FEASIBILITY OF EXTENDED TREATMENT TIME ON HAEMODIALYSIS AND EFFECT ON PATIENT OUTCOMES

Thesis submitted for degree of Doctor of Philosophy

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ABSTRACT

The majority of patients requiring renal replacement therapy are dependent upon haemodialysis (HD). Although outcomes have improved significantly, the prognosis for patients reliant on HD remains sub-optimal.

To improve outcomes the focus has been on intensive dialysis regimens, primarily facilitated by more frequent or intermittent nocturnal HD but with limited results. Centres advocating extended treatment time (TT), along with international registries, have demonstrated an association between extended TT and improved patient outcomes. But, the feasibility and efficacy of providing extended TT within in-centre thrice weekly shift-based day-time dialysis has not been formally examined.

This thesis examines the effect of extended TT of 6 hours on thrice weekly HD versus standard TT of 4 hours in a prospective randomised cross-over study and demonstrates improved blood pressure control, nutritional status, patient experience and quality of life. This is despite both the 6-hour and 4-hour arms exceeding the minimum national dialysis dose target, as measured by a quotient of small molecule clearance, spKt/V. This finding challenges the accepted use of spKt/V as a single marker of adequate dialysis and promotes the use of a composite of meaningful patient-centred outcome measures alongside hard clinical endpoints.

To assess the feasibility of extended TT within shift based day-time HD provision the opinions of both local and national staff were surveyed. The survey results provided unique insights into the difficulties of limited slots contrasting with increasing patient numbers and the limited circumstances under which extended TT is prescribed. This is primarily in patients who would otherwise be under-dialysed, indicated by a below target spKt/V.

This thesis advances knowledge of the impact of extending TT as a means of intensifying HD prescription on markers of nutritional status, cardiovascular disease and patient experience. These findings justify incorporation of TT in HD quality standards.
ACKNOWLEDGEMENTS

I would firstly like to thank my supervisory team, Drs Peter Choi, Neill Duncan and Professor Charles Pusey for their very valuable advice and support. In addition, I am grateful to my friend Dr Albert Power for his challenging suggestions and encouragement throughout the study.

I am especially indebted to my academic supervisor, Professor Edwina Brown, who has been immensely supportive and helpful, providing me with the guidance needed to complete this study. Her ability to steer me in the right direction gave me the confidence to complete the process more positively than I would otherwise. I am extremely grateful for her pragmatic advice and ever open door.

I would also like to acknowledge the hard working team of nurses at all the participating haemodialysis units for their efforts in this study that have made this thesis possible, particularly Head Nurse Kathleen Lynch and the team at St Charles satellite unit whose enthusiasm and drive were very much appreciated.

I am also grateful to Professor Susan Procter whose advice on the qualitative data collection and analysis was invaluable, Dr Janet Lee’s team at the Leslie Brent laboratory who were very generous in allowing me to use their equipment and facilities and Dr Fabiana Gordon for providing statistical advice and analysis.

Finally I am so very grateful to my husband Baljinder, for all his help, not only in making this thesis presentable, but who together with my children, Jaspal and Jasnam, provided the balance to my day. I thank them for helping me keep the challenges in perspective, calming me on stressful days, and encouraging me to laugh – even if I was the subject of many of the jokes!
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PUBLICATIONS AND PRESENTATIONS

Peer-reviewed journals


Oral presentation at national conference


Poster presentations at national and international conferences


Analysis of my pilot data of incident haemodialysis patients at Imperial College Healthcare NHS Trust, found treatment time greater than 4 hours to be associated with improved patient survival. Following its presentation as a poster at the American Society of Nephrology Conference, San Diego, USA, November 2009, a study of treatment time (TT) and patient survival was provisionally considered at our local centre, but abandoned due to the large sample size required to demonstrate treatment effect.

In January 2010 Consultant Nephrologist, Dr Peter Choi, and I began designing a cross-over study to further investigate TT and used serum albumin, a marker of wellbeing, as the primary outcome measure. Patient experience and tolerance of extended TT was noted as an integral area of study and so health related quality of life (HRQoL) was included in the protocol. This clinical trial was submitted as part of an application to the National Institute of Health Research (NIHR) for a clinical academic doctoral training fellowship in June 2010, which was awarded in November 2010 and commenced in March 2011.

A patient outcomes research group chaired by my academic supervisor, Professor Edwina Brown, Professor of Renal Medicine and Consultant Nephrologist, Imperial College, London, adopted the trial and acted as a steering committee. The group advised the protocol be amended to include body composition analysis as well as assessment of post-dialysis fatigue (PDF), measured by time to recovery (TTR). Patient interviews for qualitative analysis were also included to more robustly address the issue of patient experience.
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Appendix 2: Local Ethics R&D approval letter

Appendix 3: Ethics amendment approval letter to include a withdrawal questionnaire

Appendix 4: Ethics amendment approval letter to include a blood flow control group
DECLARATION OF ORIGINALITY

Except where acknowledged, I declare that this thesis is entirely my own work and is based upon research carried out in Renal and Transplant Services, Imperial College Healthcare NHS Trust, London, during my clinical academic doctoral training fellowship.

All screening, recruitment and investigations were conducted solely by me, except the laboratory assays, where I centrifuged and stored samples for batch analysis by the main pathology laboratory at Hammersmith Hospital, London.

All basic statistical analyses were performed by me and were verified by an independent statistician. In the case of more complex statistical models, an independent statistician carried out the analysis including sample size calculation.
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## ABBREVIATIONS AND ACRONYMS

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<tr>
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<th>Full Form</th>
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<tr>
<td>AAMI</td>
<td>Association of Advancement of Medical Instruments</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>Angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td>AIIA</td>
<td>Angiotensin II antagonists</td>
</tr>
<tr>
<td>ANZDATA</td>
<td>Australian and New Zealand Dialysis and Transplant Registry</td>
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<tr>
<td>AVF</td>
<td>Arterio-venous fistula</td>
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<tr>
<td>BCM</td>
<td>Body cell mass</td>
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<tr>
<td>BFR</td>
<td>Blood flow rate</td>
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<td>BHS</td>
<td>British Hypertension Society</td>
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<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BNP</td>
<td>B-type natriuretic peptide</td>
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<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson comorbidity index</td>
</tr>
<tr>
<td>CHANCE</td>
<td>Chronic Haemodialysis and New Cardiac Markers Evaluation</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>cTNI</td>
<td>Cardiac troponin I</td>
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<tr>
<td>CVC</td>
<td>Central venous catheter</td>
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<tr>
<td>DFR</td>
<td>Dialysis flow rate</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DOPPS</td>
<td>Dialysis Outcomes Practice Patterns Study</td>
</tr>
<tr>
<td>ECW</td>
<td>Extracellular water</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetra-acetic acid</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ERD</td>
<td>Established renal disease</td>
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<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
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<tr>
<td>eKt/V</td>
<td>equilibriated Kt/V</td>
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<tr>
<td>FFM</td>
<td>Fat-free mass</td>
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<td>FHN</td>
<td>Frequent haemodialysis network</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>GI</td>
<td>Gastro-intestinal</td>
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<td>HD</td>
<td>Haemodialysis</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HEMO</td>
<td>Hemodialysis study</td>
</tr>
<tr>
<td>HGS</td>
<td>Hand-grip strength</td>
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<tr>
<td>hs-CRP</td>
<td>High-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>IDH</td>
<td>Intra-dialytic hypotension</td>
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<tr>
<td>IDWG</td>
<td>Intra-dialytic weight gain</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
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<tr>
<td>IQR</td>
<td>Inter-quartile range</td>
</tr>
<tr>
<td>ISRNMM</td>
<td>International Society of Renal Nutrition and Metabolism</td>
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<tr>
<td>KDQoL-36</td>
<td>Kidney disease quality of life-36 questionnaire</td>
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<tr>
<td>Kt/V</td>
<td>Dialysis adequacy quotient</td>
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<tr>
<td>LP</td>
<td>Volume of blood processed</td>
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<td>LVH</td>
<td>Left ventricular hypertrophy</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MCS</td>
<td>Mental health composite score</td>
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<tr>
<td>MIA syndrome</td>
<td>Malnutrition inflammation atherosclerosis syndrome</td>
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<tr>
<td>MIS</td>
<td>Malnutrition inflammation score</td>
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<tr>
<td>MPO</td>
<td>Membrane permeability outcome study</td>
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<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>NCDS</td>
<td>National Cooperative Dialysis Study</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NRES</td>
<td>National Research Ethics Service</td>
</tr>
<tr>
<td>PA</td>
<td>Phase angle</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical health composite score</td>
</tr>
<tr>
<td>PD</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>PDF</td>
<td>Post dialysis fatigue</td>
</tr>
<tr>
<td>PEW</td>
<td>Protein energy malnutrition</td>
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<tr>
<td>pmp</td>
<td>Per million population</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<td>SGA</td>
<td>Subjective global assessment</td>
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<tr>
<td>spKt/V</td>
<td>Single pool Kt/V</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>-----------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>TAC&lt;sub&gt;urea&lt;/sub&gt;</td>
<td>Time averaged concentration of urea</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour necrosing factor-alpha</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial master folder</td>
</tr>
<tr>
<td>TT</td>
<td>Treatment time</td>
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<tr>
<td>TTR</td>
<td>Time to recovery</td>
</tr>
<tr>
<td>UF</td>
<td>Ultrafiltration</td>
</tr>
<tr>
<td>UFR</td>
<td>Ultrafiltration rate</td>
</tr>
<tr>
<td>UKM</td>
<td>Urea kinetic modelling</td>
</tr>
<tr>
<td>URR</td>
<td>Urea reduction ratio</td>
</tr>
<tr>
<td>V</td>
<td>Urea distribution volume</td>
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</table>
CHAPTER 1

1 INTRODUCTION

1.1 Overview of chronic kidney disease

Chronic kidney disease (CKD) is defined as impaired function and or structure for a sustained period of time by the National Institute for Health and Care Excellence (NICE) Guideline 182. This is classified into 5 stages indexed by glomerular filtration rate (GFR) Table 1-1.

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<th>Stage</th>
<th>eGFR (ml/min/1.73m²)</th>
<th>Function</th>
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<td>G1</td>
<td>&gt;90</td>
<td>Normal</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mild decrease</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mild to moderate decrease</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderate to severe decrease</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severe decrease</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Table 1-1: Classification of stages of chronic kidney disease

Adapted from NICE clinical guideline 182

CKD stage G5 refers to irreversible kidney failure and may either be treated conservatively with symptom control or renal replacement therapy (RRT). The adult prevalence in the UK for requirement of RRT is 861 per million populations (pmp) which represents a 64% increase from the 523 pmp rate in 2000. The preferred mode of RRT is transplantation with its superior clinical outcomes, but this accounts for only half of patients presenting with established renal disease (ERD) (Eloot, Van Biesen et al.), the remaining are reliant upon some form of dialysis.

Dialysis is a life-sustaining treatment which attempts to replace endemic kidney function, and so maintain electrolyte and fluid homeostasis by the removal of solutes.
1.2 Treatment of established renal disease with haemodialysis

The majority of patients are treated with haemodialysis (HD) in-centre on a thrice weekly basis, with smaller numbers on peritoneal dialysis (PD) or home HD, Figure 1-1.

**Figure 1-1: Increase in modes of RRT in prevalent UK population (1997-2013)**

HD involves the diffusion of solutes and fluid across a semi-permeable membrane between patient blood and a buffer solution, dialysate. A counter-current flow, where the blood in the extracorporeal circuit is flowing in the opposite direction to the dialysate maintains a concentration gradient maximising movement of solutes across the membrane, Figure 1-2.

**Figure 1-2: Diagram of movement of solutes by diffusion**

Fluid is removed by ultrafiltration (UF), creating a transmembrane pressure gradient between blood and dialysate compartments causing free water and some dissolved solutes to move across the membrane.
HD is routinely performed thrice weekly and the efficiency of each treatment session may be varied by altering the:

1. Length, treatment time (TT).
2. Osmotic gradient, difference between the dialysate and blood flow rate.
3. Porosity and surface area of the semi-permeable membrane or dialyser.

A HD prescription specifies each of these three components and their sub parts.

Our practice is to increase TT only when all other treatment variables, blood flow rate (BFR), dialysate flow rate (DFR) and increasing dialyser size have been maximised. Currently 53% of our patients are dialysed for 4 hours.

1.3 Dialysis prescription and adequacy

As TT is a composite of the HD prescription, it is important to explore the parameters that constitute adequate dialysis and appraise current methods of quantifying and prescribing HD. The accuracy and power of accepted markers of dialysis adequacy also affect how TT is prescribed. A description of early dialysis treatments facilitates an understanding of how markers of dialysis adequacy have evolved and allows critical review.

1.4 Early history of uraemia and dialysis

Kidney disease and its associated clinical signs and symptoms were first termed, uraemia by Christison in 1829. This was reiterated in 1836 by Richard Bright, when a small molecular weight solute, urea, was implicated as the major retention solute in kidney disease.

Uraemia literally translates to “urine in the blood” and it was so called due to accumulation in the blood of solutes normally excreted by the kidneys (Depner 2001). Although it was first noted by Vaquelin in 1821 that urea itself was not toxic, its high concentration in patients with kidney disease was perceived as an implication that it was the primary toxin of uraemia. A review of the history of treatment of early uraemia suggests this theory was challenged early on when there was found to be no correlation between blood urea concentration and severity of clinical signs and symptoms of kidney disease (Richet 1988).

As other solutes accumulating in kidney disease were identified, a search for methods of removing these toxins and so relieve the symptoms of uraemic syndrome began. The first use of the term
“dialysis” was by Thomas Graham in 1854 who conducted experiments demonstrating the diffusion of solutes across a semi-permeable membrane (Gotch, Sargent et al. 2000). Application of this process to remove active solutes from the circulating blood of animals was defined as “vividiffusion” by Abel in 1913 and was reported in the New York Times January 18, 1914 (Eknoyan 2009):

“The wonderful apparatus devised by John Hopkins Physicians is called the artificial kidney because it removes the undesirable constituents of the blood as that organ does.”

But the first amelioration of the clinical symptoms of uraemia in humans using an extracorporeal blood dialyser called an “artificial kidney” was conducted more than 20 years later by Willem Kolff treating patients with acute kidney disease. The artificial kidney consisted of cellophane tubing wound around a drum immersed in dialysis solution, the rotation of the drum directed blood flow in the absence of a blood pump. Figure 1-3 shows the original Kolff rotating drum dialyser.

![Figure 1-3: Nurse Maria ter Welle modelling the first artificial kidney in the Netherlands](http://www.lib.utah.edu/collections/photo-exhibits/willem_kolf.php)

However, the thick cellophane membranes that were used were noted to have only negligible clearance of large molecules and so the reversal of uraemic coma was widely attributed to the removal of low molecular weight solutes, of which urea was the most abundant (Kolf 1944), although Kolff commented:

“Urea is at the utmost only partly co-responsible for the clinical symptoms of uraemia but nevertheless we chose it as a measure for the results of the dialyses. Smaller molecules will dialyse more rapidly and bigger ones less so.”

Despite this awareness of the limitations of urea as generic marker of dialysis, the percentage of urea extracted continued to be used to gauge the quantity of dialysis delivered. The association of high urea levels with severity of uraemic syndrome and worsening kidney disease led not only to
promote dialysis as a means of urea removal but also the employment of dietary measures in a bid to decrease urea generation. As urea was an end product of protein catabolism, conservative dietary management of uraemic syndrome involved restriction of protein with energy requirements being met by carbohydrate from sugars and fat from butter. But the level of protein restriction was noted as being “yet to be determined” (Borst 1948).

The Kolff dialysis machine was modified following collaboration with a team from the Peter Bent Brigham Hospital in Boston to facilitate sterilisation of the dialyser, allow blood sampling, temperature control and most importantly increase surface area of cellophane in contact with blood. The modified apparatus was then renamed the Kolff-Brigham artificial kidney (Nissenson and Fine 2005). The impact of increasing surface area on large molecular weight solute clearance was noted and eventually led to the introduction of sheet or flat plate dialysers which paired the high extraction of solutes with less resistance to blood flow (Scribner, Caner et al. 1960, Twardowski 2008).

The first successful treatment of two patients suffering from uraemia secondary to chronic glomerulonephritis with intermittent dialysis was by Scribner in 1960. He described the dialysis sessions of 24 to 60 hours duration with 4 to 6 layers of flat plate or sheet dialysers and inter-dialytic intervals ranging from 4 to 21 days (Scribner, Buri et al. 1960). But recovery from symptoms was short lived and repeated HD sessions were necessary. Despite acceptable levels of blood urea nitrogen the control of symptoms associated with uraemic syndrome was sub-optimal. This served to increase speculation that the major uraemic toxins were of significantly larger molecular weight, approximately 1-2kDa, than urea. These molecules were not adequately removed by the Cuprophan membranes used at that time.

1.4.1 The middle molecule hypothesis

Speculation regarding the role of molecules which because of their size offered resistance to diffusion (Scribner, Fergus et al. 1965) and so were not readily removed on dialysis led to the formulation of a hypothesis which proposed the existence of “middle molecules”. This was put forward following the observation that PD patients were well without symptoms of uraemic neuropathy despite significantly higher urea levels (Tenckhoff and Curtis 1970). It was argued that these middle molecules may be more easily transported across the peritoneal membrane than the cellophane HD membranes. The slower movement of the middle molecules was evidenced by repeated observations that symptoms of uraemic nephropathy were relieved by increasing the length of the dialysis session (Jebsen, Tenckhoff et al. 1967).
Albert Babb attempted to quantify the removal of these middle molecules and in so doing gave rise to the square metre hour hypothesis (Babb, Popovich et al. 1971). This hypothesis, generated from mathematical modelling, suggested that the amount of solute removed was related to the product of the dialyser surface area and the hours of dialysis per week using vitamin B12 as a surrogate for other middle molecules. He later developed the first quantitative description of “adequate dialysis” named the Dialysis Index which took into account body surface area, weekly dialysis time, middle molecule clearance and residual clearance.

In the absence of agreement on a definitive marker of adequate dialysis, under-dialysis was assessed primarily by clinical impression and so TT varied greatly with a number of studies highlighting the benefits of shorter dialysis schedules (Manji, Maeda et al. 1976, Trafford, Sharpstone et al. 1979) without any apparent ill effect. These studies highlighted the social and economic benefits:

“...patients have more free time and more patients can be treated with the same number of staff and dialysis stations. As in many areas there is a shortage of places for patients needing dialysis, a short regimen is recommended.”

So despite direct comparisons between long and short dialysis demonstrating poor creatinine clearance, symptom and blood pressure control in the latter, shorter treatment times continued to be advocated (Alvarez-ude, Ward et al. 1976).

To address the absence of an agreed standard for dialysis adequacy, a conference on dialysis adequacy was held in California, USA, in 1974, sponsored by the Artificial Kidney Chronic Urea Program (Lowrie 1983). The need for a prospective randomised controlled trial (RCT) to determine adequate dialysis dose was established and a multi-centre clinical trial, the National Cooperative Dialysis Study (NCDS) was commenced.

### 1.4.2 Urea kinetic modelling and the National Cooperative Dialysis Study

The urea kinetic model (UKM) was put forward by Gotch & Sargent to describe dialysis quantity and so facilitate prescription of a dose of dialysis. This was based on dietary protein and kinetic analysis of its metabolite, urea nitrogen (Gotch, Sargent et al. 1976). This mathematical description of the rate of change of urea concentration in the body over time permitted calculation of the volume of urea distribution and net urea generation rate.
The model assumed a single body compartment or pool, avoiding the need to account for the rebound resulting from inter-compartmental transport, see Table 1-2. This model was employed to guide dialysis dose and was used to quantify TT so that blood urea concentrations were held within what was considered to be an acceptable range.

