, treatment of AbMR, and primary immunosuppressive medication. This analysis suggests that Advagraf may reduce the incidence of AbMR in UK renal transplant recipients and therefore, represent a clinically and economically appropriate choice for immunosuppression in renal transplant recipients in the UK. The key implication here is that UK, local and national payers might now consider funding Advagraf ahead of Prograf due to its clinical and economic benefits.

5.6 Chapter Summary

This chapter presented three studies evaluating the budget impact analysis of immediate-release tacrolimus (Prograf) compared with prolonged-release tacrolimus (Advagraf) in post-renal transplantation immunosuppression therapy from a UK, NHS payer perspective. Each study made a significant contribution to knowledge in this field and hence addressing the gap in literature. The results across the three studies suggest that Advagraf is clinically effective in terms of graft survival and cost saving compared with Prograf in post renal transplant immunosuppression from a UK setting. However, the key limitation of these analyses was the heterogeneity of the clinical data used to model graft loss for example data on within patient variability and risk of graft loss was taken from two different trials with different patient population and hence uncertainty around the results. The key implication of these BIAs is that they can now be used in the UK and after adaptation can be utilised with other countries to inform local payers funding, formulary and product adoption which consequently impact patient access to immunosuppressive medicines. The next chapter presents a summary, conclusions and recommendations of the thesis.

Chapter 6: Summary, Conclusions and Recommendations

6.1 Summary

Globally the number of patients living with renal and liver transplantation is increasing. The prevalence, clinical and economic burden of ESRD and ESLD leading to the need for transplantation and effective immunosuppression therapy to ensure patient and graft survival was highlighted in Chapter 2 of the thesis. Given the need for constant immunosuppression in these patients the clinical and economic impact of immunosuppressive regimens should be established and periodically reviewed to ensure that patient and graft survival are optimised and payers are making the best use of increasingly strained healthcare budgets.

The aim of the thesis was to evaluate the clinical and economic impact of immunosuppressive therapy in the treatment and management of adult renal and liver transplant recipients. Through the presentation and critical review of eight publications, the clinical and cost effectiveness together with the budget impact analysis of immunosuppression therapy was assesed. Each paper was used to demonstrate the clinical and or economic impact of immunosuppression therapy to patients, payers and healthcare decision makers. The thesis highlights how the eight publications have formed a cohesive body of evidence which can be used by policy makers to inform the development and or updating of clinical and reimbursement guidelines which ultimately impact patients access to immunosuppression therapy. The findings of this research provides clinical and economic evidence supporting the use of prolonged release, once daily tacrolimus (Advagraf) as the cornerstone of primary immunosuppressive therapy in liver and renal transplant recipients. However, further research is needed to establish the long term clinical effectiveness of immunosuppression in renal and liver transplantation.

This chapter examines the contribution of the research, reviews the implications and limitations of the thesis and highlights recommendations for future research.

6.2 Contribution to Research

Chapter 3, examined the relative effectiveness of immunosuppressive therapy used in adult renal and liver transplant. The two publications presented in this chapter described an update on immunosuppressive clinical effectiveness evidence in adult post renal and liver transplantation which added knowledge to the field. The Indirect treatment comparison of belatacept versus tacrolimus in renal transplant immunosuppression was the first ITC analysis comparing tacrolimus formulations with both belatacept more intense and less intense dosing regimens to be published in a peer reviewed journal updating research in this field. Equally, the systematic review and meta-analysis of tacrolimus versus ciclosporin as primary immunosuppression after liver transplant updated evidence in this area. This meta-analysis was the first study of post-transplant immunosuppression in liver transplant recipients conducted based exclusively on RCTs published since 2000, representing the most recent available data and therefore reflecting current clinical practice and modern liver transplant era.

Chapter 4, presented three articles which summarised and critiqued the approach taken in the development of cost utility and effectiveness analyses in renal and liver post–transplant immunosuppression. The studies provided new knowledge and significant update on economic analyses of post renal and liver transplant immunosuppression therapy. The Cost utility analysis of immunosuppressive regimens in adult renal transplant recipients in England and Wales represented the first cost-utility analysis to be published on post-renal transplant immunosuppression that captured the effects of patient adherence specifically to tacrolimus formulations. Furthermore, the analysis represents a significant update to the health economic evidence base in renal post-transplant immunosuppression in the UK since the publication by Woodroffe *et al.,* [2005]. The Cost-utility analysis of prolonged-release tacrolimus relative to immediate-release tacrolimus and ciclosporin in liver transplant recipients in the UK was the first health economic analysis to be conducted in this area and hence adding new knowledge in this field. Similarly, the cost-effectiveness of prolonged-release tacrolimus relative to immediate-release tacrolimus in liver transplant patients represented the first within-trial analysis of cost effectiveness in liver transplant recipients using routine clinical practice data and hence generating new knowledge.