Table 1-2: Patient and treatment variables used in the urea kinetic model

<table>
<thead>
<tr>
<th>Patient-related variables</th>
<th>Dialysis-related variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of urea distribution</td>
<td>TT and frequency</td>
</tr>
<tr>
<td>Protein catabolism</td>
<td>Blood flow rate</td>
</tr>
<tr>
<td>Residual renal function</td>
<td>Dialyser clearance</td>
</tr>
<tr>
<td>Vascular access recirculation</td>
<td>Dialyser flow rate</td>
</tr>
<tr>
<td>Inter-dialytic weight gain</td>
<td>Ultrafiltration</td>
</tr>
</tbody>
</table>

The NCDS employed this model to examine small and middle molecular weight solute clearance. Urea was used as a generic low molecular weight solute and TT served as a marker of middle molecule clearance. The theoretical assumptions of the study were that the toxicity of low molecular weight solutes was directly proportional to urea and that the generation rate identical to urea.
Patients were randomised to one of four experimental groups and dialysis dose was gauged by blood urea nitrogen concentration (BUN) (Lowrie, Laird et al. 1983), see Table 1-3. To control for variance in urea levels with longer weekend and shorter mid-week dialysis-free periods, the pre- and post-urea concentrations were mathematically modelled to generate a time averaged concentration of urea ($TAC_{urea}$) (Sargent 1983).

**Table 1-3: Control parameters for experimental groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Experimental control</th>
<th>Treatment time (hours)</th>
<th>Pre-dialysis mid-week BUN (mg/dl)</th>
<th>Time averaged BUN (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>4.5-5</td>
<td>60-80</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>High BUN</td>
<td>4.5-5</td>
<td>110-130</td>
<td>100</td>
</tr>
<tr>
<td>III</td>
<td>Short time</td>
<td>2.5-3.5</td>
<td>60-80</td>
<td>50</td>
</tr>
<tr>
<td>IV</td>
<td>High BUN and short time</td>
<td>2.5-3.5</td>
<td>110-130</td>
<td>100</td>
</tr>
</tbody>
</table>

The patients were modelled in a lengthy pre-randomisation phase to achieve an individualised set of dialysis parameters which would facilitate the specific mid-week BUN specified within the protocol. Early data demonstrated that group IV had significantly higher mortality than other groups and so this intervention was removed from the protocol. Also these deaths occurred following withdrawal from the study and return to usual dialysis prescription and so it was concluded that the detrimental effects of high $TAC_{urea}$ were long term.

The main findings of the study were that primary failure, categorised by death, and secondary failure, categorised by morbidity or hospitalisation, were independently associated with older age and high prevalence of hospitalisation prior to enrolling in study; shorter dialysis TT; and high BUN/$TAC_{urea}$. But low BUN was only protective if protein intake was adequate. The probability of failure was highest in those with lowest protein intakes <0.8g/kg/day irrespective of BUN or $TAC_{urea}$ (Lowrie, Laird et al. 1981).
A mechanistic analysis was conducted which expressed quantity of dialysis as total treatment clearance of urea as a fraction of body water, Kt/V, a dimensionless quotient representing dialyser urea clearance (K), TT and urea distribution volume (V).

The Kt/V model facilitated a diagrammatic representation of the conclusions of this mechanistic analysis, produced by analysing carbon dioxide concentration, as an indirect measure of blood urea levels, against protein catabolism and Kt/V, see Figure 1-4. Domain A and B were undefined in order to conform to study design with prescribed Kt/V increasing linearly with dietary protein intake. Therefore there were no patients with dietary protein intake <0.8g/kg/day (Groups I & II) and prescribed Kt/V>0.8, equally patients prescribed high Kt/V 0.8 did not have high BUN levels. Domain E was designated as adequate with respect to prescribed Kt/V between 0.9-1.5 and protein intake 0.8-1.4g/kg/day.

![Figure 1-4: Probability of failure domains NCDS](Adapted from (Gotch and Sargent 1985))

This analysis suggests a “step-like” relationship between Kt/V and morbidity and mortality, with probability of failure highest with Kt/V <0.8 and no improvement between Kt/V 0.9-1.5 (Shinaberger 2001).
However, analysis of a more complete dataset revealed that the relationship was continuous and that there may be some benefit from increasing Kt/V above 0.9, r=0.86 and is illustrated in Figure 1-5 (Keshiviah 1993).

![Figure 1-5: Step and continuous relationship between Kt/V and probability of failure](image)

(Adapted from Keshiviah 1993)

Relative to the dominant effect of high TAC$_{\text{urea}}$ on probability of failure the effects of TT although large, 80% higher in the short-time groups, III and IV, than long-time groups, traditional tests of significance proved inconclusive with p value of 0.06 (Chertow, Kurella et al. 2006).

The absence of proven benefit of longer TT supported the continued use of short-time dialysis treatments whose efficiency or adequacy was gauged by Kt/V. Although some centres such as Tassin, France, persisted with long nocturnal dialysis treatments professing improved blood pressure control and prolonged patient survival (Charra, Calemard et al. 1983), new studies suggested comparable survival rates achieved with high efficiency dialysis facilitated by shorter TT of 9 hours per week (Rubin and Berlyne 1987).

1.4.3 Evolution of the single pool Kt/V model to derive simplified equations

However, the arithmetic was complicated and necessitated computerised calculation in addition to clinical dialysis data as well as blood sampling at three time points for urea concentration. Therefore simplified equations were sought to allow clinical usage and assist dialysis prescription without formal UKM analysis.
The simplest of these was the urea reduction ratio (URR).

\[
URR = 1 - \frac{C_1}{C_0}
\]

Where \( C_0 \) = Pre-dialysis urea concentration and \( C_1 \) = Post-dialysis urea concentration.

The percentage reduction of urea, introduced by Lowrie & Lew in 1991 was found to correlate closely with Kt/V despite the absence of any correction for UF and had the advantage of being easily measured (Sherman, Cody et al. 1995). The URR does not facilitate evaluation of sampling errors nor take into account UF and so its interpretation should be limited.

Logarithmic equations were algebraic representations of the UKM simplified to account for UF (Daugirdas 1995). However, these require nearly all the data collection as formal UKM analysis minus the third urea sample to assess urea generation. The absence of formal calculation of urea distribution volume means that like URR, post-urea sampling errors may be overlooked.

\[
sp\text{Kt/V}_{\text{urea}} = -\ln(R-0.008*TT) + (4-3.5*R) \frac{UF}{W}
\]

Where \( R \) = post/pre urea ratio, \( TT \) = treatment time, \( UF \) = ultrafiltration volume and \( W \) = post weight.

The single pool model assumes urea distribution is equivalent to total body water and that this is a single compartment whose concentration is in equilibrium both during and after dialysis. It is assumed that the compartment is of variable volume, that is, it expands and contracts evenly during inter- and intra-dialytic periods. But in reality this is not the case and the flux between the intracellular and extracellular compartments infers some inaccuracies to the calculation of urea distribution volume (Daugirdas and Smye 1997). This is particularly true of high efficiency dialysis where there is a rapid initial decrease in blood urea and an equally rapid post-dialysis increase and \( V \) is underestimated. As a result the Kt/V quotient is artificially elevated. This led to the advent of an equilibrated Kt/V (eKt/V) which used double pool kinetic modelling incorporating a correction factor to account for the rebound in urea post dialysis (Daugirdas, Greene et al. 1999). The Tattersall equation, below, suggested that standard spKt/V could be corrected by multiplying by \( t/(t+40) \) and is based on comparison of Kt/V calculated using blood urea samples taken 60-minutes post dialysis (Tattersall, DeTakats et al. 1996).

\[
e\text{Kt/V} = sp\text{Kt/V} \frac{t}{(t+40)}
\]

Where \( t \) = time on dialysis
An examination of the different equations used to simplify assessment of dialysis dose has generated a spectrum of results from eKt/V, spKt/V to urea reduction ratio, underlining the need for a consensus not only on what is deemed to be adequate but also on which calculation should be applied (Movilli 1996).

To facilitate comparison of frequent dialysis regimens the concept of a standard weekly Kt/V has been developed. This has the advantage of also quantifying and comparing with intermittent and continuous dialysis therapies such as peritoneal dialysis (Diaz-Buxo and Loredo 2006). A simplified two-step approach based on conversion of spKt/V calculated from pre and post urea treatment sampling to eKt/V and using this to construct nomograms for different treatment frequencies (Leypoldt, Jaber et al. 2004).

\[
\text{Standard Kt/V} = \frac{168(1-\exp \left[ -\frac{\text{ekt/V}}{t/60} \right])}{(1-\exp \left[ -\frac{\text{eKt/V}}{\text{eKt/V} + (168/N)/(t/60) - 1} \right])}
\]

Where \( t \) = treatment time in minutes and \( N \) = number of treatments per week

Despite the improvement in application and accuracy of these equations they still do not acknowledge the limitation of application to solutes that do behave differently from Urea (Meyer, Sirich et al. 2011).

1.4.4 Suggested influence of dialysis prescription on patient survival rates

A national analysis of random sample of more than 600 patients in the United States brought into question the reported survival rates with short treatment length, demonstrating significantly higher 3-year mortality risk for those dialysed for less than 3.5 hours per session (Held, Levin et al. 1991).

Concern grew when this finding was associated with poor achievement of the accepted measure of dialysis adequacy; 53% of patients were prescribed Kt/V <1.0 (Blagg 1993) and patients in the US were also found to have lower rates of survival than those in Europe and Japan (Held, Brunner et al. 1990). This led for the call to re-examine HD adequacy and a symposium on morbidity, mortality and prescription of dialysis was held to address this in Dallas, USA, 1989.

One of the conclusions of the symposium was that TT was strongly correlated to dialysis dose as measured by Kt/V and that Kt/V less than 1 correlated with TT less than 3.5 hours (Gotch, Yarian et al. 1990). However, rather than underlining the importance of TT this finding was further used to reinforce the reliance upon Kt/V as a measure of adequate dialysis.
HD prescription was very intuitive and largely based on BUN levels so that patients with low BUN secondary to poor protein intake often had dialysis TT shortened because it was assumed that this was secondary to a decreased need for dialysis (Hull and Parker lli 1990). Furthermore it was also confirmed that delivered dialysis dose was up to 20% less than prescribed and that regular quantitative assessment of dose using UKM would serve to identify delivery of dialysis below prescription target and should be conducted regularly (Sargent 1990). These recommendations led to the commissioning of the Haemodialysis (HEMO) study to investigate the relationship between dialysis dose and mortality.

In the interim, during the 1990s, a number of observational studies highlighted the positive effect of increasing dialysis dose on mortality and was confirmed in later studies (Owen, Lew et al. 1993, Hakim, Breyer et al. 1994, Bloembergen, Stannard et al. 1996, Held, Port et al. 1996, Port, Pisoni et al. 2004, Singh, Choi et al. 2013).
HEMO, the large prospective multicentre RCT reviewing HD dose, compared a standard versus high
dialysis dose but failed to find a survival benefit (Eknoyan, Beck et al. 2002). Table 1-4 highlights the
difference in TT and dialysis dose of the high and standard dose arms in this study.

<table>
<thead>
<tr>
<th></th>
<th>Prescribed standard dose (Delivered)</th>
<th>Prescribed high dose (Delivered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>spKt/V</td>
<td>1.25 (1.32)</td>
<td>1.65 (1.71)</td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.05 (1.16)</td>
<td>1.45 (1.53)</td>
</tr>
<tr>
<td>URR (%)</td>
<td>65.0 (66.3)</td>
<td>75.0 (75.2)</td>
</tr>
<tr>
<td>TT (mins)</td>
<td>190 ± 23</td>
<td>219 ± 23</td>
</tr>
</tbody>
</table>

The limited separation between the standard and high dose arms and small increase in TT was noted but it was concluded that there was no justification to increase recommendations for minimum dialysis dose. For the first time there was some consensual acknowledgement that small solute clearance as measured by Kt/V may not be the optimal guide to gauge dialysis adequacy. Uraemic symptoms and poor outcomes persist in patients who are seemingly well dialysed and achieving target Kt/V.

1.4.5 Methods of intensifying dialysis

Since this hallmark study, the need to “intensify” dialysis as a strategy to improve patient survival has been highlighted (Kliger 2009). The negative outcomes of uraemia are not limited to urea clearance alone but relate to many factors including hypertension, volume control, anaemia, malnutrition and comorbidity. Therefore, intensive forms of dialysis need to address these significant factors (Locatelli and Canaud 2012) appropriately.

Methods of intensifying dialysis involving maximising clearance by using larger membranes, which more effectively remove the many other retention solutes of uraemia, and increasing blood and dialysate flow rates can be implemented with relative ease and so have already been tried. However, increasing dialysis frequency and or duration is more complex.
1.4.6 High flux dialysis

Advances in technology have resulted in design of high flux dialysis membranes. These have the advantage of increased pore size facilitating both improved clearance of uraemic retention solutes and biocompatibility with reduced induction of inflammatory mediators (Clark, Hamburger et al. 1999). Observational studies have related the improved clearance of middle molecules in high flux dialysis to lower mortality (Woods and Nandakumar 2000, Port, Wolfe et al. 2001). Additionally improved clearance of middle molecule B2-microglobulin (Pickett, Cruickshank et al. 2002) may be associated with a benefit in the progression of amyloidosis and bone disease (Drueke 2000, Dember and Jaber 2006). The increase in pore size also promotes faster removal of fluid and to avoid sudden changes blood pressure replacement fluid is used to control ultrafiltration more accurately but due to the risk of transporting contaminants or endotoxins from the dialysate higher standards of water quality are necessary than for low flux dialysis (Schiffl 2011).

However this has not been substantiated in RCTs. The HEMO study randomised patients to high or low flux dialysis with significantly higher clearance of B2-microglobulin on the high flux arm. Although total mortality was not significantly changed post hoc analysis suggested there was a reduction in RR of death and hospitalisation secondary to cardiac disease (Eknoyan, Beck et al. 2002). But the HEMO study was criticised for enrolling relatively fitter prevalent patients who had been treated with high flux dialysis prior to recruitment. Therefore the Membrane Permeability Outcome (MPO) study was designed to recruit incident patients who had greater mortality risk. Although the study failed to demonstrate an overall survival benefit for all patients treated with high flux membranes, at risk patients at time of recruitment, defined by serum albumin levels <40g/dl, benefited from a 37% decrease in mortality and post hoc suggested positive outcomes for diabetics (Locatelli, Martin-Malo et al. 2009).

A systematic review was in agreement with both European and international guidelines recommending the use of high flux dialysers for patients with high mortality risk and long dialysis vintage (Tattersall, Canaud et al. 2010, Palmer, Rabindranath et al. 2012).

1.4.7 Increasing dialysis frequency

The rationale for increasing frequency was primarily to remove the peak concentration profile seen prior to HD that is the hallmark of intermittent HD. This is particularly significant before the first HD session of the week (Locatelli, Buoncristiani et al. 2005).
Increasing the frequency of dialysis avoids the high levels of water and solute retention which are causative of intra- and inter-dialytic symptoms. Daily HD avoids the high solute peaks of intermittent HD and as inter-dialytic weight gains are significantly lowered fluid removal on HD is more gradual with lower ultrafiltration rate (UFR).

Daily dialysis regimens tend to be of short-term duration, 2 to 2.5 hours per week, and have been investigated by the Frequent Haemodialysis Network (FHN) group. Patients averaged more than 5 sessions per week resulting in a decrease in hazard ratio for the co-primary endpoints of death or change in physical health score (Chertow, Levin et al. 2010) but there was an observed increase in vascular access complications. Other studies have demonstrated improvement in blood pressure control (Woods, Port et al. 1999), nutritional intake (Galland, Traeger et al. 2001) and quality of life (Heidenheim, Muirhead et al. 2003).

1.4.8 Increasing treatment time

The group from Centre de Rein Artificiel de Tassin, France, has been championing their experience of long TT for over 30 years. The group reports good patient survival rates of 87%, and 43% at 5 and 20 years respectively (Charra, Calemard et al. 1992). These laudable mortality rates are attributed to improved cardiovascular mortality accompanied by better blood pressure control achieved through optimal fluid management (Charra, Calemard et al. 1983).

Longer TT facilitates lower UFRs and consistent achievement of dry weight with reduced episodes of intra-dialytic hypotension (Kurella and Chertow 2005). The importance of low UFRs has been reinforced by analysis of Dialysis Outcomes and Practice Patterns Study (DOPPS) data (Saran, Bragg-Gresham et al. 2006) demonstrating the lowered mortality risk associated with increased TT and inversely that increased UFR above 10ml/min/kg were associated with higher mortality risk (Flythe and Brunelli 2011).

The benefit of longer TT may also be related to improved clearance of solutes of higher molecular weight or those that are protein bound (Eloot, Van Biesen et al. 2008) and move slowly from intracellular spaces to the blood (McFarlane 2009). It is ironic that these molecules are more likely to contribute to the symptoms of uraemia than urea and their clearance is more dependent upon TT and their concentration remains high during dialysis and yet urea removal continues to be a primary arbiter for dialysis prescription change. In quantifying dialysis dose by removal of urea which is a small molecule that rapidly diffuses across the dialysis membrane, the possible benefits of longer TT may have been masked (Kliger 2009).
There are a number of observational studies primarily from international registries that have demonstrated an improvement in risk of death with increased TT (Marshall, Byrne et al. 2006) (Lacson, Wang et al. 2010, Ok, Duman et al. 2011) (Tentori, Zhang et al. 2012). However, these are primarily nocturnal HD and the use of longer TT within thrice weekly in-centre HD has not been formally assessed in a RCT.

1.5 Nutritional status on haemodialysis

Protein energy wasting (PEW) is common in HD patients with prevalence rates of between 30-50% being cited. Its association with increased mortality and morbidity has ensured the importance of PEW as a key issue (de, Grootendorst et al. 2008) in patient outcomes on HD. In fact in a cohort of non-dialysis dependent patients with CKD, predominantly stage 3 and 4, 83% were found to have at least one marker of PEW and similar associations with mortality were exhibited as in dialysis populations. But unlike the general population, patients with kidney failure demonstrate a paradoxical relationship with traditional mortality risk factors referred to as the reverse epidemiology, where higher body mass index (BMI) is protective (Kalantar-Zadeh, Block et al. 2003).

According to the International Society of Renal Nutrition and Metabolism (ISRNRM) guidelines, assessment of nutritional status and diagnosis of PEW should be made using at least three of the four criteria: serum biochemistry, measures of body mass, measures of muscle mass and dietary intake. Diagnosing PEW can be difficult and measures have their limitations, for example hypoalbuminaemia can be secondary to decreased albumin production and not represent PEW. Similarly weight or BMI maybe confounded by fluid gain. Hence the recommendation that a minimum of three criteria be used ensures some degree of accuracy. Composite scores which facilitate this have also been established, and are an amalgamation of different measures (Kovesdy, George et al. 2009). Examples of such composite stores are discussed later in this chapter, section 1.5.2.

1.5.1 Malnutrition inflammation atherosclerosis syndrome and nutritional status

Higher concentrations of pro-inflammatory cytokines are associated with increased mortality and hospitalisation (Kalantar-Zadeh, Block et al. 2004) and are predictors of cardiovascular events (Zyga, Christopoulou et al. 2011).