Chapter 5, presented three studies which evaluated the budget impact analysis of immediate-release tacrolimus compared with prolonged-release tacrolimus in post-renal transplantation

immunosuppression therapy from a UK, NHS payer perspective. These were the first post-renal transplant immunosuppression BIAs in the UK to be published in peer reviewed journals. Each study made a valuable contribution to knowledge in this field and also addressed a significant gap in literature which existed prior to the publication of these studies.

6.3 Implications of the Thesis

This research represent a well integrated body of work the ultimate objective which was to demonstrate the clinical and economic impact of immunosuppression therapy with a view to recommending the most effective immunosuppressive product(s) for renal and liver transplant recipients. Prior to 2013, no health economic evaluation on immunosuppressive therapy was done in liver transplantation in the UK. The renal economic analysis was dated with the last evaluation published by Woodrofee *et al.,* [2005] and no budget impact analyses had been published in renal transplant. The clinical effectiveness data was also limited to old products and clinical trials in both renal and liver transplant as the previous meta-analyses lacked comparison of newer immunosuppressive products and formulations from recent RCT data.

This body of work utilised a broad range of clinical evidence, including SLR, ITC, NMA and routine clinical practice data for comparative effectiveness. A number of modelling approaches were also employed to demonstrate the clinical and economic impact of immunosuppression therapy in post renal and liver transplant patients. The thesis provides an example to other therapuetic areas on how to update and generate new evidence using widely accepted evidence generation and synthesis methodologies. Importantly, the economic models presented in this thesis though from a UK perspective they can be adapted to other healthcare systems potentially impacting reimbursement guidelines and consequently patient access to immunosuppression in other countries. The clinical evidence generated from this thesis is transferable across healthcare systems and therefore, could be used to influence and inform reimbursement policies, clinical guidelines and practice in the UK and healthcare systems across the world. Consequently, impacting renal and liver transplant patients access to immunosuppression therapy and improvement in their survival and quality of life in a cost effective way.

Another key implication for the thesis is centred around the budget impact analyses of immunosuppressive therapies. Basically, budget impact analysis provides useful information to

tackle the new hurdle of affordability, after having fulfilled the better-known hurdles of added clinical value of new treatments over existing ones [Marshall *et al.,* 2008; Orlewska and Mierzejewski, 2004]. In this regard BIA is key in terms of product adoption and patient access to medicine. Therefore, the BIAs in this research can be used in the UK to inform local payers formulary and product adoption decisions. Unlike CEA which can be used for priority setting at a national level. The BIA can be used for assessing affordability and sustainability at a local level in line with the health economy budgets. The BIA in this thesis after adaptation can be used as a template by payers in other countries to inform their reimbursement, formulary and adoption decisions at a national, regional and local level. Therefore, the BIAs in this thesis have the potential to influence reimbursement and formulary decisions in the UK and other healthcare systems across the world. Consequently impacting renal transplant patients access to immunosuppressive medicines.

6.4 Limitations of the Thesis

This thesis has presented an update and generated new data on immunosuppression therapy clinical and cost effectiveness evidence in post renal and liver transplant recipients. As discussed above in section 6.2 this research has addressed a gap that existed in literature at the same time contributing to new knowledge in the field. However, there are limitations of the thesis that need to be acknowledged. Firstly regarding cost effective analyses all the economic studies presented in this thesis were conducted from a healthcare payer perspective. This approach excludes a number of important societal aspects such as productivity costs for example time lost from work, out of pocket expenses for the patient, family and friends. Both renal and liver transplant are associated with significant loss of productivity. Therefore, a societal perspective would have captured all relevant costs and benefits to society as a whole regardless of the source of immunosuppression funding. It can therefore, be argued that the economic evaluations presented in this thesis provide a conservative estimate of the costs and benefits that can be realised at a societal level since payer perspective does not include all relevant costs and benefits in their analyses.

Secondly, most of the data used to inform the relative clinical effectiveness is based on meta-analyses of RCTs. The RCT data presented in this thesis is derived from 12 month outcomes data which is then extrapolated for the rest of the economic model time horizon. However, the RCT data might not reflect what happens in routine clinical practice in the long term as the

disease evolves such as future complications and more importantly benefits in the form of improved productivity and or patient quality of life. Due to the limited treatment and follow up period, economic models based on RCT data risk missing important effects of transplantation in the long-term which could have significant economic implications. This can be addressed by conducting real world studies with a long-term follow up to capture what actually happens in routine clinical practice.