Coronary disease is accelerated by inflammatory cells which proliferate and infiltrate vessel walls resulting in atherosclerosis and stenosis (Kalantar-Zadeh, Ikizler et al. 2003). Three clinical entities malnutrition, inflammation and atherosclerosis coexist and their constant interaction mediated by
inflammatory cytokines has suggested the presence of a syndrome termed the malnutrition inflammation atherosclerosis (MIA) (Fearon, Takagi et al.) (Fearon, Takagi et al.) syndrome (Stenvinkel 2001) (Stenvinkel, Heimburger et al. 2000).

Pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumour necrosing factor-alpha (TNF-α) promote malnutrition by instigating appetite loss, delayed gastric emptying and breakdown of skeletal muscle protein (Beberashvili, Sinuani et al. 2011). Similarly IL-6 promotes atherogenic processes, increasing fibrinogen release, promotes pro-coagulator effects of platelets and by increasing release of endothelial adhesion molecules (Papagianni, Kalovoulos et al. 2003) is associated with increased carotid intimal media thickness (Kato, Odamaki et al. 2002).

The factors that give rise to both inflammation and malnutrition overlap and are all interceded by TNF-α, IL-6 and acute phase proteins, triggering atherosclerotic cardiovascular disease Figure 1-6 (Bergstrom and Lindholm 1998, Kalantar-Zadeh, Ikizler et al. 2003).

![Diagrammatic representation of the interplay of factors in MIA syndrome](image)

**Figure 1-6: Diagrammatic representation of the interplay of factors in MIA syndrome**

Adapted from (Stenvinkel, Heimburger et al. 2000)

The presence of all three risk factors: malnutrition, inflammation, and cardiovascular disease has been demonstrated to increase 3-year mortality to 75% (Qureshi, Alvestrand et al. 2002). Therefore surrogate markers of inflammation, malnutrition and cardiovascular disease may be useful in quantifying the impact of longer TT.

### 1.5.2 Malnutrition inflammation score

The malnutrition inflammation score (MIS) (Miskulin, Meyer et al.) evolved from a semi-quantitative validated technique, Subjective Global Assessment (SGA) (Beberashvili, Sinuani et al.) that combined
clinical assessment and objective measurement of nutritional status (Riella 2013) taking into consideration weight loss, gastrointestinal symptoms, dietary intake functional capacity and comorbidity. These factors were paired with clinical assessment of the patient by assessing subcutaneous fat and muscle wasting and the components scored A, B, C denoting well-nourished to severely malnourished (Detsky, McLaughlin et al. 1987).

The SGA was modified to include biochemical markers serum albumin and iron binding capacity as well as body mass index (BMI) and gave rise to the MIS (Kalantar-Zadeh, Kleiner et al. 1999). This new scoring system recognised the role of inflammation in protein energy wasting of HD patients.

The MIS has been shown to correlate with mortality and hospitalisation and may be superior to SGA in assessing nutritional status (Kalantar-Zadeh, Kopple et al. 2001). The MIS is associated with 5-year mortality in HD patients and its predictability of mortality is thought to be equivalent to more established surrogates of death risk (Rambod, Kovesdy et al. 2008). There are however a lack of controlled trials that examine changes in the MIS following intervention, with clinical outcomes.

1.5.3 Hand-grip dynamometry

Muscle wasting is a primary indicator of the PEW seen in HD patients. Estimates of muscle mass can be made using functional assessment of muscle strength in patients on HD and hand-grip strength (HGS) dynamometry has been found to be sensitive to nutritional changes and correlate with clinical outcomes (Leal, Mafra et al. 2011). It has been demonstrated that HGS measures do not differ significantly pre- or post-HD (Leal, Stockler-Pinto et al. 2011) and the high level of agreement with other measures of nutritional status, such as MIS (Silva, Matos et al. 2011) confirms its validity and reliability as a tool to diagnose malnutrition.

1.5.4 Body composition assessment using bioelectrical impedance analysis

This is a particularly useful tool in HD patients where more traditional anthropometric measures such as weight or BMI may be confounded by fluid status. Direct methods of assessing body composition include bioelectrical impedance analysis (Scalfi, Di et al.) which allows an estimate of body compartments based on the resistance to a small alternating electric current (Chumlea 2004).

Different body compartments impede the flow of current to different extents. Essentially compartments with high water content and electrolyte content such as lean muscle have very limited resistance whereas fat and bone compartments have higher resistance to flow.
Current flows through directly through fluid and indirectly through cell membranes. BIA measures impedance as the sum of resistance, impedance secondary to flow through fluid, and reactance, the bio-capacity to “hold” current by cell membranes. BIA uses this data to gauge extra cellular and intracellular fluid respectively. BIA uses modelling software to estimate body compartments and is a relatively simple non-invasive assessment, involving attaching two pairs of electrodes to the hand and foot.

Body composition assessment from BIA monitors have been validated and proven to be a robust tool for measuring body fat and lean mass (Furstenberg and Davenport 2011). However, multi-frequency BIA is preferred to single frequency as reactance and resistance is measured at multiple frequencies and extrapolated by prediction equations to give a more accurate assessment of extracellular fluid and intracellular fluid volumes compartments. As fluid in fat tissue is primarily extracellular and in lean tissue intracellular the two volumes can be used to estimate lean and fat body mass (Donadio, Halim et al. 2008) (Donadio, Consani et al. 2005, Tattersall 2009).

This assessment is most accurately measured after HD and remains consistent within 120 minutes of completing dialysis prior to ingestion of foods or drinks (Di Iorio, Scalfi et al. 2004). BIA is a reliable measure of body composition for the purposes of nutritional status but in recent years has been increasingly used to aid dry weight or target weight assessment in the HD population (Hur, Usta et al. 2013). Therefore in this study it is a very relevant assessment tool to gauge not only fluid status but also changes in body compartments, lean body and fat mass as these have been found to relate to outcomes (Beddhu, Pappas et al. 2003).

The body compartments of particular interest include body cell mass (BCM) which is the metabolically active component of body tissue and as it does not include extracellular fluid may be useful in HD patients as it is relatively resistant to sudden fluid shifts in comparison to fat-free mass (FFM) (Ismael, Savalle et al. 2014) and its relationship with energy expenditure facilitates an indication of calorie requirement (Fiaccadori, Morabito et al. 2014). The use of BCM is primarily in critically ill patients receiving acute dialysis and is calculated from measurements derived directly from the Bodystat monitor using a physiological model. The phase angle (PA) is mathematically derived from the reactance and resistance at frequency of 50kHz and is an indicator of quantity and integrity of intact cell membranes (Oliveira, Kubrusly et al. 2010) and is also a useful indicator of nutritional status.
1.6 Patient experience on haemodialysis

Measures of health related quality of life (HRQoL) refer to an individual’s own perception of their life and well-being in relation to their expectations (Kliger and Finkelstein 2009). Patient experience factors such as sleeping patterns, dialysis symptoms and the daily effect or burden of kidney disease have been demonstrated to be important determinants of HRQoL (Carmichael, Popoola et al. 2000).

Improvements in care of patients with end stage renal disease (ESRD) have focussed on benchmarking against specific clinical targets from national and international guidelines in areas such as dialysis adequacy, anaemia management and cardiovascular risk. The primary aim has been to reduce mortality and hospitalisation rates within this patient population. Although mortality is the ultimate arbiter and clearly reflects quality of care, if asked, patients do not want to live longer at any cost, that is, their quality of life is equally important if not more so. The expectation of good dialysis care is fundamental but increasingly a “whole body not organ specialist care” (Tong, Sainsbury et al. 2008) and “normalisation” of everyday life is desirable.

Dialysis providers may have centred care around clinical outcome measures that are likely to have had little impact on patient experience. For example, clinical targets for HD adequacy are now achieved more commonly and often associated with financial penalties for non-attainment but achieving a spKt/V 1.3 rather than 1.1 may not have improved a patient’s quality of life or dialysis experience (Nissenson 2014). However, this is being recognised and the dialysis community is increasingly turning towards pragmatic improvements to dialysis experience despite the fact that they may only be supported by observational or anecdotal evidence. Strategies to minimise symptoms on dialysis may not involve a clinical quality target but the absence of cramps or hypotensive episodes may greatly influence patient experience (Weiner, Brunelli et al. 2014). But as has been suggested, the achievement of some clinical targets is associated with improved quality of life (QoL) (Lacson, Xu et al. 2009), which has been correlated with mortality (Mapes, Bragg-Gresham et al. 2004). In this case minimising symptoms on dialysis is associated with the clinical targets of achieving an “accurate” dry or target weight using lower UFR. It may be possible and is very desirable to marry quality clinical targets with patient QoL.

1.6.1 Measures of quality of life

Patient’s perception of illness burden, adhering to a dialysis regimen, and complying with dietary and fluid restrictions are hugely influenced by their level of disablement and so assessment of HRQoL incorporates perception of physical ability and mental stress (Kimmel 2000).
HRQOL instruments may be used to qualitatively measure longitudinal changes within patients over a period of time, as in this study. The instrument we have utilised encompasses both generic health and disease-specific issues (Guyatt, Feeny et al. 1993). The Kidney Disease Quality of Life, KDQOL-36, is a validated questionnaire and assesses three primary domains: effects of kidney disease, burden of kidney disease and symptoms of kidney disease. This questionnaire also facilitates calculation of a physical health composite score (PCS) and mental health composite score (MCS).

Questions 1-12 of the SF-12 measure of PCS and MCS functioning, questions 1-12, and enquire about general health, energy and activity levels, depression and anxiety as well as ability to participate in everyday social activities. The burden of kidney disease is gauged by questions 13-16, asking to what extent kidney disease interferes with their daily life, whether this is frustrating and induces a feeling of being a burden to caregivers. The symptoms and problems questions 17-28b, are concerned with the impact of fatigue, soreness or numbness of limbs, chest pain, cramps, itchy or dry skin, shortness of breath, faintness/dizziness, lack of appetite, feeling washed out or drained, nausea, or problems with dialysis access. The effects on daily life questions, 29-36, are more general and capture the level of intrusion on a patient’s ability around the house, travel, sex life, personal appearance and effort with dietary and fluid restrictions (Hays, Kallich et al. 1994).

### 1.6.2 Time to recovery

Another important factor not entirely captured in the KDQOL-36 is a measure of post-dialysis fatigue. This commonly experienced symptom debilitates patients on HD and has considerable effect on HRQoL (Jhamb, Weisbord et al. 2008). In an attempt to quantify post-dialysis fatigue the Daily Haemodialysis Study Group validated the response to a single question “How long does it take you to recover from a dialysis session?” The question was easily interpreted and responses were standardised and demonstrated to be stable and sensitive to change (Lindsay, Heidenheim et al. 2006). Longer time to recovery (TTR) is associated with poorer overall HRQoL and increased risk of hospitalisation and mortality (Rayner, Zepel et al. 2014).

Therefore in this clinical trial I have incorporated measures of assessing HRQoL as any change in perception of well-being would be a crucial assessment parameter. The potential positive clinical efficacy of a dialysis regimen is limited if unacceptable to patients due to an underlying detrimental impact on their HRQoL.
1.7 Biomarkers on haemodialysis

ESRD results in many metabolic changes with multiple body systems being implicated and deranged levels of biomarkers for these systems are demonstrated to have detrimental effects (Chaykovska, Tsuprykov et al. 2011). Stratifying levels of these biomarkers that are indicative of increased morbidity or mortality risk facilitates identification of patient to be targeted. Biological markers are defined as (Biomarkers Definitions Working 2001):

“A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

The primary causes of death in patients on dialysis is either an infective episode leading to sepsis or cardiovascular disease, Table 1-5 (Pruthi, Steenkamp et al. 2013). Therefore biomarkers of these disease entities are potentially very valuable identifiers of at-risk patients.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>n = 2576</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>693</td>
<td>27</td>
</tr>
<tr>
<td>Infection</td>
<td>437</td>
<td>17</td>
</tr>
<tr>
<td>Malignancy</td>
<td>208</td>
<td>8</td>
</tr>
<tr>
<td>Treatment withdrawal</td>
<td>498</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>528</td>
<td>21</td>
</tr>
<tr>
<td>Uncertain</td>
<td>212</td>
<td>8</td>
</tr>
</tbody>
</table>

Traditional risk factors alone do not explain the increased risk of morbidity and mortality secondary to cardiovascular disease seen in dialysis patients.
Non-traditional factors that are specific to renal disease (Parfrey and Foley 1999) and demonstrate the interplay between the factors malnutrition, inflammation and atherosclerosis may be useful in gauging the increased risk (Stenvinkel 2001) in the HD population. Table 1-6, highlights these uraemia-specific factors.

<table>
<thead>
<tr>
<th>Traditional risk factors</th>
<th>Uraemia-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Inflammation/hypoalbuminaemia</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increased oxidant stress and atherosclerosis</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Pro-thrombotic factors</td>
</tr>
<tr>
<td>Age</td>
<td>Volume overload</td>
</tr>
<tr>
<td>Gender</td>
<td>Calcium phosphorus abnormalities</td>
</tr>
</tbody>
</table>

The biomarkers discussed below are established in the general population and overlap both traditional and uraemic categories by being validated in the dialysis population.

1.7.1 High-sensitivity C-reactive protein

C-reactive protein (CRP) is a positive acute phase protein whose synthesis and release is triggered by cytokines such as interleukins and TNF-α. In this process the production of negative acute phase proteins such as albumin are decreased (Pannen and Robotham 1995). Therefore hypoalbuminaemia is not a marker of malnutrition and may only be associated with increased morbidity and mortality by way of its relationship with CRP. The latter is a better predictor of morbidity and mortality than albumin (Yeun, Levine et al. 2000).

CRP is related to outcome in dialysis patients and has also been implicated in atherosclerosis (Stenvinkel and Lindholm 2005), as a predictor of cardiovascular mortality (Yeun, Levine et al. 2000). CRP does not only reflect overall inflammatory effect but it may also play a direct part in
pathogenesis of atherosclerosis. CRP may directly mediate vascular disease by binding to damaged cells and very low density lipoproteins as well as stimulating the production of monocytes (Arici and Walls 2001).

Conventional CRP and high-sensitivity-CRP (hs-CRP) differ only in the efficiency of the range reported; the latter extends measurement to that below the conventional and so allows a measure of inflammation in addition to evaluation of infection or tissue injury. The American Heart Association has stratified cardiovascular risk by hs-CRP levels; those less than 1mg/L indicate low risk, 1-3mg/L moderate risk and above 3mg/L high risk. DOPPS data support this demonstrating high mortality with increasing CRP above 1mg/L (Kawaguchi, Tong et al. 2011).

1.7.2 B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a vasoactive hormone that plays a role in blood pressure and volume homeostasis. It is released from the ventricles in response to myocardial wall stress and has been suggested as a useful biomarker of heart failure in the general population (Wang, Larson et al. 2004). However, it has not been applied to the dialysis population as levels may be elevated secondary to poor renal clearance (Mark, Stewart et al. 2006) and may reflect volume status with elevated levels correlating with over hydration as evidenced by extracellular water (ECW) (Jacobs, van de Kerkhof et al. 2010).

Decrease in volume overload and achievement of reduced dry weight is desired outcome in HD patients and has been proven to improve systolic blood pressure in the Dry-weight Reduction In hypertensive haemodialysis Patients (DRIP) study (Agarwal, Alborzi et al. 2009).

As many hospitalisations are related to volume overload BNP was investigated as a marker of fluid excess. However, these studies were limited by relatively small numbers and use of BIA to assess fluid excess. Although pre- and post-dialysis BNP levels were significantly correlated with overhydration there was association with reduction in BNP with normal hydration or underweight (Lee, Song et al. 2003). The decline in BNP post dialysis has not been found to be related to ultrafiltration and magnitude of decrease in weight (Agarwal 2013).

However BNP is highly correlated to echocardiographic measures of myocardial function, left ventricular mass and function, (Mallamaci, Zoccali et al. 2001, Roberts, Srivastava et al. 2008), so despite the absence of a specific cut off it may be useful in assessing cardiovascular risk in dialysis patients (Wang 2012).
1.7.3 Cardiac troponin I

Cardiac troponin I (cTNI) is a regulatory protein that controls contraction of cardiac muscle and elevated levels are indicative of cardiac injury. Although they have been used to diagnose myocardial infarction they are also prognostic markers (Sharma, Jackson et al. 2004) with elevated levels in dialysis patients being predictive of increased mortality (Khan, Hemmelgarn et al. 2005).

The Chronic Haemodialysis and New Cardiac Markers Evaluation (CHANCE) study has validated cTNI as a marker of cardiovascular risk, indicating the presence of ischaemic hard disease and left ventricular hypertrophy (LVH) in asymptomatic HD patients (Iliou, Fumeron et al. 2001). The effect of individual HD sessions on cTNI has been reviewed to conclude no significant effect (Mongeon, Dorais et al. 2009), but the effect of extending dialysis TT has not been investigated.

1.7.4 Combination of markers in risk stratification

Combination of these three markers, CRP, BNP and cTNI, together may be useful in stratifying risk in dialysis patients (Boulier, Jaussent et al. 2004, Bargnoux, Morena et al. 2013). The combined impact on these markers by extended HD TT has not been investigated.

1.8 Conclusion and outline of thesis

Approximately 70% of the patients presenting with kidney failure are reliant upon HD as a mode of RRT. Despite technical improvements in the delivery of conventional thrice weekly dialysis the prognosis for chronic patients remains sub-optimal with mortality rates remaining high.

The role of extended TT has emerged as a means of intensifying dialysis. Although there is observational data to support such a strategy, there is a lack of robust evidence or expert agreement. I have investigated the effect of extended TT on markers of malnutrition, inflammation and atherosclerosis as the major contributors to morbidity and mortality in this small patient population in a prospective randomised controlled cross-over study.

The hypothesis to be tested is: “Extended haemodialysis TT of 6 hours duration is well tolerated and will significantly improve biomarkers of key patient outcome measures influencing survival: nutrition; inflammation; and cardiovascular disease; compared to standard TT of 4 hours duration over a 6-month period.” This thesis will review the effect on each of these outcomes in turn.

The study serves also to assess the feasibility of extended TT by investigating patient acceptability as well as the impact on service provision. Recruitment was used to gauge patient acceptability and the
importance of any interaction between this and staff attitudes to extended TT will be probed by surveying opinion of both local and national dialysis staff.

Finally, I will consider the effect of extended TT on quality of life and use semi-structured interviews to generate narratives to qualitatively explore patients’ perception of their “dialysis experience”.
CHAPTER 2

2 STUDY DESIGN AND POPULATION

2.1 Haemodialysis population

This clinical study was conducted at Imperial College Healthcare NHS Trust, London, with a large HD population numbered at 1430 patients dialysed in nine satellite HD units. The satellite units are geographically diverse ranging from Watford as the most northern to eight other units scattered across West London with the base unit at Hammersmith Hospital, see Figure 2-1.

![Geographical locations of satellite dialysis units](image)

1 Watford, 2 Brent, 3 St Charles and Hammersmith, 4 Charing Cross, 5 Ealing, 6 West Middlesex, 7 Hayes, 8 Northwick Park, H Hammersmith Hospital

*Figure 2-1: Geographical locations of satellite dialysis units*

2.2 Study design

A randomised cross-over study design was used to test the null hypothesis that there is no difference in markers of nutritional status, cardiovascular disease, inflammation and quality of life between those receiving extended TT on HD, 6 hours versus a standard TT of 4 hours. This was primarily done to ensure sufficient separation of the two treatment arms to demonstrate treatment effect and was not based on specific criteria.
The study design is illustrated in Figure 2-2. The distinguishing characteristic of a cross-over study is that it allows each patient to act as his or her own control (Hills and Armitage 1979). It is this feature that made it appropriate to use such a study design in this clinical trial. This is useful as it circumvents issues of comparability of the control versus the study group with respect to confounding variables. It negates the need to control or correct for confounders and inter-patient variability. Age and gender may be matched relatively easily but characteristics such as comorbidity or dialysis vintage are less easily accommodated. Importantly the statistical tests that may be used to assess treatment effect are such that sample size is greatly reduced (Wellek and Blettner 2012).

The drawback of employing this study design is that the two treatment arms under comparison must be separated by a wash-out phase of sufficient length to discount a carry-over effect, i.e. the effects of the first treatment should not be present when the second treatment commences.

As we were effectively conducting a trial of different quantities of dialysis, we envisaged carry-over effect to be related to dialysis dose. To avoid this effect we ensured that dialysis dose, as measured by small molecule clearance, returned to pre-treatment levels within the 4-week wash-out period. We were satisfied that this wash-out period was of sufficient length to avoid any cross-over effects.
2.3 Strategy for controlling dialysis dose

During the study design process the effect of increasing TT on dialysis dose was investigated because it was unclear whether small molecule clearance would change significantly on the 6-hour arm per unit time. To quantify this we reviewed the achieved spKt/V of those patients routinely dialysing for longer TT, i.e. greater than or equal to 5.5 hours and for a single midweek session reduced their TT to 4 hours and reassessed spKt/V. The results are presented in Table 2-1 below.

Table 2-1: Effect of changing treatment time on measures of small molecule clearance

<table>
<thead>
<tr>
<th>Patient</th>
<th>% URR at &gt;5 hours</th>
<th>% URR at 4 hours</th>
<th>spKt/V at &gt;5 hours</th>
<th>spKt/V at 4 hours</th>
<th>Litres processed at &gt;5 hours (L)</th>
<th>Litres processed at 4 hours (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65.9</td>
<td>60.2</td>
<td>1.3</td>
<td>1.1</td>
<td>135</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>73.0</td>
<td>69.3</td>
<td>1.6</td>
<td>1.4</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>84.0</td>
<td>81.6</td>
<td>2.2</td>
<td>2.0</td>
<td>125</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>67.2</td>
<td>70.8</td>
<td>1.4</td>
<td>1.4</td>
<td>122</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>76.7</td>
<td>67.3</td>
<td>1.8</td>
<td>1.3</td>
<td>141</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>82.0</td>
<td>77.7</td>
<td>2.1</td>
<td>1.8</td>
<td>90</td>
<td>89</td>
</tr>
</tbody>
</table>

There was found to be a significant decrease in spKt/V, mean reduction 0.23 and eKt/V, mean reduction 0.60. A large variation in spKt/V with relatively small changes in % URR was also noted. This inaccuracy of URR as a measure of dialysis adequacy may be attributed to the absence of correction for ultrafiltration (Sherman, Cody et al. 1995). Therefore spKt/V was used to gauge small molecule clearance.
The change in spKt/V with variation of TT was verified by National Kidney Federation clinical practice guidelines on dialysis adequacy. These suggest that the impact of TT on small molecule clearance is sustained at duration of 6 hours and that eKt/V plateaus at TT greater than 8 hours, outside of our proposed TT on the intervention arm, Figure 2-3. Therefore it was concluded that the protocol required a control element for dialysis dose.

\[ eKt/V \]

**Figure 2-3: Small molecule clearances with treatment time**

A run-in phase was introduced on both treatment arms so that a control for dialysis dose could be included. This facilitated quantification of the litres of blood processed on the standard treatment arm. The mean volume of blood processed during 12 sessions of 4 hours of dialysis was calculated. This was then targeted on the intervention, extended TT arm. BFR was reduced proportionately on the long treatment arm to ensure equal blood volume was processed during dialysis.

Measuring dialysis adequacy on the standard TT arm prior to randomisation, introduced a safety check and ensured that patients who had a study TT greater than the standard arm prior to enrolment were able to achieve minimum clinical targets for dialysis dose as measured by spKt/V 1.2. In this way we were able to confirm that they were not disadvantaged during the study, which would otherwise have resulted in their withdrawal.
2.4 Primary outcome measure

Serum albumin was chosen as the primary outcome measure as it was considered a well-established prognostic marker. On analysis of variance of serum albumin in the HD population by a statistician, it was calculated that a sample size of 52 patients would need to be recruited to demonstrate a 2g/dL change.

2.5 Secondary outcome measures

Change in nutritional status as demonstrated by variation in:

- Malnutrition inflammation score.
- Hand-grip strength.
- Dietary energy and protein intake.
- Body composition.

Change in cardiovascular and inflammatory biomarkers and blood pressure control as measured by:

- Cardiac troponin I.
- B-type natriuretic peptide.
- High-sensitivity-CRP.
- 24-hour blood pressure control.

Change in patient experience and quality of life as measured by:

- Effect of kidney disease score.
- Burden of kidney disease score.
- Symptoms of kidney disease score.
- Physical health composite score.
- Mental health composite score.
- Semi-structured interviews.

2.6 Recruitment

Participants were recruited between July 2012 and October 2013. Screening was first commenced at the largest satellite unit with the intent that the majority of patients would be recruited from a single centre. When it was confirmed that the recruitment target would not be fulfilled at this centre it was extended to five other centres. All patients dialysing for less than 4 hours were excluded on the basis that even the standard treatment arm would represent an increase.
Patients were also excluded from participating in the study if their expected survival was less than 12 months or they had a planned change in renal replacement modality, for example planned live-related transplant within the timelines of the study.

The nurse manager for each unit was asked to identify those individuals who were thought to be unsuitable to participate on the grounds they would not be able to fully comply with study protocol, e.g. non-compliant patients who have a history of missing dialysis sessions or those with significant comprehension difficulties which would impede completion of the assessments. The remaining eligible patients who did not have any obvious barriers to complying to study protocol were approached to provide informed consent.

Once the potential participants were identified as suitable for the study, they were approached by me to discuss their potential interest in participating and given a patient information sheet. They were able to read and reflect on the patient information sheet, which described the study and their potential role, over a period of at least 36 hours. They were then seen again at either their next, or mutually agreed, dialysis session where they could ask further questions about the study and if in agreement provide informed consent. Where patients were still undecided they were given another 36 hours to consider their involvement in the study.

This was conducted at five dialysis centres until 31st October 2014; the deadline for last recruitment. This was set pragmatically to allow time for data analysis within fellowship timelines, taking into account the study protocol required 52 weeks to completion.

Each consenting patient then commenced a run-in phase of 4 weeks where small molecule clearance could be measured consistently to quantify the volume of blood processing to be matched on the 6-hour arm, and so calculate the prescribed BFR as previously described. An enrolment form was also completed highlighting baseline dialysis characteristics and demographic data.
The numbers recruited by satellite unit are described in Table 2-2.

<table>
<thead>
<tr>
<th>Unit</th>
<th>Total number patients</th>
<th>Number meeting inclusion criteria</th>
<th>Number recruited</th>
<th>Number randomised</th>
<th>% randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>277</td>
<td>158</td>
<td>4</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>145</td>
<td>118</td>
<td>11</td>
<td>11</td>
<td>9.3</td>
</tr>
<tr>
<td>3</td>
<td>142</td>
<td>114</td>
<td>7</td>
<td>6</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>126</td>
<td>71</td>
<td>3</td>
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<td>4.2</td>
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<td>6</td>
<td>30</td>
<td>21</td>
<td>4</td>
<td>2</td>
<td>9.5</td>
</tr>
<tr>
<td>Trial total</td>
<td>830</td>
<td>546</td>
<td>32</td>
<td>29</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Of those screened 34% (284/830) were not considered suitable for the study and did not meet inclusion criteria. We note that 65% of patients did not recruit to the study and this may be related to acceptability of extended TT to our patient population. When designing the study a questionnaire was sent out to all patients at a single HD satellite unit at our centre to assess the likelihood that we would be able to recruit individuals to a clinical trial looking at the effect of extended TT. Only 28% of patients disagreed with the statement “I would be prepared to dialyse for 6 hours”. This suggests patients were not averse to recruiting to a study based on an intervention of increased treatment time. Currently 14% of our patients dialyse for 5 hours and the results of the pre study survey used to design this study demonstrate that patients value outcome studies which serve to promote patient benefit by increasing both longevity and functional capacity. However we note that canvassing opinion at a unit where the researcher is a service provider may have biased our conclusions as patients may have felt negative opinions maybe considered disloyal or uncooperative.

### 2.7 Randomisation

Randomisation was used to allocate the initial treatment arm. This sequence was organised using a schedule produced by the statisticians whereby there were equal numbers allotted to each treatment arm after every six patients randomised. After 24 weeks, patients switched back to their
usual dialysis TT for a 4-week wash-out phase before commencing a further 24 weeks on the alternative treatment arm.

2.8 Ethical considerations

The study adhered to the principles of the Declaration of Helsinki and ethical approval was obtained in April 2011 (REC reference 11/LO/0505) by the Stanmore Research Ethics Committee (Appendix 1).

Recruitment commenced, with eight patients having been randomised by 26th September 2011. However recruitment was halted on 31st October 2011 when a routine local clinical governance audit revealed absence of written local NHS Research and Development (R&D) approval within the trial master folder (TMF) and recruitment was therefore suspended pending review. Verbal assurance had been given by a member of the R&D team, who subsequently left their post, stating that permissions would be granted and that issue of a formal letter was imminent. The review was conducted in November 2011 and concluded that local approval notification had, in error, never been issued. This represented a breach of ethics approval and was reported to National Research Ethics Service (NRES) which suspended the study in February 2012.

The suspension was successfully appealed in April 2012 and suspension lifted pending receipt of written local R&D approval. This was finally received on 10th July 2012, (Appendix 2) representing an approximate 9-month suspension to recruitment. All previously recruited patients, of which there were 8, were formally withdrawn and all collected data discounted. Recruitment was recommenced in July 2012 as described above.

Amendments to ethical approval were made (Appendix 3) to examine the reasons why patients who enrolled onto the main study may have elected to leave the study prematurely and what circumstances may have led to this decision. This took the form of a participant withdrawal form.


2.9 Patient demographics

Thirty-two patients were consented but three patients were not randomised; two of which because the consultant nephrologist in charge of their care felt that they would not be sufficiently compliant of the study protocol and one patient who unexpectedly transferred their care to another unit. The clinical and demographic characteristics of the patients at enrolment are outlined in Table 2-3.

Table 2-3: Clinical and demographic patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>63.3 ± 13.3</td>
</tr>
<tr>
<td>Dialysis vintage (mean years ± SD)</td>
<td>5.1 ± 5</td>
</tr>
<tr>
<td>Pre-study TT (mean hours ± SD)</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>Dry weight (mean kg ± SD)</td>
<td>79.3 ± 23</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.8 ± 5.3</td>
</tr>
<tr>
<td>Arteriovenous fistula as vascular access</td>
<td>24 (83%)</td>
</tr>
<tr>
<td>Smokers (past/present %)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Indo-asian ethnicity</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Diabetic nephropathy as cause of ESRD</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>6.6 ± 2.1</td>
</tr>
</tbody>
</table>

The population was predominantly male, with a mean age of 63.3 ± 13.3 years and consistent with our local population there was a high percentage of patients of Indo-asian and black ethnicity. Consistent with this ethnic mix there was a high percentage of patients with diabetes as the primary cause of ESRD. All patients were established on HD, for at least 90 days, with a mean dialysis vintage of 5.9 ± 5.8 years.

Comorbidity is an important method of describing the case mix of study cohorts and has been associated with patient survival (Miskulin, Meyer et al. 2003). Therefore the Charlson comorbidity
index (CCI) was measured in each study participant as a profile of disease burden. The CCI has been validated as a prognostic indicator of comorbidity (Charlson, Pompei et al. 1987) in the general as well as dialysis populations (Di Iorio, Cillo et al. 2004) including adapted versions. Mean CCI levels of 6.4 ± 2.5 in our population have been stratified as high risk and consistent with published data (Beddhu, Bruns et al. 2000, Chae, Song et al. 2011).

Those not recruited to the study had a treatment time of 4.2 hours and is lower than the recruited patients, therefore patients already dialysing for longer TT were more disposed to recruitment as the extension in TT may have been less significant. We did not collect data on social circumstances of patients at screening so are unable to associate recruitment and likelihood of participation with factors such as carer status and employment.

2.10 Dialysis treatment characteristics

All patients were dialysed using standard flux Sureflux™-L hollow fibre triacetate dialysers (Nipro Corporation, Osaka, Japan). The surface area of dialysers varied from 1.9m^2-2.1m^2 but was constant for each individual patient throughout the study. Dialysate flow was constant at 800ml/min and blood flow rate maximised during 4-hour treatment time and reduced to match litres processed on the 6 hour arm as described previously. Dialysate fluid composition varied only with respect to K concentration 1mmol/L, 2mmol/L and 3mmol/L with sodium magnesium and calcium concentrations remaining constant. The delivered dialysate sodium concentration was fixed at 140mmol/l. The temperature of the dialysate bath was standard at 37 degrees Celsius. Ultrafiltration rate was kept constant throughout each dialysis and the use of sodium profiling as a means of facilitating fluid removal is not practised at our centre.

Routine monitoring of patient’s blood pressure and pulse, and if indicated temperature, was conducted prior to initiation of treatment, at least once during treatment, more frequently if indicated, and on completion of treatment. This was to ensure patients were monitored for signs of hypotension during treatment as these may be subtle and asymptomatic until blood pressure falls below a critical level.

Also with our high usage of central venous catheters as primary vascular access we routinely checked the leur lock connection. This was conducted separately by two qualified renal nurses to ensure they are tight, correctly fixed and blood lines are appropriately taped to reduce risk of access disconnect.
All blood samples were taken pre dialysis except that taken for post dialysis urea concentration for dialysis adequacy assessment. This was taken using the slow flow method where the blood flow rate was reduced to 50ml/min for one minute and blood sample taken from the venous line.

### 2.11 Adverse events

Any deviation from standard dialysis procedures was considered an adverse event. Nursing staff were asked to complete an adverse event form indicating the nature of the event from a list of possibilities, ticking all that applied: vomiting/nausea, cramp, hypotensive episode, life threatening, hospitalisation or other. A brief description of the event was noted on the form and its relationship to the research intervention: unrelated, unlikely, possible, probable or definite and details of relevant tests and interventions e.g. blood pressure readings, volume of saline given etc. It was also noted whether the event resolved and if the sponsor, Research and development offices of Imperial College NHS Trust, were informed. This was indicated only for serious adverse events.

There were two adverse events and one serious adverse event, all considered to be unrelated, on the 6 hour arm. The serious adverse event took place after the first 6-hour dialysis session, the patient complained of unwell and chest pain whilst awaiting transport home and was subsequently admitted. Pre-dialysis study blood results revealed an elevated Troponin prior to initiation of dialysis. The patient was known to both renal and cardiology team. The patients with adverse events were both admissions related to vascular access, one a coagulopathy and the other a recurrent exit site infection where the patient had previously been highlighted for change of central venous catheter.

The two adverse events on the 4 hour arm were both serious and related to collapse at home, one secondary to a cerebrovascular accident and the other a cerebral mass, the latter resulted in initiation of palliative care.

Underlying reasons for individual withdrawal from the study are discussed in detail along with tolerance to treatment regimens in Chapter 7.
2.12 Patient flow

![Patient flow diagram](image)

**Figure 2-4: Patient flow diagram**

2.13 Statistical methodologies

All data was collated onto a database with one row per recruit per time period, so that patient x had 4 row entries “1” and “2” representing pre and post each treatment arm. The treatment arm was coded as “A” for 6 hours and “B” for 4 hours. The treatment order A then B or B then A was also collated. Where patients withdrew from the study post results were taken at time of withdrawal and if only one treatment arm was completed the data sets for the alternative treatment arm were categorised as missing data and left blank. The complete database including missing data was submitted to an external statistician for analysis. There were six voluntary or treatment related withdrawals on the 6 hour arm and five on the 4 hour arm therefore it was assumed that missing
data was as a result of random drop out. An adjustment for covariates which may relate to a systematic dropout: time variable or treatment order, age, co-morbidity and dialysis vintage was conducted. This suggested that data was missing at random and analysis produced unbiased estimates.

The descriptive statistics are expressed as the mean ± standard deviation (SD) or median with the interquartile range (IQR) as appropriate. The continuous and categorical variables were modelled using mixed models for cross-over trials on Statistical Package for Social Sciences (SPSS) version 22 and Stata version 13 (StataCorp LP, College Station, TX, USA) by the statistician. Statistical significance was defined as p<0.05.
CHAPTER 3

3 SURVEY OF STAFF OPINIONS ON EXTENDED TREATMENT TIME

3.1 Introduction

A small number of patients were recruited on to this study despite more than 75% of patients who were screened meeting the inclusion criteria. This represented a recruitment rate of less than 6%, with marked variation between the satellite units. Despite senior members of the multidisciplinary team being supportive of the study it became increasingly clear that there were logistical issues accommodating the study.

As all recruitment was conducted by a trained single study investigator it was hypothesised that unit-specific factors may be influential in explaining the variance in recruitment. Therefore a further study was set up to determine the challenges of recruitment to this clinical trial.

The potential impact on service provision was explored as was the influence of clinical staff opinions to extended treatment duration upon patient’s willingness to participate in the clinical trial. This was conducted using a simple survey which was initially disseminated locally and then nationally.
3.2 Methods

The head and senior nurses forming the management team at each of the five recruiting HD centres were contacted and asked to complete a simple short survey to capture their opinions of longer dialysis TT including impact on service provision and staff working practices. They were asked to disseminate the survey to all qualified nursing staff at their respective centres and return completed surveys either via fax, internal post or email. The nurses were reassured that all replies were entirely confidential and the staff name and centre were not disclosed to the investigators. The survey was made up of five statements, Figure 3-1. Staff were asked to specify the extent to which they agreed or disagreed with the statements.

![Table of survey statements and responses]

**Figure 3-1: Staff survey**

The first statement relates to staff opinion of whether longer TT, greater than four-and-a-half hours, is thought to be of clinical benefit. The second and third statements relate to whether the extended times are tolerated by patients and if staff are able to accommodate these when prescribed. The fourth statement differentiates between accommodating an individual and the overall impact on service provision of longer TT. Finally the fifth statement asks whether they would recommend longer TT.

The survey was designed to measure, firstly, if longer TT were felt to be a positive initiative and consequently whether it was felt that this positive initiative could be recommended. The two should go hand in hand but the presence of a dis-joint would suggest that the implications of recommending the treatment were detrimental, either to the patient or the staff. To differentiate
between these two possibilities we questioned the extent to which patients tolerated the initiative and the ease with which staff were able to facilitate this.

To explore the extent to which our local nursing opinion was representative of national opinion another survey was devised and disseminated to multidisciplinary staff at 72 renal units with HD service provision via a multi-professional national renal body. The local survey was amended only by the addition of two questions to identify the respondent’s profession, and whether their unit had experience of prescribing and delivering longer TT.

The reliability of the survey was gauged by the numerical coefficient, Cronbach’s alpha, with higher values denoting greater reliability. A score between 0.7 and 0.9 is considered acceptable.1

The results of the survey were analysed using direct analysis from survey software. The association of response by profession and survey, local or national was analysed using Fishers exact test using Statistical Package for Social Sciences (SPSS), (Version 19.0). Statistical significance was assigned to p values < 0.05.

3.3 Results

The local survey was completed by 56/134 nursing staff across the recruiting satellite HD units, representing a response rate of 42%. The national survey received 37 staff replies from 15 dialysis centres across the UK, 46% (17/37) doctors, 35% (13/37) HD nurse managers, 11% (4/37) other health professionals and 8% (3/37) were service leads or service managers. 60% of the dialysis centres had experience of prescribing and delivering extended TT.