Thirdly, the economic evaluations did not include any sub-group analysis. Patient and disease characteristics such as severity and comorbidities are expected to influence cost effectiveness and therefore it is important to conduct evaluations in different population subgroups [Studer *et al.*, 2004]. This limitation is more specific to the Muduma *et al.,* [2016] cost utility analysis in which the model was restricted to liver transplant patients with non-recurrent indications.

Finally, the economic models included in the present thesis excluded costs associated with adverse events of immunosuppression therapy such as hypertension and NODAT. This was due to lack of data to provide informative estimates on the risk of these adverse events in particular with prolonged release tacrolimus. Relatedly, due to lack of data none of the economic models incorporated treatment switches due to patients changing therapy as a result of either adverse effects or lack of therapuetic effect that you could expect to see in routine clinical practice. Therefore, there is need to collect RWE on both treatment switches and adverse events across all the relevant immunosuppresion therapies. This data could be incorporated into the economic models to reflect what happens in routine clinical practice and hence address the generalisability and relevance of these results to patients and payers respectively.

In respect of clinical effectiveness the data generated from ITC and meta-analyses is derived from RCTs which limits the generalisability of results. Due to the stringent inclusion/exclusion criteria the samples in the RCTs may not be reflective of the the general transplant population in routine clinical practice. Consequently, it can be argued that you cannot apply the findings of these analyses to the general transplant population. Also as already mentioned the RCT data is limited to 12 months outcomes and hence not reflective of what could happen in the long-term. Again this could be addresed by collecting longitudinal RWE which is in line with payer requirements [Stegenga *et al.,* 2017].

6.5 Recommendations for Further Research

Based on the findings from this thesis a number of recommendations can be made as to where future research should be centered to further augment our understanding of the clinical and economic impact of immunosuppression therapy in adult renal and liver transplant recipients. With respect to clinical effectiveness presented in Chapter 3. Most of the comparative clinical effectiveness data is based on RCTs. However, as discussed above (section 6.4) this data has some limitations, notably the protocol driven nature of RCTs, short follow up time, small and highly selected sample. Consequently, there might be issues in terms of the generalisability of this data to the renal and liver post-transplant population in routine clinical practice. In addition, the outcomes from the RCT data might not reflect what happens in the real world in the long-term as the disease evolves. Therefore, there is need to conduct real world studies in both post renal and liver transplant recipients. The studies could take the form of either a prospective routine clinical practice study or retrospective database analysis. However, the latter might be limited in terms of the data captured in the databases. RWE using longitudinal studies would provide an opportunity to gather long-term clinical and economic outcomes of immunosuppression therapy in routine clinical practice mitigating the limitations of RCT data. However, it should be pointed out that studies that generate RWE are less statistically rigorous than RCTs with inadvertent biases [Stegenga *et al.,* 2017]. This could be addressed by integrating RWE with RCT data for example in post liver transplantation where there is emerging routine clinical data comparing tacrolimus formulations [Adam *et al.,* 2015]. Recent studies have reported quantitative approaches to combining data from randomized and non-randomized studies using Bayesian hierarchical models and adjusting study estimates for potential confounders using differences in patient characteristics between study arms [McCarron *et al.,* 2010]. This could provide an avenue for further research on the relative clinical effectiveness of ciclosporin and tacrolimus formulations in renal transplant recipients. There is currently ongoing research of this nature in post liver transplant, which the present author is contributing to. This research would ensure comparison of all key primary immunosuppression therapies and also incorporation of all relevant available clinical data from both RCT and observation studies which would make the results more comprehensive, robust, generalisable and informative for payers.

In order to address the lack of direct comparisons and long term outcomes among the competing interventions in both renal and liver transplantation. It is recommended that direct head to head RCTs with long term follow up be conducted comparing the primary immunosuppression in both renal and liver focusing on the key outcomes discussed in this thesis. This would address to a certain extent the dosing issue and also provide new data on

outcomes to add to the current meta-analyses and ITC making the body of evidence more robust.

Regarding cost effectiveness presented in Chapter 4. In many areas of medicine, the costs in the year prior to significant clinical events rise substantially [Hwang 2009; Tanuseputro 2015; Geue 2014]. In the UK the costs of transplantation are well established [NHS, 2016]. However, knowledge about the healthcare resource utilisation and associated costs during the last year before graft failure for kidney or liver transplant patients are limited. The health economic studies presented in this thesis and those in the literature to date do not include the cost associated with graft loss. Traditionally, economic evaluations in the field of transplantation have taken into consideration potential changes in post-transplantation costs [Jurgensen, *et al.* 2010]. However, cost variations using graft failure as the index date have generally not been accounted for in economic models. Therefore, it is recommended that observational studies be undertaken to estimate the total cost of healthcare resource use (HRU) observed in the year prior to the date of kidney or liver transplant failure.

These HRU data prior to kidney or liver transplant failure would be of use for input into economic evaluations of kidney or liver immunosuppression where so far little attention has been paid to the costs incurred in year prior to graft failure. This would help in capturing the true cost associated with graft loss. There are likely to be significant cost-saving implications for immunosuppression therapy that can be shown to delay the time to graft failure. The present author conceived research which is on-going on HRU and costs associated with graft loss in both renal and liver transplant. When completed this research would greatly improve current economic models by integrating this data into the post-transplant immunosuppression economic evaluations making the analyses more comprehensive and useful for payers as they capture these significant costs which have an implication on a health economy budget.

The accuracy of the cost effectiveness analyses presented in this thesis could be improved if updated with routine clinical practice data with longitudinal dosing data. This has been highlighted as a source of uncertainty in current studies. Finally, there is a great opportunity to further develop the economic models to include subgroup analysis for example in patients with recurrent conditions particularly HCC and HCV in post liver transplantation. Future studies should also try to expand on existing studies by taking a societal perspective, including more costs and benefits in their analyses.

6.6 Conclusions

In conclusion, the research presented in this thesis has demonstrated that tacrolimus is the most cost and clinically effective treatment in both renal and liver transplant recipients. Specifically, Advagraf the once-daily prolonged release tacrolimus formulation has been shown to be clinically and economically more effective than the current standard of care Prograf, twice-daily immediate release tacrolimus formulation. Advagraf was more cost and clinically effective relative to Prograf from a UK, payer perspective. A finding that is likely to influence clinical and reimbursement guidelines for post renal and liver transplant immunosupression in the UK. The discussed clinical evidence limitations of this research can be addressed through the design of an RCT with a long term follow up comparing all the key immunosuppression therapies that is tacrolimus, ciclosporin and belatacept.

This should be complemented by a routine clinical practice data analysis in the form of a longitudinal observational study capturing patient and graft survival, NODAT, renal dysfunction, hypertension, AbMR, and dosing regimes in the real world. These studies should be conducted in both renal and liver transplant. Finally, economic analyses could be improved by taking a societal perspective, incorporating costs associated with graft failure, and use of real world data in economic models comparing all relevant interventions.

References

Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A; All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012; 57(3):675-88 Activity_report.jsp (accessed 11th April 2011)

Adam R, Karam V, Delvart V, Trunečka P, Samuel D, Bechstein WO, et al. Improved Survival in Liver Transplant Recipients Receiving Prolonged-Release Tacrolimus in the European Liver Transplant Registry. Am J Transplant. 2015; 15(5):1267±1282. doi: 10.1111/ajt.13171 PMID: 25703527

Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98

Afendy A, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G,et al. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther 2009; 30:469-476.

All Wales Medicines Strategy Group. AWMSG Secretariat Assessment Report – Advice No. 1712 Belatacept (Nulojix). May 2012

Alqahtani SA. Update in liver transplantation. Discov Med. 2012; 14(75):133-41

Anand S, Asaf B, Thomas G. The Gap between End-Stage Renal Disease and use of therapy. Plos One Journal 2013, 8 (8): e72860

Arogundade F, Barsoum R. CKD prevention in Sub-Saharan Africa: a call for governmental, nongovernmental, and community support. *Am J Kidney Dis* 2008; 51: 515–23.

Baboolal K, McEwan P, Sondhi S, Spiewanowski P, Wechowski J, Wilson K. The cost of renal dialysis in a UK setting--a multicentre study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2008; 23(6):1982-9.

Beaudet A, Palmer JL, Timlin L, Wilson B, Bruhn D, Boye KS, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. Journal of medical economics. 2011; 14(3):357-66.

Blachier M, Leleu H, et al. The burden of liver disease in Europe. A review of available data. Journal of Hepatology. 2013 vol.58:593-608.

Bleyer AJ, Tell GS, Evans GW, Ettinger WH, Jr., Burkart JM. Survival of patients undergoing renal replacement therapy in one center with special emphasis on racial differences. *Is J Kidney Dis* 1996; 28:72–81?

Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to Meta-Analysis. West Sussex, United Kingdom: Wiley, 2009

Boronia AM, Romero I, Jimenez C, et al. Trough tacrolimus concentrations in the first week after kidney transplantation are related to acute rejection. TherDrug Monit 2009; 31:436–42

Borra LC, Roodnat JI, Kal JA, et al. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. Nephrol Dial Transplant 2010; 25:2757–63

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.

Burra P, Germani G, Gnoato F, Lazzaro S, Russo FP, Cillo U, Senzolo M. Adherence in liver transplant recipients. Liver Transpl. 2011; 17(7):760-70

Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004; 77(5):769–776.

Cardenas A, Gines P. Management of patients with cirrhosis awaiting liver transplantation. Gut 2011; 60: 412–421

Chamberlain G, Baboolal K, Bennett H*, et al.* The economic burden of posttransplant events in renal transplant recipients in Europe. *Transplantation* 2014; **97**: 854

Chisholm MA, Lance CE, Mulloy LL. Patient factors associated with addherence to Immunosuppressant therapy in renal transplant recipients. AMJ Health Syst Pharm. 2005;62:1775-1781

Collins AJ, Foley RN, Chavers B, et al. US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis* 2014; 63:A7.

Constantiner M, Cukor D. Barriers to immunosuppressive medication adherence in high-risk adult renal transplant recipients. *Dial Transpl.* 2011; 40:60–66

Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, Schäfer-Keller P, Schaub S, De Geest S. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int. 2005; 18(10):1121–33

Department of Health. National Service Framework for Renal Services – Part Two: Chronic kidney disease, acute renal failure and end of life care. London: UK: Department of Health. 2005.

Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, Switzer GE, Zomak R, Kormos RL, Greenhouse JB. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation. 2007;83(7):858–73.

Dharancy S, Giral M, Tetaz R, Fatras M, Dubel L, Pageaux GP. Adherence with immunosuppressive treatment after transplantation: results from the French trial PREDICT. Clin Transplant. 2012; 26(3):E293-9.

EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016 Feb;64(2):433-85. doi: 10.1016/j.jhep.2015.10.006. Epub 2015 Nov 17

Eberlin M, Otto G, Kra¨mer I. Increased medication compliance of liver transplant patients switched from a twice-daily to a once daily tacrolimus-based immunosuppressive regimen. Transplant Proc. 2013;45(6):2314–20.

European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus FK506) and cyclosporin in prevention of liver allograft rejection. Lancet 1994; 344:423-8

Florman S, Alloway R, Kalayoglu M, Lake K, Bak T, Klein A, et al. Conversion of Stable Liver Transplant Recipients From a Twice-Daily Prograf-Based Regimen to a Once-Daily Modified Release Tacrolimus-Based Regimen. Transplant Proc. 2005; 37:1211±3. doi: 10.1016/j.transproceed.2004.11.086

Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013. doi: 10.1016/S0140-6736(13)60595-4

Geue C, et al. Population ageing and healthcare expenditure projections: new evidence from a time to death approach. The European journal of health economics: HEPAC: health economics in prevention and care 2014; 15: 885–96.

Gilg J, Rao A, and Fogarty D. UK Renal Registry 16th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2012: National and Centre-specific Analyses.Bristol, UK: UK Renal Registry, 2012.

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351:1296–305.

Goicoechea M, de Vinuesa S, Gomez-Campdera F, Luno J. Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD). *Kidney Int Suppl 2005:S35*–8.

Goring SM, Levy AR, Ghement I, et al. A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients. Curr Med Res Opin 2014; 30:1473-87

Graudal N, Leth P, Marbjerg L, Galloe AM. Characteristics of cirrhosis undiagnosed during life: a comparative analysis of 73 undiagnosed cases and 149 diagnosed cases of cirrhosis, detected in 4929 consecutive autopsies. *J Intern Med* 1991; 230:165–171.

Gutteling JJ, de Man RA, van der Plas SM, Schalm SW, Busschbach JJ, Darlington AS. Determinants of quality of life in chronic liver patients. Aliment Pharmacol Ther 2006; 23:1629-1635.

Halloran P. Immunosuppressive Drugs for Kidney Transplantation. New England Journal of Medicine. 2004; 351:2715-29.

Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009] The Cochrane Collaboration, 2009. Available from: http://www.cochranehandbook.org. [Accessed February 11, 2010].

Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons Ltd; 2008

Higgins JPT, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003, 327:557-60.