The reliability of the questionnaire to assess attitudes to extended TT was assessed as relatively good with a Cronbach’s alpha score of 0.698.

3.3.1 Is extended treatment time beneficial?

Of non-nursing healthcare professionals who expressed an opinion, 100% considered extended TT to be beneficial compared to 70% locally (p<0.001) and 72% of nurses (p<0.01).
3.3.2 Would you recommend extended treatment time?

The national survey revealed that 70% would recommend extended TT to their patients compared to 36% of local staff (p<0.0001). When analysed by profession, only 42% of nurses would recommend extended TT to their patients, in contrast with 95% of non-nursing healthcare professionals (p<0.0001).

3.3.3 Impact of extended treatment time on service provision

The majority of respondents felt that extended dialysis TT impacted on HD service provision, but this was not significantly higher in nurse respondents, 83%, than in non-nursing healthcare professionals, 63% (p=0.10).

3.3.4 Is extended treatment time well tolerated?

Although 41% of local survey respondents felt extended TT was well tolerated by patients, nationally this was significantly higher at 70% (p<0.05). Again when analysed by profession, 45% of nurses felt that it was well tolerated versus 75% of non-nursing healthcare professionals (p<0.05). However, a number of respondents selected “neither agree/disagree” or the “don’t know” options in both local 21%, and national surveys, 38% (p=0.09).
3.3.5 Themes of qualitative analysis

Three themes were identified from qualitative analysis of the comments made on the national survey: clinical benefit; service implications; and patient choice and experience, Figure 3-2. The need to facilitate shifts within a finite time period led one centre to comment:

“We cannot prescribe longer treatment time as this would affect other patient’s dialysis times.”

The pressure on staff to allocate spaces or slots for new patients was indicated by the comment:

“Unlikely to happen at present due to reduced availability of slots as it is.”

When asked whether their unit currently prescribed extended TT. This was reiterated by other staff who explained why their unit did not prescribe extended TT:

“We close at 22:00 hours and we would have to extend this time or stop the evening shift and only do two shifts a day.”

![Figure 3-2: Themes identified from qualitative analysis](image)

The prescription of extended TT was often based on clinical indication, to meet urea clearance targets or facilitate adequate fluid removal. This practice was self-limiting, as one clinician commented:
“Only in a very small minority of cases, that’s how the unit can accommodate it.”

Patient choice and impact on quality of life was considered by the HD staff, this was evidenced by comments from two clinicians at different centres:

“Needs to be a conversation between clinician and patient weighing up pros and cons - not sure we can offer extended treatment time routinely, not that we are very good about having that conversation,” and “letting some people have less (having accepted the risks) and some people have more dialysis”.

Others commented on patient acceptance:

“....clearly quality of life is important too”.

One respondent agreed that longer session lengths were reluctantly tolerated remarking:

“A number of patients have 5-plus hour session, these can be tolerated and are generally accepted without too much grumbling!”

### 3.4 Discussion

Our survey results demonstrate that the majority of respondents from both surveys feel that extended TT as a strategy is clinically beneficial but there is a conflict between this understanding and its prescription and delivery. This is highlighted in the disparity between nursing and non-nursing staff opinion. Nurses are less likely to agree that extended TT is well tolerated and therefore recommend it to their patients. The consensus from both the national and local surveys is that there is an impact on HD service provision and this may have influenced the extent to which HD staff felt able to recommend participation in the study.

Like the FHN group we found recruiting from multiple sites difficult, with centres of high volume at near maximal patient and staff capacity being particularly challenging (Sergeyeva, Gorodetskaya et al. 2012). Heavy clinical workload of care providers is a significant barrier to recruitment and may have been influential in our study, particularly in view of comments regarding scarcity of spaces or slots (Costescu and Cullimore 2013).

Nursing staff may be less motivated to increase the TT for two patients when in the same time-frame; three patients could be dialysed with standard treatment duration. These logistical issues are highlighted in the comments from the national survey and also serve to explain the difference in opinion between nursing staff responsible for HD service delivery at a “shop floor” level compared to
medical and managerial staff that may have been more distanced from the practical day-to-day juggling involved with dialysis space allocation.

More than half of the respondents of the national survey had first-hand experience of facilitating extended TT into a shift structure designed for standard TT.

However, the survey suggested TT would be extended by centres in special circumstances, specifically if urea clearance were below national minimum levels. This may occur more frequently as national tariffs are imposed to encourage best practice and regulatory authorities increasingly use financial penalties to ensure service delivery standards. It is ironic therefore that without appropriately powered clinical trials we would not be able to provide the evidence to set these minimum standards.

The views of nursing staff regarding clinical trials are trusted by patients and may promote or deter their decision to participate (Mueller 2004). This may bias certain sub groups of patients. Older, more comorbid or frail patients may not agree to take part if care providers make moral judgements on merits of enrolling in a study which may inconvenience the patient (Israni, Halpern et al. 2004). Although nursing staff were committed to the study they attempted to act as patient advocates and effectively discourage patients from enrolling if they felt the patient would be excessively inconvenienced. Logistical issues are also important barriers to recruitment (Newington and Metcalfe 2014), with patients who were themselves carers for spouses or other family members least likely to provide consent. This is evidenced by the significantly greater proportion of nurses disagreeing with the statement that extended treatment is well tolerated.

The potential conflict between the role of recruiter versus care provider can be a factor (Donovan, Paramasivan et al. 2014) in poor recruitment. We attempted to limit this by ensuring that care providers, dialysis nursing staff, were not directly involved in the recruitment process. All aspects of recruitment were undertaken by a single study investigator. Although the nursing teams did not have any involvement in recruitment, including administration, discussing patient information documentation or consenting, their views may have impacted on the numbers of patients willing to offer their consent. The nurse manager for the unit was consulted at the screening process to identify those patients who they felt were unable to give informed consent or who had a planned change in treatment modality in the time frame of participation to the study.

Measures were taken to minimise any disruption and inconvenience to the nursing teams. Operation times of the unit, that is opening and closing times, were not altered and patient’s consent was taken on the understanding that they were not permitted to change their day or dialysis slot. Also
the study investigator took sole responsibility for processing blood samples and conducting assessments including arranging for couriers to pathology services when necessary. Only one patient required reorganisation of transport to and from dialysis and this was arranged by the ward clerk for the unit.

Strategies enabling integration of the clinical team responsible for care and the academic team responsible for the clinical trial with shared responsibilities for recruitment have proven to be successful by ensuring that all potentially eligible patients were invited and encouraged to participate. As we have found in our study, harnessing support from the clinical team is often a bigger determinant of successful recruitment than support from participants themselves hence an integrated approach to recruitment may yield better results (Thomson, Morley et al. 2008).

The limitations of the results of our survey include the low response rate but the level of agreement between local and national responses may serve to promote the reliability of the findings and conclusions drawn. The main themes that emerge as factors influencing recruitment to our study on extended TT are patient choice and experience; potential clinical benefit; and ability to facilitate extended TT within clinical service.

Clearly the acceptability of extended TT to patients is of paramount importance, in considering the role played by staff opinion and service implications we do not wish to undermine the power of this factor as a barrier to recruitment. But we highlight the influence of staff attitude on patient choice and decision making. If, as may be likely, staff attitude is based on service provision rather than clinical benefit then patient choice is negatively influenced.

We are in the process of collecting qualitative data on patients’ experience of extended TT and also their experience of participating in a study of HD prescription using semi-structured interviews. This is essential as the recruitment of insufficient numbers to achieve statistical power to detect a treatment effect may result in potentially beneficial interventions being abandoned. Irrespective of perceived uptake of an intervention establishing the intervention to be beneficial is fundamental to health service development and improvement.

This survey of staff opinion both locally and nationally highlights the difficulties in implementation of intensive dialysis strategies that may play a role in alleviating the suboptimal patient survival we see in our HD populations (McFarlane 2009). The current structure of in-centre HD thrice weekly shift programmes are designed for maximal patient throughput and this may not be concomitant with the prescription of longer TT. We as a dialysis community may need to consider how best to employ longer TT and consider settings which afford greater flexibility (Masterson 2008).
CHAPTER 4

4 EFFECT OF EXTENDED TREATMENT TIME ON MARKERS OF NUTRITIONAL STATUS

4.1 Introduction

PEW is characterised by a decrease in somatic muscle and circulatory protein and fat mass. In the HD population this may be secondary to either reduced nutrient intake or other non-nutritional causes (Dukkipati and Kopple 2009). With advancing renal disease there is a decline in appetite (Chazot 2009) and most commonly reported is the decrease in dietary protein intake (Ikizler, Greene et al. 1995) which persists despite initiation of adequate HD.

The HEMO study group noted that despite only 8.8% of their cohort self-reporting their appetite as being poor or very poor, decreased appetite was associated with significantly increased hospitalisation (Burrowes, Larive et al. 2005). This has been further evidenced by DOPPS data which links poor appetite to symptoms of nausea and confirms the association of impaired appetite to not only increased hospitalisation rate but also increased risk of death (Lopes, Elder et al. 2007). So, reduced appetite may have a direct impact on patient outcome or may have an indirect relationship and be a surrogate of “wellness”.

However, if we take into consideration that nutritional requirement in HD may be increased, the potential short fall in energy or protein intake is more pronounced. The European best practice guidelines and British Renal Dietitians Group suggest an energy intake of 30-40Kcal/kg ideal body weight and a protein intake of 1.1g/kg ideal body weight (Fouque, Vennegoor et al. 2007, Naylor, Jackson et al. 2013). These guidelines take into account the increased requirement due to the catabolic effects of uraemia. Metabolic acidosis is associated with insulin resistance and increased activity of the ubiquitin-proteasome pathway resulting in decreased protein synthesis, including albumin, and increased protein catabolism respectively (Kalantar-Zadeh, Mehrotra et al. 2004).

The non-nutritional causes of PEW relate to the metabolic effects of renal failure and dialysis itself. Although dialysis adequacy and nutritional status are linked in that a significant proportion of the toxic substances accumulating in ESRD are by-products of protein metabolism, the presence of a relationship between dialysis dose is not proven (Schulman 2004).
The impact of HD prescription, specifically TT, on appetite and so dietary intake, is unknown. Poor appetite has been correlated with increased comorbidity and increased TTR after HD (Bossola and Tazza 2013). The effect of extended TT on TTR and patient experience will be reviewed in Chapter 7.

Other non-nutritional causes of PEW include the effects of the chronic inflammatory state; the MIA syndrome, which persists in advanced kidney disease, where the concentration of positive acute phase proteins, e.g. CRP, TNF-α, IL-6 increases, and negative acute phase proteins, e.g. albumin and transferrin decreases. These pro-inflammatory cytokines not only affect protein catabolism and synthesis but also result in reduced appetite (Kalantar-Zadeh, Ikizler et al. 2003).

The effect of extended TT on inflammatory response is unknown. It is well established that the dialysis procedure itself appears to be catabolic. Investigations involving “sham” dialysis circuits suggest blood-membrane contact activates the complement system triggering an inflammatory response and subsequent release of amino acids from skeletal muscle (Lindholm, Wang et al. 1998). Confirmation that inflammatory molecules are mediators of the protein catabolism seen in HD is evidenced when this proteolytic effect is impeded by the use of anti-inflammatory agents (Ikizler 2004).

Although we hypothesise that extended TT will go some way to correct the inflammatory causes of anorexia and poor nutritional intake in HD patients, it may well be that increased exposure to the extracorporeal HD circuit increases the degree of systemic inflammation and so has a negative impact on PEW.

### 4.2 Methods

The ISRNM recommends assessment of nutritional status should be made using indices of inflammation, body mass and composition as well as nutritional intake. Detection of the presence of any change in nutritional status involved all four indices.

- Malnutrition inflammation score.
- Hand-grip strength.
- Dietary intake.
- Body composition.
4.2.1 Malnutrition inflammation score

The MIS has 10 components, each with four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components ranges from 0 (normal) to 30 (severely malnourished); a higher score reflects a more severe degree of malnutrition and inflammation. The 10 components were divided into four sections nutritional history, physical or functional measures, BMI, and laboratory values.

The history section includes five components adopted from the original SGA. Weight change is determined as the change in dry weight defined as oedema-free post-HD body weight in the past 6 months. The lowest score 0, is given if weight loss is less than 0.5kg or there is an increase in body weight. Score 1 indicates a minor loss of at least 0.5kg, but less than 1.0kg. Score 2 is given for weight loss of at least 1.0kg, but less than 5% of body weight, and score 3 indicates weight loss of 5% or greater.

Dietary intake is scored 0 if it is the usual intake of solid foods, with no recent decrease in amount or quality of meals. A score of 1 indicates a slightly suboptimal solid diet, 2 denotes a full-liquid diet or moderate decrease in food intake, and 3 indicates a daily nutrient intake that would be incompatible with life on a chronic basis.

Gastrointestinal (GI) symptoms are scored 0 if the patient has a good appetite and no GI symptoms; 1, mildly decreased appetite or mild nausea; 2, occasional vomiting or other moderate GI symptoms, such as abdominal pain; and 3, diarrhoea, frequent vomiting, or severe anorexia.

Functional capacity is scored 0 for normal functional capacity or a considerable improvement in level of previous functional impairment. A score of 1 indicates mild or occasional difficulty with baseline ambulation or feeling tired frequently; 2, difficulty with independent activities; and 3, restriction to light activity or a persistent bed- and/or chair-bound state.

Comorbidity includes dialysis vintage and is scored 0 if there are no other medical illnesses and the patient has undergone HD therapy for less than 1 year; 1, mild comorbidity, excluding major comorbid conditions such as congestive heart failure or severe coronary artery diseases, moderate or severe chronic obstructive pulmonary disease, and metastatic malignancies, or dialysis therapy for 1 to 4 years; score 2, moderate comorbidity, that is, a major comorbid conditions or dialysis therapy for more than 4 years; and score 3, two or more major comorbid conditions.

The scoring was completed whilst patients were awaiting commencement of dialysis either in the waiting area or whilst sitting in their dialysis chair.
4.2.2 Hand-grip strength

HGS was conducted using a Jamar hand-grip dynamometer, prior to commencement of dialysis in a sitting position with the patient in:

- either standard hospital chair with arm rest, in the waiting area, with both feet on the ground, Figure 4-1a.
- or reclined in dialysis chair, at approximate 30° angle, with forearm supported on an arm rest and legs stretched out, Figure 4-1b.

![Figure 4-1a & 4-1b: Sitting posture and reclined posture for hand-grip strength measurement](image)

It was ensured that the elbow was in 90° flexion, shoulder adducted and neutrally rotated. Clear instructions were given to the patient after first demonstrating how they should hold the machine and that the handle would not move with their hand grip but that it would measure the force exerted. They were also informed that the purpose of the test was to evaluate nutritional status only.

Consistent instructions were given to each patient when measurements were taken. “Are you ready?” and “Squeeze as hard as you can” and “Relax”. Three measurements were taken with 1-2 minutes interval between each assessment. Measurements were made using the non-dominant arm, except where this was the site of an arterio-venous fistula (AVF). An average of the three measurements was recorded.

Our method of assessment is consistent with published protocols (Roberts, Denison et al. 2011), although some studies have elected to take up to 6 measurements (Dodds, Syddall et al. 2014). We standardised the timing of all assessments by undertaking measurements before dialysis had commenced although it has been reported that HGS is not associated with dialysis-related
determinants and readings do not vary significantly pre and post dialysis (Leal, Stockler-Pinto et al. 2011)

4.2.3 Dietary intake

Patients were asked to record all meals and snacks for three consecutive days in a food diary, and to include both a non-dialysis day and a weekend. The patients were instructed on how to record portion sizes and if possible record weights and the importance of including snacks and drinks was explained.

The patients were reassured that this was to improve accuracy of reported intake and would not be used to reinforce dietary advice or to refer to their usual dietitian.

All completed diaries were validated at the time of completion by the dietitian, clarifying any ambiguities and where necessary food portion size was estimated using a visual guide. The diaries were analysed using the nutrition analysis software Dietplan 6 (Forestfield Software Ltd.) for energy and protein content.

4.2.4 Body composition

Body composition was measured using the Bodystat Quadscan 4000™ (Bodystat, Isle of Man, UK; www.bodystat.com) Bioelectrical Impedance Monitor. All BIA measurements were taken approximately 10 minutes post dialysis and after the patients had weighed themselves. The patient’s height and post-dialysis weight were entered into the monitor as were their waist and hip measurements. The waist and hip measurements were taken using stretch-resistant tape whilst the patient was standing. The point of measurement for waist circumference was one inch above the umbilicus, and the hip measurement at the widest point of the buttocks.
The non-fistula or dominant side of the body was used for measurement. Foot rests, watches and metal jewellery were removed and the skin cleaned with an alcohol wipe and allowed to dry prior to attaching the electrodes. A pair of electrodes was placed on the dorsal surface of the hand over the third metacarpophalangeal joint and wrist. A second pair of electrodes was placed on the surface of the ipsilateral third metatarsophalangeal joint and ankle, as shown in Figure 4-2, at least 3cm apart.

Figure 4-2: Positioning of electrodes for bioelectrical impedance analysis

The leads were then attached to the electrodes with the red clips nearest the fingers and toes and to the electrodes with the black clips at the wrist and ankle. It is important to ensure there is no resistance to the path of the current and so patients were asked to place their arms on the dialysis chair arm rests, away from the trunk, and keep their legs and feet slightly apart. Once the patient was in the correct position the measurements were taken and the results recorded.
4.3 Results

4.3.1 Baseline levels

Table 4-1 describes the baseline levels of nutritional markers.

<table>
<thead>
<tr>
<th>Nutritional marker</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry weight (mean kg ± SD)</td>
<td>79.3 ± 23</td>
</tr>
<tr>
<td>MIS (mean n ± SD)</td>
<td>4.9 ± 1.6</td>
</tr>
<tr>
<td>HGS (mean kg ± SD)</td>
<td>18.6 ± 8.8</td>
</tr>
<tr>
<td>Serum transferrin (mean g/L ± SD)</td>
<td>170.1 ± 29.8</td>
</tr>
<tr>
<td>Serum albumin (mean g/L ± SD)</td>
<td>34.9 ± 3.7</td>
</tr>
<tr>
<td>Serum phosphate (mean mmol/L ± SD)</td>
<td>1.60 ± 0.51</td>
</tr>
<tr>
<td>Phase angle (degrees ± SD)</td>
<td>6.9 ± 2.7</td>
</tr>
<tr>
<td>Fat mass (mean kg ± SD)</td>
<td>25.7 ± 11.0</td>
</tr>
<tr>
<td>Body cell mass (mean kg ± SD)</td>
<td>34.3 ± 9.0</td>
</tr>
</tbody>
</table>
4.3.2 Effect of extended treatment time on malnutrition inflammation score

There was a significant decrease in MIS on the 6-hour arm (mean, 95% CI), 5.6 (4.6-6.0) to 4.4 (3.7-5.2), p<0.05, Figure 4-3, but no significant change on the 4-hour arm 4.9 (4.2-5.7) to 5.5 (4.7-6.3). Dialysis vintage had a significant effect on MIS; a year increment in vintage was associated with a 0.1 unit increase in MIS, p<0.05.

![Figure 4-3: Significant decrease in MIS with extended treatment time](image)
MIS was found to be inversely correlated with both HGS $r=-0.509$ $p<0.05$, Figure 4-4, and serum transferrin $r=-0.604$ $p<0.01$, Figure 4-5, on the 6-hour arm, resulting in an increase in both markers of nutritional status with decrease in MIS.

**Figure 4-4: Correlation of malnutrition inflammation score with hand-grip strength**

**Figure 4-5: Correlation of malnutrition inflammation score with serum transferrin**
4.3.3  Effect of treatment time on hand-grip strength

There was a significant increase in HGS on the 6-hour arm (mean, 95% CI) 18.9 (15.6-21.5) to 21.2 (18.1-24.2), p<0.001. There was no change on the 4-hour standard TT arm 18.4 (15.3-21.4) to 18.9 (15.9-22.1), p=0.537, Figure 4-6. Dialysis vintage was found to have a significant inverse effect on HGS, a year increment in vintage results in a 0.845kg decrease in HGS, p<0.01.

Figure 4-6: Increase in hand-grip strength with extended treatment time
HGS was found to correlate well with body cell mass, \( r = 0.693 \ p<0.01 \), determined from body composition analysis, Figure 4-7.

![Figure 4-7: Correlation of hand-grip strength with body cell mass](image)

**4.3.4 Correlation of measures of muscle mass with KDQol domains on extended treatment time**

HGS correlated with effects of kidney disease \((p<0.05)\), and symptoms \((p<0.05)\) quality of life domains expressed in the KDQoL questionnaire, but not with physical health score, Table 4-2.

<table>
<thead>
<tr>
<th></th>
<th>Disease effect</th>
<th>Symptoms and problems</th>
<th>SF-12 Physical health score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation with HGS</td>
<td>-0.547*</td>
<td>-0.524*</td>
<td>-0.133</td>
</tr>
<tr>
<td>Correlation with BCM</td>
<td>-0.708**</td>
<td>-0.453</td>
<td>-0.216</td>
</tr>
</tbody>
</table>

*\(p<0.05\), **\(p<0.01\)

BCM also correlated with effects of kidney disease \((p<0.01)\) but the correlation with symptom score failed to reach significance, \(p=0.068\). Neither marker of muscle mass was found to correlate with physical health score.
4.3.5 Effect of treatment time on serum phosphate

Serum phosphate levels were found to decrease significantly on the extended 6-hour TT arm from 1.65mmol/L (1.48-1.82) to 1.28mmol/L (1.10-1.46), p<0.001, Figure 4-8. This was accompanied by a decrease in phosphate binder use. In 24% (7/29) of patients binders were stopped altogether, in 10% (3/29) the dose was reduced and another 10% (3/29) had a decrease in numbers of agents required.

Figure 4-8: Significant decrease in serum phosphate on extended treatment time
Conversely levels increased significantly on the 4-hour TT arm from 1.53mmol/L (1.34-1.71) to 1.88mmol/L (1.70-2.06), p<0.001, Figure 4-9. Phosphate binder use was manipulated to counteract this increase with 17% (5/29) of patients having their dose increased and one patient had an increase in dose of their existing agent in addition to having a second agent initiated.

*Figure 4-9: Significant increase in serum phosphate on standard treatment time.*
4.3.6 Effect of treatment time on dietary intake

There was a significant increase in dietary calorie intake on the extended 6-hour TT arm from 1835 to 2157Kcal, p<0.01, and no significant change on the 4-hour arm 1503 to 1557Kcal, p=0.169, Figure 4-10. There was a significant negative interaction with age. Dietary calorie intake was found to decrease with increasing age, p<0.01. Similarly protein intake also increased on the 6-hour arm but this was not significant 79.6g to 83.6g, p=0.173.

Figure 4-10: Increase in dietary calorie intake with extended treatment time
4.3.7 Effect of treatment time on body weight and composition

There was no significant change in target dry weight on either TT arm, 78.2kg ± 14.7 to 79.2kg ± 15.2, on the 6-hour arm and 78.3kg ± 15.4 to 79.1kg ± 15.4, on the 4-hour arm. The increase in % ECW standardised by dry weight, Figure 4-11 on the 4-hour arm (21.9 ± 3.2 to 23.6 ± 2.5) was not statistically significant.

![Figure 4-11: Effect of treatment time on % extracellular water](image)

There were no significant changes in other body components; BCM and fat mass on either treatment arm, Table 4-3.

**Table 4-3: Change in body components with treatment time**

<table>
<thead>
<tr>
<th></th>
<th>Pre 6-hour arm</th>
<th>Post 6-hour arm</th>
<th>p-value</th>
<th>Pre 4-hour arm</th>
<th>Post 4-hour arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BCM (kg ± SD)</td>
<td>34.5 ± 6.3</td>
<td>34.2 ± 6.3</td>
<td>p=0.602</td>
<td>33.8 ± 7.3</td>
<td>34.2 ± 6.5</td>
<td>p=0.205</td>
</tr>
<tr>
<td>Mean fat mass (kg ± SD)</td>
<td>23.3 ± 6.3</td>
<td>23.3 ± 7.0</td>
<td>p=0.906</td>
<td>23.5 ± 6.8</td>
<td>22.8 ± 7.6</td>
<td>p=0.954</td>
</tr>
</tbody>
</table>
4.3.8 Effect of treatment time on biochemical markers of nutritional status

There was a trend to increase in mean serum albumin levels on the 6-hour arm 34.6g/L ± 4.4g/L to 36.4g/L ± 4.9g/L, but this did not reach significance, p=0.050, Figure 4-12.

![Figure 4-12: Change in serum albumin on 6-hour treatment arm](image)

The change on the 4-hour arm was not significant, 35.8g/L ± 3.9g/L to 36.3g/L ± 4.6g/L, p=0.523. There was no change in serum transferrin 169mg/L ± 39mg/L to 172mg/L ± 39mg/L and 163mg/L ± 29mg/L to 165mg/L ± 40mg/L on the 6- and 4-hour arms respectively.

4.4 Discussion

This is the first randomised cross-over study to demonstrate an improvement in markers of nutritional status with extended TT. The positive impact is evidenced by lowered MIS and serum phosphate, as well as increased HGS and dietary energy intake. This is particularly interesting at a time when the HD community has turned their focus away from the traditional concept of dialysis dose and small molecule clearance to TT. Although we note the limitations of small patient numbers, this study suggests that increased TT as an intervention may be a method of improving nutritional status in HD patients.

There is an absence of studies investigating the effects of nutritional status with HD prescription. International registries analysing observational data have indicated lower serum phosphate levels with increased TT (Tentori, Zhang et al. 2012) but these may have been confounded by patient-
related factors: larger patients of higher dry weight with better dietary intakes may be prescribed longer dialysis. Our use of a cross-over study design was employed to counteract this.

Our baseline nutritional assessment values superficially indicate our study cohort is not significantly malnourished with a BMI of 27.8kg/m² but the reduced HGS of 18.6kg is indicative of sarcopenia with normal levels exceeding 32kg in men and 20kg in women (Alley, Shardell et al. 2014).

We also found serum phosphate to decrease significantly with increased TT, and decreased reliance on phosphate binders. Phosphate is commonly elevated in HD patients and relates not only to reduced glomerular clearance but also dietary phosphate intake. However, restricting dietary phosphate whilst maintaining protein intake can be difficult (Fouque, Horne et al. 2014) as foods with high protein content are often high in phosphate (Kidney Disease: Improving Global Outcomes 2009). The detrimental effects of hyperphosphataemia are primarily related to vascular calcification and bone disease (Fouque, Roth et al. 2013). Therefore phosphate binders are employed to avoid overly limiting dietary protein intake, which has its own negative impact on mortality, and to facilitate a recommended protein intake of 1.2g/kg/day (Fouque, Vennegoor et al. 2007) whilst maintaining serum phosphate within acceptable levels (Lynch, Lynch et al. 2011).

The serum phosphate level of dialysis-dependent patients is controlled by three factors:

- avoidance of high phosphate:protein ratio foods.
- optimal use and compliance with phosphate binders.
- maximal dialysis clearance.

In this study both dose and number of phosphate binding agents were reduced and patients did not receive additional dietary counselling. Phosphate behaves similarly to middle-sized molecules in that its clearance on dialysis is dependent upon length of TT (Eloot, Van Biesen et al. 2008). This is because it is a relatively large molecule; present in both the intracellular and deep tissue compartments with slow limited transfer; and bound to other molecules (Galassi, Cupisti et al. 2014). The extended 6-hour TT affords mobilisation of phosphate from tissue compartments and facilitates greater net phosphate removal (Kjellstrand, Ing et al. 2011). Phosphate levels increased significantly on the 4-hour arm and this may relate to decreased clearance on dialysis because, for 69% of patients, the standard 4-hour arm was in fact a reduction from their pre-study TT.

Although we did not detect a change in dry weight, we did note an increase in dietary calorie intake with extended TT. This may be partially related to increased intake on dialysis days on the 6-hour
arm. Our unit does not discourage eating on dialysis as we have no experiential evidence to suggest that there is any increased risk of GI or hypotensive adverse events and this is consistent with published data (Kalantar-Zadeh and Ikizler 2013, Kistler, Fitschen et al. 2014). An international survey of practices found that food intake on HD was common place. Although many units did not provide food on dialysis the majority allowed and encouraged intake and negative ramifications were rarely observed (Kistler, Benner et al. 2014).

But it could be that increased length of time away from home may have been influential in patients consuming more snacks or other food items while on dialysis. It is unclear why the increased energy intake did not result in an increased body weight but it is plausible that there was an increase in energy expenditure that may have negated the impact of increased food intake.

Energy expenditure in HD patients has been demonstrated to be equivalent to that of healthy age-matched controls with a positive correlation with BMI and in addition to recognised determinants of resting energy expenditure, age and FFM, CRP was also an independent predictor (Kamimura, Draibe et al. 2007). Studies of pre-dialysis patients have demonstrated higher CRP to be associated with increased resting energy expenditure. Resolution of underlying causes of inflammation and infective episodes has resulted in a corresponding decrease in expenditure (Utaka, Avesani et al. 2005). It may well be that there was an increase in CRP in our study, secondary to increased exposure to the extracorporeal circuit, and this resulted in a subsequent increase in energy expenditure. Therefore the competing effects of increased energy intake versus increased expenditure may have negated the overall effect.

The increase in energy expenditure on the extended TT arm corresponded with an increase in HGS which implies an increase in functional ability suggesting some consistency with a theory of increased activity. Also it is well established that there is an increase in resting energy expenditure in HD patients (Ikizler, Wingard et al. 1996, Cuppari, de Carvalho et al. 2004). This may have been an underlying factor in the absence of flesh weight gain. The increase in resting energy expenditure has been demonstrated to be disproportionately higher in those patients who have low BMI (Vilar, Machado et al. 2014) but this was not thought to be a significant factor in this study as all patients had BMI greater than 20kg/m² and 58% had BMI greater than 25kg/m².

The correlation of HGS with HRQoL domains of effect of kidney disease and problems and symptoms further reinforces this theory. If increased muscle strength was associated with patients less likely to experience symptoms of fatigue, cramp and intrusion to their daily lives then it may be more likely that they increased activity levels. In line with published data, we also found HGS to correlate with
MIS (Silva, Matos et al. 2011), HGS increasing with decrease in MIS. HGS has been identified as an independent predictor of poor outcomes of pre-dialysis mortality or dialysis dependency, the risk of these outcomes increased by 10% with HGS <20.15kg.

But we found no evidence with respect to body composition data to support the increased functional capacity evidenced by increased HGS, as there was no change in BCM or fat mass. The seasonal variation in these body compartments has been investigated and BCM has been found to decrease in winter. So for those patients who commenced the 6-hour arm in the summer and were reassessed in the winter, any increase may have been buffered. Similarly with increased ECW in the summer, the increase on the 4-hour arm may have been adjusted downwards if measured during the winter months (Broers, Usvyat et al. 2014). Therefore it is possible that the increase in ECW on the lower TT may have masked a decrease in flesh weight.

Biochemical biomarkers of nutritional status were measured to counteract the limitations of self-reported dietary intake with diet diaries (Carrero, Chen et al. 2014). The use of 3-day diet diaries limits analysis to macronutrients and so we analysed energy and protein intake. We did not detect a significant change in serum transferrin, the biochemical marker of nutritional status, but the serum albumin increase was bordering on significance. Serum transferrin was measured directly but has its limitations in that HD patients have variations in iron status secondary to periodic iron supplementation and this can affect transferrin synthesis (Carrero, Chen et al. 2014). As previously discussed serum albumin is an acute phase protein and heavily influenced by inflammatory processes (Friedman and Fadem 2010).

Baseline CRP levels are elevated in HD patients even in the absence of overt infection and it is recognised that inflammatory molecules affect dietary intake, so that there is a persistent state of suppressed appetite. In a cross-sectional study of predictors of nutritional status, which included HGS and anthropometric measures, serum albumin was found to correlate with SGA and inflammatory markers but was not found to be a reliable indicator of change in nutritional status (Gama-Axelsson, Heimburger et al. 2012). For these reasons this clinical trial has used serum albumin as a marker of well-being rather than nutritional state, as it is believed that its use as a solo nutritional marker is limited but it may still be useful when incorporated into a score such as MIS or in combination with other nutritional markers or criteria (Kovesdy and Kalantar-Zadeh 2012) providing a more comprehensive overview.

We are able to confirm the association of decreased MIS and HGS with increasing dialysis vintage as suggested previously (Chertow, Johansen et al. 2000). Similar to other studies, we did not find a
significant change in body composition with dialysis vintage but these effects may be subtle and progress gradually and so were not highlighted in our relatively short follow-up (Johansen, Kaysen et al. 2003). Using a phase angle value of 5.0 as the cut-off only 5 out of 29 patients would be considered to be malnourished; only one of these patients also had a % BCM <35 (Oliveira, Kubrusly et al. 2010) and yet diagnosis by HGS would indicate the majority, 26 out of 29 patients may need nutritional intervention of which 16 would be considered weak, so it is clear that one single marker or cut-off is not wholly reliable.

Eighteen patients (62%) would be classified as being overweight with BMI >25kg/m² and this is associated with lower BCM and more at risk of protein malnutrition despite the high calorie intake (Guida, De Nicola et al. 2001). This again highlights the need for multiple methods of assessing nutritional status.

However, body composition has been proven to be a reliable method of diagnosing malnutrition (Rosenberger, Kissova et al. 2014) but the size of our study cohort may have limited our findings. We would expect body composition to correlate with measures of comorbidity, CCI, and with domains for the HRQoL domains particularly physical health scores. But there are inaccuracies with measuring body composition with BIA. We attempted to limit these by using multi-frequency BIA as this has been shown to be a more reliable method of measuring BCM in HD patients (Donadio, Halim et al. 2008).

4.5 Conclusion

Extended TT of 6 hours appears to have a positive impact on markers of nutritional status, promoting improved dialysis clearance of phosphate and dietary calorie intake. However, there was no detectable change in body weight or composition to support this.
CHAPTER 5

5 EFFECT OF EXTENDED TREATMENT TIME ON DIALYSIS PARAMETERS AND BLOOD PRESSURE

5.1 Introduction

As discussed earlier there are published data from international registries that have highlighted the benefits of extended TT on patient mortality. International data from DOPPS I, II and III representing analysis of over 37,000 patients has demonstrated a positive effect on mortality with increased TT. Analysis of TT as a continuous variable revealed that every 30-minute increase in TT was associated with a 6% decrease in relative risk of death (Tentori, Zhang et al. 2012). Our analysis of local data also revealed a positive relationship between mortality and increased TT, with a larger 32% decrease with every 20-minute increase in TT (Singh, Choi et al. 2013). Analysis of data from Australian and New Zealand registries (ANZDATA) associates TT with mortality risk (Marshall, Byrne et al. 2006), Table 5-1 demonstrates the improvement in risk with increasing TT.

Table 5-1: Univariate analysis of mortality risk by treatment time category

<table>
<thead>
<tr>
<th>Treatment time (hours)</th>
<th>Hazard ratio (95% Confidence interval)</th>
<th>p=value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5</td>
<td>1.67 (1.22-2.32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3.5-3.9</td>
<td>1.19 (0.88-1.60)</td>
<td></td>
</tr>
<tr>
<td>4.0-4.4</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td>4.5-4.9</td>
<td>0.7 (0.59-0.85)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>≥5.0</td>
<td>0.7 (0.59-0.86)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from (Marshall, Byrne et al. 2006)

Cardiovascular disease is a major cause of morbidity and mortality in the HD population and blood pressure control is an important factor. Data from the group at Tassin, who have pursued a strategy of slow long dialysis, 8 hours thrice weekly for many decades, demonstrate the benefits to blood pressure control without the need for anti-hypertensive agents (Chazot, Charra et al. 1995). DOPPS data suggest that slow UF is key and that this results in a significantly lower incidence of intra-dialytic hypotension (IDH) on dialysis (Chazot and Jean 2008). IDH is estimated to occur in up to half of all short dialysis sessions in the United States (Twardowski 2007) and occurs due to the
removal of large volumes of water and solutes over a short period, which depletes plasma volume (Daugirdas 2001).

Rates of UF that are greater than 10ml/h/kg are associated with an increase in hypotensive episodes (Saran, Bragg-Gresham et al. 2006). These episodes usually result in cessation of fluid removal and saline is often infused to relieve symptoms. Repeated incidences often result in increase of target or “dry” weight with increase in ECW and concomitant increase in blood pressure. Therefore an approach that either limits inter-dialytic weight gain (IDWG) or lengthens TT may serve to improve tolerability of dialysis and decrease UFR.

Analysis of HEMO study data also revealed that mortality secondary to cardiovascular disease increases at the threshold UFR of 10ml/h/kg irrespective of severity of heart failure (Flythe, Kimmel et al. 2011). A large study of more than 14,000 patients attempted to distinguish between the two parameters of weight gain and TT and respective impact on mortality and quantified IDWGs less than 3kg and TT more than 4 hours to be associated with decreased mortality. TT less than 4 hours and IDWG more than 3kg were associated with a 32% and 29% increase in relative risk of death respectively (Flythe, Curhan et al. 2013). A study investigating the relationship between IDWG and pre-dialysis blood pressure in over 400 prevalent HD patients has found every percentage increase in IDWG was associated with a unit increase in systolic blood pressure (Inrig, Patel et al. 2007).

Therefore prevention of excessive IDWG is imperative in good volume control and so in turn avoidance of hypertension and its negative effects on left ventricular hypertrophy (LVH) and reduced incidence of adverse cardiovascular events (Lee, Doh et al. 2014).

IDWG and blood pressure control are also affected by net sodium (Na) flux, and the latter is affected by dialysate Na concentration which is a dialysis treatment variable. It is thought that the use of a low dialysate Na concentration, (lower than that of the patient’s plasma Na concentration), results in a net negative Na balance due to the movement of Na from the patient, high concentration, to the dialysate, low concentration (Thomson, Dixon et al. 2013). This implicates TT as an influential factor as it will govern the time available for diffusion and Na movement to occur. In the past high Na dialysate concentrations have been employed to facilitate fluid removal - Na profiling. This results in a positive Na balance accompanied by increases in IDWG and blood pressure (Santos and Peixoto 2008). Studies of low dialysate Na concentration have demonstrated a decrease in IDWG and pre-dialysis blood pressure without any increase in intra-dialytic symptoms (Munoz, Bayes et al. 2011). But analysis of large registry data has suggested that serum Na concentrations are not associated with dialysate Na and that plasma Na concentrations below 140mmol/L are associated with
increased mortality (Hecking, Karaboyas et al. 2012). This has led to the concept of an individual patient’s set point for plasma Na concentration and the need for dialysate Na concentrations that match this to avoid Na gain.

Therefore it is important to assess the differences in fluid and solute removal on extended TT and analyse how this differs from the standard treatment arm. It is hypothesised that an extended TT will facilitate achievement of dry weight, in a more graduated approach, minimising symptoms and resulting in improved blood pressure control. However, this has not been proven in randomised prospective study of day-time intermittent HD.