Hwang I, et al. Medical Costs and Healthcare Utilization among Cancer Decedents in the Last Year of Life in 2009. Cancer Res Treat 2016; 48: 365–75.

Iacobucci G. Liver disease rises in England while falling elsewhere in Europe, report says. BMJ. 2012; 345:e7931.

Jansen JP, Fleurence R, Devine B, Itzler R, et al . Interpreting Indirect Treatment Comparisons and Network Meta – Analysis for Healthcare Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons. Good Reaserch Practices:Part 1. Value in Heath;14 (2011) 417-428

Jha V, Garcia-Garcia G, Iseki K et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013; 382: 260–272

Jurgensen JS, et al. Cost-effectiveness of immunosuppressive regimens in renal transplant recipients in Germany: a model approach. The European journal of health economics: HEPAC: health economics in prevention and care 2010; 11: 15–25

Kahan BD, Welsh M, Urbauer DL, et al. Low intraindividual variability of cyclosporine A exposure reduces chronic rejection incidence and health care cost. J Am Soc Nephrol 2000; 11:1122–31

KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009 Nov;9 Suppl 3:S1-155. doi: 10.1111/j.1600-6143.2009.02834.x

Kershner RP, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. Transplantation 1996; 62:920–6

Kim H, Gurrin L, Ademi Z, et al. Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. Br J Clin Pharmacol. 2014 Jan; 77(1): 116–121.

Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. Br J Gen Pract. 2015; 65(631):54-5.

Kramer A, Pippias M, Stel VS, et al. Renal replacement therapy in Europe: a summary of the 2013 ERA-EDTA Registry Annual Report with a focus on diabetes mellitus. Clin Kidney J 2016; 9: 457. 6.

Kuypers DR, Peeters PC, Sennesael JJ, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation*. 2013;95(2): 333–340.

Lee AJ, Morgan CL, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. *Curr Med Res Opin*. 2005;21(11):1777–1783.

Lee S, Woojin C, Kyung-Rae H. Socioeconomic costs of liver disease in Korea. Korean J Hepatol. 2011; 17:274–91.

Liem YS, Bosch JL, Arends LR, Heijenbrok-Kal MH, Hunink MG. Quality of life assessed with the Medical Outcomes Study Short Form 36-Item Health Survey of patients on renal replacement therapy: a systematic review and meta-analysis. Value Health. 2007; 10(5):390–7.

Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. *Clin Liver Dis* 2008; 12: 733–746

Liu Z, Chen Y, Tao R, Xv J, Meng J, Yong X. Tacrolimus-based versus ciclosporin-based immunosuppression in hepatitis C virus-infected patients after liver transplantation: a meta-analysis and systematic review. PLoS One. 2014; 9(9):e107057. doi: 10.1371/journal.pone.0107057 PMID: 25198195

Loinaz C, Marin LM, Gonz_alez-Pinto I, et al. A single-centre experience with cyclosporine microemulsion versus tacrolimus in 100 randomized liver transplant recipients: midterm efficacy and safety. Transplant Proc 2001; 33:3439-41

Lumsdaine JA, Wray A, Power MJ, Jamieson NV, Akyol M, Andrew Bradley J, Forsythe JL, Wigmore SJ. Higher quality of life in living donor kidney transplantation: prospective cohort study. Transpl Int 2005; 18:975.

Maclean JR, Pfister M, Zhou Z, Roy A, Tuomari VA, Heifets M. Quantifying the impact of nonadherence patterns on exposure to oral immunosuppressants. *Ther Clin Risk Manag*. 2011; 7:149–156.

MacNeill S, Casula A, Shaw C, and Castledine D. UK Renal Registry 18th Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2014: National and Centre-specific analyses. 2015.

Marshall, D.A., Douglas, P.R., Drummond, M.F. Guidelines for conducting pharmaceutical budget impact analyses for submission to public drug plans in Canada. Pharmacoeconomics 26, 477–495 (2008)

Marudanayagam R, Shanmugam V, Sandhu B. Liver retransplantation in adults: a single-centre, 25-year experience. HPB(Oxford) 2010;12:217-24

Mathers C, Lopez A, Murray C. The burden of disease and mortality by condition: data, methods, and results for 2001. In: Lopez A, Mathers C, Ezzati M, et al, editors. Global burden of disease and risk factors. Washington (DC): Oxford University Press and the World Bank; 2006. p. 45–93.

Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on Good Research Practices—Budget Impact Analysis. Value Health 2007;10:336–47

Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699

Mazzoni D, Cicognani E, Mosconi G*, et al.* Sport activity and health-related quality of life after kidney transplantation. *Transplant Proc* 2014; **46**: 2231.

McCarron CE, Pullenayegum EM, Thabane L, Goeree R, Tarride JE. The importance of adjusting for potential confounders in Bayesian hierarchical models synthesising evidence from randomised and observational studies. Med Res Methodol. 2010; 10:64±72. doi: 10.1186/1471-2288-10-64 PMID: 20618973

Melato M, Sasso F, Zanconati F. Liver cirrhosis and liver cancer. A study of their relationship in 2563 autopsies. *Zentralbl Pathol* 1993; 139: 25–30.

Minino A, Xu J, Kochanek K, Tejada-Vera B. Death in the United States, 2007. *NCHS Data Brief* 2009:1–8.

Morales JM, Varo E, Lázaro P. Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain. Clin Transplant. 2012; 26(2):369-76

Muduma G, Shaw J, Hart WM, et al. Cost utility analysis of immunosuppressive regimens in adult renal transplant recipients in England and Wales. Patient Prefer Adherence 2014;8:1537-46

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498–1504

Nathan H, Segev DL, Mayo SC, et al. National trends in surgical procedures for hepatocellular carcinoma: 1998–2008. Cancer 2012; 118: 1838–1844.

National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September. 2008.

National Health Service Business Services Authority. Prescription Cost Analysis (PCA) Data. April 2013. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx Last accessed July 31, 2013.

National Institute for Clinical Excellence [homepage on the Internet]. Immunosuppressive therapy for renal transplantation in adults. Technical Appraisal 85, September 2004. Available from: www.nice.org.uk/TA85. Accessed March 3, 2014.

Neff GW, Duncan CW, Schiff ER. The current economic burden of cirrhosis. Gastroenterol Hepatol 2011; 7: 661–671

Nguyen GC, Segev DL, Thuluvath PJ. Nationwide increase in hospitalizations and hepatitis C among inpatients with cirrhosis and sequelae of portal hypertension. Clin Gastroenterol Hepatol 2007; 5: 1092–1099.

NHS Blood and Transplant (2011) Activity report 2009–10 Section 9 Survival rates following transplantation.
http://www.organdonation.nhs.uk/ukt/statistics/transplant_activity_report/transplant_
NHS reference costs 2015 to 2016 Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016

NICE Quality Standards Programme. NICE cost impact and commissioning assessment for chronic kidney disease in adults March 2011.

NICE. Guide to the methods of technology appraisal, N.I.f.H.a.C. Excellence, Editor 2008.

Orlewska, E., Gula´csi, L.: Budget-impact analyses, a critical review of published studies. Pharmacoeconomics 27, 807–827 (2009)

Orlewska, E., Mierzejewski, P.: Proposal of polish guidelines for conducting financial analysis and their comparison to existing guidance on budget impact in other countries. Value Health 7, 1–10 (2004)

Otto MG, Mayer AD, Clavien PA, et al. Randomized trial of cyclosporine microemulsion (neoral) versus conventional cyclosporine in liver transplantation: MILTON study. Multicentre International Study in Liver Transplantation of Neoral. Transplantation 1998; 66:1632-40

Penninga L, Møller CH, Gustafsson F, SteinbruÈchel DA, Gluud C. Tacrolimus versus ciclosporin as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. Eur J Clin Pharmacol. 2010; 66(12):1177±87. doi: 10.1007/s00228-010-0902-6 PMID: 20882273

Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the PBAC. (Version 4.3). Australian Government, Department of Health and Ageing, December 2008.

Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009;9(11):2597–2606.

Pruthia R, Steenkamp R, Feest T. UK Renal Registry 16th Annual Report: Chapter 8 Survival and Cause of Death of UK Adult Patients on Renal Replacement Therapy in 2012: National and Centre-specific Analyses. Bristol: UK Renal Registry. 2013.

Ray KW, Brown RS, Terrault NA, Hashem ES. Burden of liver disease in the United States: summary of a Workshop. Hepatology. 2002; 36:227–42.

Ruhl CE, Sayer B, Byrd-Holt DE, Brown DM. Costs of digestive diseases. In: Everhart J, ed. *The Burden of Digestive Diseases in the United States*. Washington, DC: US Dept of Health and Human Services, Public Health Service, National Institutes of Health, and National Institute of Diabetes and Digestive and Kidney Diseases; 2008:137-143. NIH publication 09-6443.

Sabbatini M, Garofalo G, Borrelli S, et al. Efficacy of a reduced pill burden on therapeutic adherence to calcineurin inhibitors in renal transplant recipients: an observational study. *Patient Prefer Adherence*. 2014;8:73–81.

Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications. Kidney Int Suppl 2005:S7-S10.

Scott LJ, McKeage K, Keam SJ, et al. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs 2003; 63:1247–97

Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12(2):388–399.

Silva HT, Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *Am J Transplant*. 2007; 7(3): 595–608.

Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C, Khanthavit A. Factors influencing health-related quality of life in chronic liver disease. World J Gastroenterol 2006; 12:7786-7791.

Statistics and Clinical Audit, NHS Blood and Transplant. Organ donation and transplantation. Activity report 2013/14. 2014.

Steenkamp R, Castledine C, Feest T, Fogarty D. UK Renal Registry 13th Annual Report (December 2010): Chapter 2: UK RRT prevalence in 2009

Stegenga H, Jonsson P, Chambers M, Thwaites R,Garner S. GetReal: Real-World Evidence Navigator. Value and Outcomes Spotlight. July/August 2017 VOL. 3, NO.4: 15-17

Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney international. 2007; 72(1):92-9.

Studer, S.M., Levy, R.D., McNeil, K. & Orens, J.B. (2004) "Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and cost effectiveness" *European Respiratory Journal* 24: 674-685

Swanepoel CR, Wearne N, Okpechi IG. Nephrology in Africa–not yet uhuru. *Nat Rev Nephrol* 2013; 9:610–22.

Taatz C, Taylor P, Tett S. Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant .2001; 16:1905–9

Tanuseputro P, et al. The health care cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. PloS one 2015; 26: 10:e0121759

The US Multicentre FK506 Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 1994; 331:1110-15

Timmermann W, Erhard J, Lange R, Reck T, KoÈckerling F, MuÈ ller A, et al. A randomised trial comparing the efficacy and safety of tacrolimus with microemulsified cyclosporine after liver transplantation. Transplant Proc. 2002; 34(5):1516±8. PMID: 12176463

Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW. Transition from meeting abstract to full-length journal article for randomized controlled trials. JAMA. 2006; 295(11):1281±7. doi:10.1001/jama.295.11.1281 PMID: 16537738

Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant 2011; 11: 2093

Transplant activity in the *UK. NHS* Blood and Transplant. Activity report 2012/13. http://www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/activity_report_2012_13.pdf [last accessed 6 January 2014].

UK Renal Registry. The seventeenth annual report. December 2014. https://www.renalreg.org/wp-content/uploads/2014/12/05-Chap-05.pdf [last accessed 7 March 2015].

van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308:2584–93.

van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, et al. Generic and disease-specific health related quality of life of liver patients with various aetiologies: a survey. Qual Life Res 2007;16:375-388.

Watashi K, Ishii N, Hijikata M, Inoue D, Murata T, Miyanari Y, et al. Cyclophilin B is a functional regulator of hepatitis C virus RNA polymerase. Mol Cell. 2005; 19(1):111±22. doi: 10.1016/j.molcel.2005.05.014 PMID: 15989969

Wiesner RH, Fung JJ. Present state of immunosuppressive therapy in liver transplant recipients. Liver Transpl. 2011 Nov;17 Suppl 3:S1-9

Wells GA, Sultan SA, Chen L, et al. Indirect Evidence: Indirect Treatment Comparisons in Met-Analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Weng FL, Israni AK, Joffe MM *et al.* Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol. 2005; 16(6):1839-48.

What quality of life? The WHOQOL Group. World Health Organization Quality of Life Assessment. *World Health Forum.*1996; 17:354-356.

Winkelmayer WC, Weinstein MC, Mittleman MA, Glynn RJ, Pliskin JS. Health Economic Evaluations: The Special Case of End-Stage Renal Disease Treatment. Medical Decision Making. 2002; 22(5):417-30

Wolfe R, Ashby V, Milford E, Ojo A, Ettenger R, Agodoa L, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999; 341:1725-30.

Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341:1725–30.

Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess 2005;9(21).

Wu MJ, Cheng CY, Chen CH, et al. Lower variability of tacrolimus trough concentration after conversion from prograf to advagraf in stable kidney transplant recipients. Transplantation 2011; 92:648–52

Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. Am J Gastroenterol 2001;96:2199-2205.

Younossi, Z. and Henry, L. (2015), Overall health-related quality of life in patients with end-stage liver disease. Clinical Liver Disease, 6: 9–14. doi:10.1002/cld.480

Zilmer, JC. The economic burden of end stage renal disease in Canada. Kidney Int. 2007 Nov; 72 (9):1122-9