5.2 Methods

The following were measured and collated at baseline and at each of the three dialysis sessions in the 24th week after initiation of each treatment arm.

- Dialysis treatment parameters: start and end time of dialysis, dry weight, IDWG, UFR, volume blood processed (LP), pre- and post-dialysis weight.

- 24-hour ambulatory blood pressure monitoring: This was conducted using the ABPM-04 Holter monitor™ (Meditech Ltd, Budapest Hungary). The ABPM-04 measures blood pressure by an oscillometric method and uses an algorithm that is clinically validated to the British Hypertension Society (BHS) and Association of the Advancement of Medical Instruments (AAMI) accuracy criteria. Readings were taken every 30 minutes during day time and hourly overnight. Patients were asked to leave the monitor on for a 24-hour period, most commonly commencing immediately after the midweek dialysis session.

- Blood pressure medications, including dose and frequency.

Serum urea, electrolytes and small molecule clearance as measured by spKt/V were measured at the midweek dialysis in the 24th week.

All patients were dialysed using our centre standard Na dialysate concentration, 140mmol/L, and the dialysate electrolyte content was kept constant on both treatment arms. Dialysers were also kept constant throughout the period of study.
5.3 Results

5.3.1 Baseline levels of dialysis treatment parameters

Table 5-2 describes the baseline levels of dialysis treatment parameters and medications.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline levels ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IDWG (L)</td>
<td>2.35 ± 0.89</td>
</tr>
<tr>
<td>Mean UF volume (L)</td>
<td>2.93 ± 812</td>
</tr>
<tr>
<td>Mean UFR (ml/hr/kg)</td>
<td>7.9 ±2.1</td>
</tr>
<tr>
<td>Mean litres processed</td>
<td>113.2 ± 17.4</td>
</tr>
<tr>
<td>Mean blood flow rate (ml/min)</td>
<td>406 ± 44</td>
</tr>
<tr>
<td>Mean spKt/V</td>
<td>1.74 ± 0.28</td>
</tr>
<tr>
<td>Mean serum Na concentration (mmol/L)</td>
<td>138.7 ± 6.7</td>
</tr>
<tr>
<td>Pre-dialysis systolic blood pressure (mmHg)</td>
<td>139.5 ± 22.6</td>
</tr>
<tr>
<td>Pre-dialysis diastolic blood pressure (mmHg)</td>
<td>80.1 ± 12.9</td>
</tr>
<tr>
<td>Pre mean arterial pressure</td>
<td>99.8 ± 14.4</td>
</tr>
<tr>
<td>Post-dialysis systolic blood pressure (mmHg)</td>
<td>128.7 ±20.6</td>
</tr>
<tr>
<td>Post-dialysis diastolic blood pressure (mmHg)</td>
<td>73.4 ± 17.1</td>
</tr>
<tr>
<td>Post-mean arterial pressure</td>
<td>91.8 ± 17.1</td>
</tr>
<tr>
<td>Mean number of anti-hypertensive agents (n)</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>% not on any anti-hypertensive agents</td>
<td>37.0 (n=10)</td>
</tr>
<tr>
<td>% ACE-inhibitors/ Angiotensin II antagonists (AIIA) use</td>
<td>44.4 (n=12)</td>
</tr>
<tr>
<td>% Calcium channel blockers use</td>
<td>11.1 (n=3)</td>
</tr>
<tr>
<td>% Alpha-blocker use</td>
<td>7.4 (n=2)</td>
</tr>
<tr>
<td>% Beta-blocker use</td>
<td>51.9 (n=14)</td>
</tr>
<tr>
<td>% Nitrate use</td>
<td>3.7 (n=1)</td>
</tr>
<tr>
<td>% Vasodilator</td>
<td>3.7 (n=1)</td>
</tr>
</tbody>
</table>
5.3.2 Effect of treatment time on blood pressure control

There was a significant decrease in mean arterial pressure (MAP) on the extended TT arm, 101.5mmHg (95% CI 96.2-106.9) to 92.8mmHg (95% CI 87.0-98.5), p<0.01. The increase in mean MAP on the 4-hour arm did not reach significance, 97.8mmHg (95% CI 92.0-103.7) to 107.6mmHg (95% CI 95.8-107.4), p=0.185, Figure 5-1.

![Figure 5-1: Effect of treatment time on mean arterial pressure (mmHg)]
When the effects were analysed by systolic and diastolic blood pressure, a significant reduction in median systolic blood pressure was observed on the 6-hour arm from 141mmHg to 127mmHg (p<0.05). The decrease in median diastolic BP from 81mmHg to 77mmHg was not significant (p=0.096), Figure 5-2. There was no significant change in either systolic (142mmHg to 143mmHg), p=0.070, or diastolic blood pressure (83mmHg to 81mmHg), p=0.236, on the 4-hour arm.

![Graph showing systolic blood pressure before and after 6-hour treatment](image)

**Figure 5-2: Effect of extended treatment time on systolic blood pressure**

The improved blood pressure control on the extended TT arm was accompanied by a significant decrease in requirement for anti-hypertensive medication and UFR, but without a change in IDWG (p=0.523) or UF volume (p=0.557).
There was an increase in UFR on the 4-hour arm but this did not reach significance (p=0.085) and no change in UF volume (p=0.616), Table 5-3.

Table 5-3: Effect of treatment time on dialysis-related treatment parameters

<table>
<thead>
<tr>
<th></th>
<th>Pre 6-hour</th>
<th>Post 6-hour</th>
<th>Pre 4-hour</th>
<th>Post 4-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of anti-</td>
<td>1.43 ± 1.3</td>
<td>0.69 ± 1.1*</td>
<td>1.30 ± 1.2</td>
<td>1.35 ± 1.3</td>
</tr>
<tr>
<td>hypertensive agents (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean UFR (ml/h/kg)</td>
<td>7.8 ± 2.6</td>
<td>5.7 ± 2.6**</td>
<td>8.7 ± 2.6</td>
<td>9.9 ± 3.9</td>
</tr>
<tr>
<td>Mean UF volume (ml)</td>
<td>2970 ± 925</td>
<td>2879 ± 1248</td>
<td>3182 ± 1292</td>
<td>3171 ± 1346</td>
</tr>
<tr>
<td>Mean IDWG (kg)</td>
<td>2.2 ± 1.0</td>
<td>2.3 ± 1.1</td>
<td>2.2 ± 0.9</td>
<td>2.5 ± 1.4</td>
</tr>
</tbody>
</table>

*p<0.01, **p<0.0001

The decrease in numbers of anti-hypertensive agents prescribed are detailed below, Table 5-4.

Table 5-4: Change in anti-hypertensive agent use

<table>
<thead>
<tr>
<th>Hypertensive agent</th>
<th>Pre 6-hour</th>
<th>Post 6-hour</th>
<th>Pre 4-hour</th>
<th>Post 4-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>% not on any anti-hypertensive agents</td>
<td>25.0</td>
<td>54.2</td>
<td>35.0</td>
<td>35.0</td>
</tr>
<tr>
<td>% ACE inhibitors/AIIA use</td>
<td>54.2</td>
<td>20.8</td>
<td>35.0</td>
<td>45.0</td>
</tr>
<tr>
<td>% Calcium channel blockers use</td>
<td>12.5</td>
<td>8.3</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>% Alpha-blocker use</td>
<td>12.5</td>
<td>0</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>% Beta-blocker use</td>
<td>50.0</td>
<td>29.2</td>
<td>55.0</td>
<td>50.0</td>
</tr>
<tr>
<td>% Nitrate use</td>
<td>0</td>
<td>0</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>% Vasodilator</td>
<td>4.2</td>
<td>4.2</td>
<td>5.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>
There was an increase in the % of patients not prescribed anti-hypertensive agents on the 6-hour arm but this did not reach significance (Fishers exact p =0.0753), Figure 5-3.

**Figure 5.3: Numbers of prescribed anti-hypertensive agents**

Dialysis vintage was found to have a significant effect on numbers of anti-hypertensive agents. A year increase in dialysis vintage was found to increase the odds of being prescribed lower categories of blood pressure medications, p<0.001.

### 5.3.3 Effect of extended treatment time on blood flow rate and blood volume processed

The median blood flow rate on the 6-hour arm was 279ml/min, approximately 60% lower, than on the 4-hour arm, 430ml/min, p<0.001. This was achieved by equating the blood volume processed on the 6-hour and 4-hour arms, median 100.5l and 103.6l respectively, p=0.094.
5.3.4 Effect of treatment time on small molecule clearance as measured by spKt/V

Despite equating blood volume processed on both treatment arms, dialysis adequacy was significantly higher on the 6-hour arm spKt/V 1.9 (95% CI 1.8-2.2) than on the 4-hour arm spKt/V 1.6 (95% CI 1.4-1.7), p<0.01, Figure 5-4.

![Figure 5-4: Achieved spKt/V on 6-hour and 4-hour treatment arms](image)

5.3.5 Effect of treatment time on serum sodium concentration

We found no significant difference in median pre-dialysis serum Na concentrations at the end of the 6-hour and 4-hour treatment arms, 139mmol/L (95% CI 137-140) and 139mmol/L (95% CI 137-140) respectively, p=0.952.

5.4 Discussion

This prospective cross-over study demonstrates the very positive association of extended TT on blood pressure control, significantly reducing MAP. This was achieved with less reliance on anti-hypertensive agents with the mean number of prescribed agents being halved, and a greater number of patients no longer prescribed blood pressure medication. This was not accompanied by any significant change in IDWG and UF volume but UFR decreased significantly. Although there was a corresponding increase in MAP, increased use of blood pressure medication and increase in UFR on the 4-hour arm did not reach significance.
Hypertension is common in the HD population and has been defined as an ambulatory or inter-dialytic average blood pressure ≥135/85 mmHg or treatment with an anti-hypertensive agent (Agarwal 2011). There is however no clear consensus on target blood pressure levels for the HD population. In the absence of clear prospective clinical trial data there is a degree of controversy as to clinical goals for blood pressure particularly as observational studies have highlighted the association of low blood pressure with heart failure and mortality (Zager, Nikolic et al. 1998) and indicated a J shaped curve associating blood pressure with mortality. This may explain our finding that there are greater odds of being prescribed less anti-hypertensive agents with increasing dialysis vintage.

The HEMO Group have reported mean levels of pre- and post-systolic blood pressures significantly in excess of this, 152 mmHg and 138 mmHg respectively (Rocco, Yan et al. 2001). However, pre- and post-dialysis blood pressure are thought to be inaccurate resulting in over-estimation of systolic blood pressures and ambulatory readings are considered preferable (Agarwal, Peixoto et al. 2006). We therefore undertook ambulatory blood pressure monitoring in our study in preference to pre- and post-dialysis measurements although patients were monitored for a shorter 24-hour period.

The FHN group has also recently published the effect of frequent and frequent-nocturnal HD on blood pressure control and report pre-dialysis systolic blood pressure decreases of 7.7 mmHg in the short-time daily HD group and 7.3 mmHg in the nocturnal daily HD group compared to thrice weekly HD. The decreases in diastolic blood pressure were 3.9 mmHg and 4.2 mmHg in both groups respectively (Kotanko, Garg et al. 2015). We have demonstrated a larger decrease in systolic blood pressure, 14 mmHg, almost twice that reported by the FHN group, and similar decrease in diastolic blood pressures, 4 mmHg, by extending TT to 6 hours. Also similar to our results this group found the numbers of anti-hypertensive medications prescribed to also decrease. Other studies on quotidian dialysis have also published results consistent with our study associating frequent HD with improved blood pressure control and decreased intensity of anti-hypertensive drug therapy (Nesrallah, Suri et al. 2003).

It has been demonstrated that good volume control, as measured by limiting ECW, favours improved blood pressure control (Agarwal 2011), although there may be a lag between achieving accurate dry weight and reduction in blood pressure (Agarwal 2012).

Achievement of optimal dry weight is important and this is defined as the lowest post-dialysis weight achieved without any significant symptoms or hypotension during dialysis (Perez-Garcia, Lopez-Gomez et al. 2001, Agarwal and Weir 2010).
Long-dialysis TT has been shown to attain acceptable blood pressure control by facilitating achievement of optimal dry weight by slow and gentle dry weight probing (Charra, Laurent et al. 1996) and possibly also through removal of substances that affect tone of blood vessels (Charra, Calemard et al. 1996).

Clearance of other large molecules may be increased with extended TT, even if blood and dialysate volumes are kept constant (Eloot, Vanholder et al. 2012). Recent studies have demonstrated that higher levels of a protein-bound uraemic toxin, indoxyl sulphate, are associated with a first heart failure event (Cao, Chen et al. 2015). This middle molecule promotes inflammation and atherosclerosis and it may be logical to hypothesise that increased clearance of this middle molecule may deter inflammatory processes to improve patient outcome. The use of high dialysate flow rates of 800ml/min, which is routine at our unit, and high flux dialysers have been used in conjunction with extended nocturnal HD to increase removal of large protein-bound molecules (Sirich, Luo et al. 2012). There are seven solutes of large molecular size whose concentration in ESRD is more than 30 times that with normal renal function (Vanholder, De Smet et al. 2003) and the levels of these toxins have been associated with mortality in elderly patients (Wu, Hsu et al. 2012). Although protein-bound molecules are not removed on low flux HD it may be reasonable to examine the efficacy of extended TT in clearing toxins of large molecular size.

We have demonstrated improved systolic blood pressure control but have not observed any significant change in ECW, target dry weight or indeed IDWG. Therefore we are unclear as to the mechanism of our improved blood pressure control. It may be related to Na flux as it could be postulated that the increased exposure to the dialysate on the extended TT arm may serve to promote Na diffusion from the dialysate in patients with low serum concentrations. But this would favour increase in systolic blood pressures with extended TT. We are unable to corroborate this theory as we did not observe any changes in serum Na concentrations after each TT arm. However, the levels immediately post dialysis would have been more informative of intra-dialytic movement of Na. We did not conduct pre- and post-blood sampling of individual dialysis sessions for serum Na and this therefore limits our ability to speculate on mechanisms for blood pressure decrease in this study.

Another factor that may have affected Na flux is dietary Na intake. It is advised that accurate assessments of intake of micronutrients be conducted using 7-day diet diaries, but we were limited by use of 3-day diaries with their greater compliance, therefore we were unable to quantify dietary Na intake in our study cohort.
The HEMO study participants were reported to have a salt intake of 5.15g equating to approximately 2.2mg (99mmol) of Na. Although dietary Na intake was associated with significantly increased UFR and an increase in all-cause mortality, reduction of dietary Na alone did not have a mortality effect (Mc Causland, Waikar et al. 2012).

In centres that practice dietary salt restriction, such as Tassin, average daily salt intakes are 3.8g/day (1.7mg Na and 75mmol) (Chazot 2009). There are limited published studies investigating the effect of low sodium diets on blood pressure control in HD patients, and this may relate to the difficulties in accurately measuring Na intake from diet diaries which often underestimate intake. More usually dietary Na restriction is paired with dialysate restriction in a strategy of strict volume control and one such study of more than 200 patients followed up for approximately four years has demonstrated significantly reduced: blood pressure, 150/89mmHg to 121/75mmHg; IDWG, 1440ml/day to 930ml/day; and mortality (Ozkahya, Ok et al. 2006).

Our local strategy of avoidance of high Na foods is not strictly advised or enforced; instead patients with excessive IDWG or problematic UF associated with symptoms of hypovolaemia are highlighted for dietary Na restriction by a renal dietitian. The study cohort was not targeted for specific advice on dietary Na intake during the period of investigation.

Despite the matching of blood volume processed on both the extended 6-hour and standard 4-hour treatment arms we found small molecule clearance to be significantly higher with longer TT and this may be a limitation of our study.

The mean UFR of 9.9ml/h/kg on the 4-hour treatment arm was below that associated with increased mortality in published studies, but as we did not collect data on numbers of episodes of IDH it is possible that the higher UFR on the 4-hour arm equated to a greater incidence of hypotensive episodes and more requirement for saline to provide symptomatic relief. IDH is associated with poor cardiac outcomes and relates to the incidence of reduced myocardial perfusion (Kerr 2014). Repeated intra-dialytic instances have been demonstrated to induce myocardial stunning which is defined by decrease in myocardial function greater than 20% and over time this results in irreversible decline in left ventricular function (Burton, Jefferies et al. 2009).

5.5 Conclusion

The positive effects of extended TT on dialysis parameters and blood pressure may advocate a move away from evaluating dialysis quality based purely on dialysis urea clearance and turn towards a quality strategy based on more widespread benefits. These benefits include those described in this
Chapter: improved blood pressure control; lowered UFR; better haemodynamic stability; and possibly, removal of molecules which due to their size are not readily removed with standard dialysis (Zsom, Zsom et al. 2008), an approach that places greater importance on TT.
CHAPTER 6

6 EFFECT OF EXTENDED TREATMENT TIME ON BIOMARKERS OF MIA SYNDROME

6.1 Introduction

Surrogate biomarkers of the risk factors relating to the increased morbidity and mortality observed in the dialysis population are established. These biomarkers have significant prognostic value and so are used to evaluate the risk of an adverse event, often in the absence of any overt symptoms.

The biomarkers selected for investigation in this study are hs-CRP, cTNI and BNP. These biomarkers are primarily used to diagnose infective episodes, myocardial injury and underlying cardiac disease respectively. It is hypothesised that in patients with renal insufficiency elevated levels of cTNI and BNP may be indicative of chronic volume overload and resultant hypertrophic cardiomyopathy (Parfrey 2000, Sharma, Jackson et al. 2004). Elevated cTNI and BNP levels are common in patients on HD (Havekes, van Manen et al. 2006) and this may reflect the changes in blood pressure and haemodynamic instability, with a third of dialysis sessions being complicated by IDH (Bos, Bruin et al. 2000).

There is evidence to suggest that dialysis may induce reduced myocardial blood flow and a decrease in excess of 30% from pre-dialysis levels is associated with impaired left ventricular function even after normal perfusion is restored and is termed myocardial stunning (McIntyre, Burton et al. 2008). Repeated acute cardiac ischaemic episodes may have a cumulative effect and result in more prolonged dysfunction that is associated with development of heart failure in patients on HD (Selby and McIntyre 2007). The presence of impaired left ventricular function during dialysis has been associated with increased ultrafiltration volumes, decreased systolic blood pressure and significantly higher levels of cTNI (Burton, Jefferies et al. 2009).

Studies assessing the effect of dialysis regimens on myocardial stunning have suggested that more frequent dialysis results in: lower UF volumes; less pronounced reduction of systolic blood pressure; lower incidence of myocardial stunning. Those patients dialysing nocturnally five times also had significantly lower cTNI, BNP and hs-CRP levels (Jefferies, Virk et al. 2011). We hypothesise that extended TT on dialysis may have similar effects and improve volume and blood pressure control that may also be reflected in improved levels of these biomarkers.
However, it may be that increased levels of inflammatory molecules may result from increased exposure to the extracorporeal HD circuit driving systemic inflammation. Therefore in gauging the effects of these biomarkers we may in fact be assessing the outcome of competing effects; increased inflammatory triggers versus improved volume and blood pressure control.

6.2 Methods

Pre-dialysis blood samples were used for all assays. Dialysis nursing staff took samples from either the arterial needle for patients with AVF prior to introduction of heparin or saline or if primary access was a central venous catheter (CVC), from the arterial limb after discarding a 10ml aliquot to avoid contaminating with line lock solutions.

6.2.1 B-type natriuretic peptide

Samples were collected in plastic collection bottles containing ethylenediaminetetra-acetic acid (EDTA) and immediately placed on ice. They were centrifuged within 30 minutes of sampling and aliquots stored at -40 degrees Celsius. Samples were mixed thoroughly after thawing and batch analysis was conducted of the EDTA plasma sample to quantify human BNP using the Architect-chemiluminescent microparticle immunoassay. The results obtained were in units, pg/ml. A conversion of 1pg/ml = 0.2887pmol/l was used to compare with published data.

6.2.2 Cardiac troponin I

Samples were collected in plastic collection bottles containing EDTA. They were refrigerated and centrifuged within 30 minutes of sampling and aliquots stored at -40 degrees Celsius. Samples were mixed thoroughly after thawing and batch analysis of the EDTA plasma sample was conducted to quantify cTNI using the Architect-chemiluminescent microparticle immunoassay. The results obtained were in units ng/ml.

6.2.3 High-sensitivity C-reactive protein

Samples were collected in serum separating tubes, refrigerated and centrifuged within 30 minutes of sampling. The separated blood serum was removed from the coagulated cells by pipette and transferred for storage at -40 degrees Celsius. Samples were mixed thoroughly after thawing and batch analysis of the serum was conducted using an enzyme-linked immunosorbent assay (ELISA) to quantify human CRP. The results obtained were in mg/L.
6.3 Statistical methods

Mann-Whitney U test was used to assess the effect of diabetic status on baseline levels of biomarkers. Statistical significance was defined as $p<0.05$.

6.4 Results

6.4.1 Baseline levels

Table 6-1 describes the median baseline levels of biomarkers.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline Median level</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml [IQR])</td>
<td>193.7 [292.2]</td>
</tr>
<tr>
<td>Serum cardiac troponin (ng/ml [IQR])</td>
<td>19.0 [42.2]</td>
</tr>
<tr>
<td>Serum hs-CRP (Mmg/L [IQR])</td>
<td>3.4 [6.4]</td>
</tr>
</tbody>
</table>

We found no significant difference in baseline levels of biomarkers BNP ($p=0.343$), cTNI ($p=0.432$) and hs-CRP ($p=0.494$) by diabetic status.
6.4.2 Effect of treatment time on biomarkers

There was no significant difference in median BNP, cTNI and hs-CRP levels on the extended TT arm but 4-hour treatment arm was associated with significantly elevated cTNI levels, p<0.05, Table 6-2.

Table 6-2: Differences in biomarkers by treatment arm

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Variable</th>
<th>BNP</th>
<th>cTNI</th>
<th>hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median pre (IQR)</td>
<td>261.8 (284.2)</td>
<td>35.0 (43.4)</td>
<td>3.4 (6.7)</td>
</tr>
<tr>
<td>6 hour</td>
<td>Median post (IQR)</td>
<td>212.5 (370.6)</td>
<td>31.8 (31.9)</td>
<td>7.1 (4.4)</td>
</tr>
<tr>
<td></td>
<td>Z value</td>
<td>0.569</td>
<td>0.379</td>
<td>1.713</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.597</td>
<td>0.721</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>Median pre (IQR)</td>
<td>192.5 (419.6)</td>
<td>25.0 (60.5)</td>
<td>3.6 (5.5)</td>
</tr>
<tr>
<td>4 hour</td>
<td>Median post (IQR)</td>
<td>256 (434.5)</td>
<td>39.0 (36.1)</td>
<td>5.4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Z value</td>
<td>0.804</td>
<td>2.166</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.455</td>
<td>0.03*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*p <0.05

6.4.3 Correlates of B-type natriuretic peptide pre- and post-6-hour treatment arm

BNP was not correlated to demographic variables, age, dialysis vintage, CCI or dry weight. However, it was highly correlated with cTNI and numbers of anti-hypertensive agents. The negative relationship with serum transferrin indicates that nutritional status decreases with increasing BNP levels, Table 6-3.

Table 6-3: Variables significantly correlated with BNP on 6-hour arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>BNP (Pre 6-hour arm)</th>
<th>BNP (Post 6-hour arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTNI (ng/ml)</td>
<td>0.900**</td>
<td>0.763**</td>
</tr>
<tr>
<td>Serum transferrin (g/L)</td>
<td>-0.518*</td>
<td>-0.373</td>
</tr>
<tr>
<td>Anti-hypertensive agents (n)</td>
<td>0.586*</td>
<td>0.727**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

After 24 weeks on the 6-hour TT arm BNP levels continued to correlate with cTNI and numbers of anti-hypertensive agents but there was no relationship with serum transferrin.
6.4.4 Correlates of B-type natriuretic peptide pre- and post-4-hour treatment arm

Again BNP was not correlated to demographic variables, age, dialysis vintage, CCI or dry weight. Similar to the 6-hour treatment arm, BNP was highly correlated with cTNI and numbers of anti-hypertensive agents but also UFR. But after 24 weeks on the 4-hour arm it was no longer correlated to any of the factors, Table 6-4.

Table 6-4: Variables significantly correlated with BNP on 4-hour arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>BNP (Pre 4-hour arm)</th>
<th>BNP (Post 4-hour arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTNI</td>
<td>0.820**</td>
<td>0.261</td>
</tr>
<tr>
<td>Anti-hypertensive agents (n)</td>
<td>0.624*</td>
<td>0.248</td>
</tr>
<tr>
<td>UFR</td>
<td>0.526*</td>
<td>0.130</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

6.4.5 Correlates of cardiac troponin I pre- and post-6-hour treatment arm

cTNI also correlated with the number of anti-hypertensive agents but additionally post levels correlated with MAP, Table 6-5.

Table 6-5: Variables significantly correlated with cTNI on 6-hour arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>cTNI pre 6-hour arm</th>
<th>cTNI post 6-hour arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml)</td>
<td>0.900**</td>
<td>0.763**</td>
</tr>
<tr>
<td>Anti-hypertensive agents (n)</td>
<td>0.528*</td>
<td>0.591*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>0.17</td>
<td>0.522*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01
6.4.6 Correlates of high-sensitivity C-reactive protein on both treatment arms

hs-CRP was correlated with MIS on both the pre 6-hour and pre 4-hour arms respectively, $r=0.567$ ($p<0.05$) and $r=0.532$ ($p<0.05$). Additionally, after 24 weeks on the 4-hour arm, hs-CRP also correlated significantly with serum haemoglobin, $r=-0.564$ ($p<0.05$), Figure 6-1.

![Figure 6-1: Correlation of hs-CRP with serum haemoglobin](image)

6.4.7 Clearance of B-type natriuretic peptide on extended treatment

There was no significant difference in serum BNP clearance between the extended 6-hour dialysis and standard 4-hour TT sessions, 19.3% versus 21.7% ($p=0.81$).

6.5 Discussion

We did not find the concentration of biomarkers to be significantly affected by TT, only cTNI was significantly increased on the standard TT arm. There was an increase in hs-CRP on the 6-hour arm but this did not reach significance. Similarly, we did not find a significant difference in clearance of BNP between the two treatment arms. The study is likely to have been underpowered to detect changes in these biomarkers.

BNP is a marker of the extent and severity of cardiac disease in HD patients (Nishikimi, Futoo et al. 2001, Niizuma, Iwanaga et al. 2009). Mean BNP levels at baseline were indicative of the presence of
significant coronary artery disease given that normal levels in a healthy individual are <25pg/ml (Wang 2012).

In a study correlating BNP levels with functional measures of heart failure and LVH, levels above 220.4pg/ml were associated with significant abnormality (Zoccali, Mallamaci et al. 2001). But BNP levels have been demonstrated to vary over time in HD patients and are higher in those with evidence of malnutrition (Snaedal, Qureshi et al. 2014). Although the mean dry weight of our study population would not indicate they were malnourished, the severely reduced functional ability reflected by HGS implies a significant degree of muscle wasting.

It has been suggested that BNP is also a marker of volume status with fluctuations in fluid status and post-dialysis blood pressures being well correlated with fluctuations in BNP (Roueff, Martin et al. 2008). However, much of the evidence is from studies in the PD population (Papakrivopoulou, Lillywhite et al. 2012) but it may be that serial measurements of BNP are preferential to the single measurements conducted in this study and more likely to demonstrate relationships (Davenport 2012). However, the contrary has been argued in HD patients, in a cross-sectional study investigating dry weight probing, decrease in post-dialysis weight was not correlated to BNP nor was BNP correlated with UF (Agarwal 2013).

We did not find a difference in BNP levels on either treatment arm but we did find BNP to correlate positively with MAP on the 6-hour arm. In contrast BNP levels on the standard 4-hour treatment arm did relate to UFR indicating some association with fluid removal. However, it is important to note that in these studies the anti-hypertensive agents prescribed were kept constant whereas in our study blood pressure medication was amended as clinically indicated. The reliability of our results may be affected by the difficulties in measuring BNP and its relative instability with a half-life of 20 minutes. A precursor of BNP, n-terminal Pro BNP, is thought to be more stable with a longer half-life of 2 hours but is more affected by impaired renal clearance therefore BNP was elected as the superior marker (Wang 2012) in this circumstance.

We found baseline levels of cTNI to be elevated from normal and levels increased significantly on the standard treatment arm but there was no change on the extended treatment arm. But after 24 weeks on extended TT we did find cTNI levels to be significantly correlated with numbers of anti-hypertensive agents and MAP. As discussed in Chapter 5, it may be that the increased cTNI levels seen on the 4-hour arm are indicative of increased episodes of IDH and myocardial ischaemia and stunning with associated loss of cardiac function (Burton, Jefferies et al. 2009).
CRP levels were also elevated at baseline representing significantly increased mortality risk. Multivariate analysis has revealed inflammatory mediators, including CRP, are lowest in patients with AVFs as their primary vascular access compared to those dialysing via CVCs. Although our local experience with use of CVCs has been very positive (Duncan, Singh et al. 2004, Power, Singh et al. 2011), we have an unusually high percentage of patients in whom CVCs are the primary source of vascular access and this may contribute to the chronic elevation of CRP in our study cohort.

There was a trend towards increased CRP levels on the extended TT arm, although this did not reach significance, and may have been secondary to increased contact with the extra-corporeal circuit. We did not have a large variance in CRP nor were there any patients with extremely high levels, suggestive of an acute episode of infection at the time of blood sampling. Therefore the change in CRP with extended TT is likely to reflect chronic low level inflammatory processes.

6.6 Conclusion

There was limited effect on the measured biomarkers overall and this may relate to under-powering. Only cTNI increased significantly on the shorter treatment arm compared with extended TT and this may reflect loss of myocardial function.
CHAPTER 7

7 EFFECT OF EXTENDED TREATMENT TIME ON QUALITY OF LIFE AND PATIENT EXPERIENCE

7.1 Introduction

The effects of increased TT on patient outcomes, irrespective of how positive they may be, are limited by the impact on patient experience and QoL.

In designing this study a questionnaire was sent out to all patients at a single HD satellite centre to assess the likelihood that we would be able to recruit individuals to a clinical trial looking at the effect of TT.

Some inherently younger and fitter patients expecting a change in treatment modality, or transplantation, did not consider participating.

For others there was potential to improve their time on dialysis and evaluate the effect of a dialysis prescription change. The prescription change might add to their treatment burden because of the extra time commitment required for dialysis. Conversely it may ultimately affect the quality of a patient’s life by improving not just the dialysis experience and symptoms but improve their general health away from the dialysis. For a smaller minority, the idea of dialysing beyond their usual time was unthinkable and also not pragmatic due to comorbidities and frailty (Vandecasteele and Kurella Tamura 2014).

This demarcates the HD population into those for whom dialysis is:

- an interim treatment.
- long-term treatment.
- final treatment.

It is the group for whom HD is likely a long-term treatment that may be more likely to take up the potential benefits of extended TT.

If the results of observational studies are noted, the potential impact of extended TT on clinical outcomes may be powerful, so much so that TT has been named as a quality improvement measure in the United States (Parker, Straube et al. 2012). But with the spectrum of clinical goals described
above, a patient-centred approach is needed and evaluation of the clinical effects of extended TT must be countered with the primary needs of the individual patient.

Currently the accepted quality measure of HD is urea clearance either as spKt/V or more simply by URR. Yet it has been demonstrated that symptoms such as fatigue, general lethargy, headaches, hypotensive episodes and cramps are common place and up to 25% of patients take 24 hours to recover from dialysis (Caplin, Kumar et al. 2011) despite achieving median spKt/V of 1.7, significantly above recommended target levels. This brings into question the suitability of a single measure of dialysis quality which is based on clearance of small molecules which are unrepresentative of other uraemic toxins.

Up to half of all HD patients are reported to have either psychological symptoms of depression or physical symptoms of pain and assessment of their HRQoL demonstrates significant impairment of PCS and MCS (Belayev, Mor et al. 2014). Often chronic pain results in sleep disturbances and impacts on illness burden and QoL (Cohen, Patel et al. 2007). The presence of symptoms on HD is common; 75% of patients have between 6 and 13 symptoms with more than half of patients complaining of fatigue, joint or bone pain and skin problems or itching. The burden and extent of physical symptoms were found to influence emotional health scores and to correlate significantly with impaired quality of life (Weisbord, Fried et al. 2005). Although the severity and prevalence of symptoms on HD are high, dialysis staff were found to either underestimate the severity or poorly recognise their presence (Weisbord, Fried et al. 2007). The extent to which these symptoms affect a patient’s functional ability to perform daily tasks increases as they age and results in greater dependency on support services and carers (Cook and Jassal 2008). It is clear that physical symptoms, comorbidities and general well-being are influential in the presentation of depression and HRQoL (Hung, Wu et al. 2011).

Ultimately HRQoL includes components that are: physical; psychological; or social.

- Physical areas include functional capacity and ability to undertake work.
- Psychological realms refer to well-being, self-esteem, presence of anxiety or depression and personal feelings of satisfaction.
- Social aspects refer to pastimes and interaction with family and friends.
An individual’s perception of what each of these components means differs, so much so that patients with similar health status can have very different perceptions of their HRQoL (Valderrabano, Jofre et al. 2001).

So when reviewing the effect of TT, it was considered crucial to also incorporate a study of how extended TT impacts on patient’s general well-being, the level of intrusion into their daily lives as well as more clinical markers of their dialysis experience such as intra- and inter-dialytic symptoms. This was conducted in addition to the hard clinical endpoints discussed in previous chapters.

7.2 Methods

The impact of extended TT on QoL and individual patient experience was gauged by measurement of:

- time to recovery (TTR).
- quality of life.
- withdrawal from the study.
- narratives from semi-structured patient interviews.

7.2.1 Time to recovery

This was used to measure intensity of post dialysis fatigue (PDF) and assessed from the patient’s response to the open ended question: “How long does it take you to recover from a dialysis session?” The answer was recorded in units of minutes. Patients were asked this whilst in the waiting area or directly before dialysis. Answers given in minutes were recorded without need for manipulation but other variants in response were converted as follows:

- Hours multiplied directly by 60.
- “Couple of hours” patient was asked to qualify what they meant by “couple” and verify that it was 2 hours and if incorrect the specified hours were recorded as above.
- Half day/next day attributed a value of 720 minutes.
- “One day” attributed a value of 1440 minutes.
- “More than a day” attributed a value of 2160 minutes.
7.2.2 Quality of life

This was measured by the Kidney Disease Quality of Life Questionnaire (KDQoL-36). Patients were provided with a pen and informed that it would take 10-15 minutes to complete and they had the option of completing: whilst on dialysis; or if they preferred, complete at home and return at the next dialysis session. The patients were reassured that there were no correct/incorrect answers and that where they were unsure how to answer to choose their first or initial “reflex” response.

The study investigator and clinical care staff were not permitted to administer the questionnaire or interpret specific questions if asked by the patient. On completion of the questionnaire it was checked to ensure that no items were left unanswered. Where an item was left unanswered the patient was asked to provide an answer and complete the questionnaire.

7.2.3 Withdrawal from the study

A withdrawal from study questionnaire which asked patients to highlight the main reasons for voluntary exit from the study was used. The questionnaire also asked if anyone, including relatives, carers or healthcare professionals, had influenced their decision to withdraw and whether the study or clinical staff could have assisted or supported them differently to enable them to remain in the study.

The questionnaire was completed by the patient and if agreed, comments or issues highlighted in the form were discussed later.

7.2.4 Semi-structured patient interviews

Semi-structured patient interviews were organised in advance with the patient on their usual dialysis day to avoid extra visits to the dialysis unit and this was preferred by all patients. In order to comply with this request it was not always possible to interview in a private dialysis area and so some patients were asked if they were happy to be interviewed on the unit in their usual dialysis position.

The patients were informed that all interviews would be recorded and the audio-tapes transcribed for analysis. The patients were advised that the topics of discussion would not be disclosed to their immediate care team. They were reassured that the sole purpose of the interviews was to provide some insight into their experience of participating in the clinical trial of TT and assess their perception of a good dialysis and gauge to what extent, if any, either of the treatment arms fulfilled this perception.
The study investigator ensured patients were aware that their insight would inform the feasibility of extended TT regardless of the potential clinical benefits and so poor experiences would not be received negatively.

The following questions were used to provide a framework to the interviews and ensure that all interviews were uniform in structure and also permitted further probing dependent upon the individual’s response.

1. “What in your mind is a good dialysis?”

2. “Which of the two treatment arms most closely matches a good dialysis experience for you?”

3. “Did you feel any different on either treatment arm?”

4. “What could we as health professionals do to make your dialysis experience more positive?”

5. “Is there a point at which the benefits of treatment are not worth the ‘cost’ to you personally?”

Patients were selected for interview using a purposive sampling strategy. The narratives were used to capture a diverse range of opinions, perspectives and experiences. Therefore the numbers interviewed reflected the inclusion of male and female patients, from different ethnic backgrounds and age groups.

Care was taken to ensure there was representation from each satellite HD centre and included narratives from those who withdrew from the study of their own accord and those who withdrew due to cadaveric transplantation. The number of interviews conducted was based pragmatically on feasibility within fellowship timelines but ultimately was based on an absence of new themes or sub-themes being identified.

All interviews were audio-taped and transcribed by an external transcriber who did not have any connection with the study team or department. All transcriptions were read thoroughly to get an overall sense of the areas covered and then phrases or words relevant to TT and the study outcomes were highlighted. Different facets of patients’ experience of their HD treatment were used to identify recurrent themes.
7.3 Results

7.3.1 Effect of treatment time on time to recovery from a haemodialysis session

TTR decreased significantly on the 6-hour treatment arm from 426 minutes ± 292 minutes to 131 minutes ± 199 minutes, p<0.001.

Conversely TTR increased on the 4-hour arm from 350 minutes ± 322min to 519 minutes ± 510 minutes but this did not reach significance, p=0.214, Figure 7-1.

![Figure 7-1: Time to recovery after treatment time of 4 hours and 6 hours](image)
The percentage of patients with recovery times less than 2 hours increased from 11.1% to 50.0% on the 6-hour arm, but did not change on the 4-hour arm, Figure 7-2.

Figure 7-2: Distribution of time to recovery with extended and standard treatment time
TTR data was skewed and the square root of TTR was used in the mixed model to assess treatment effect, Figure 7-3. TTR was found to be significantly affected by CCI, $p<0.05$ but there was found to be no change for levels of CCI>7.

*Figure 7-3: Effect of square root of time to recovery with treatment time*
### 7.3.2 Effect of treatment time on KDQoL sub domain - symptom score

An increase in symptom score reflects an improvement in symptoms. Symptom score was found to increase significantly with extended TT from 74.6 ± 11.9 to 81.5 ± 14.5, p<0.05. The converse was true with symptoms scores decreasing from 77.6 ± 14.7 to 74.3 ± 15.1, p=0.282, illustrated in Figure 7-4.

Dialysis vintage was found to have a significant positive effect on symptom score with extended TT, 1.44 p<0.01, but had a negative effect on the standard 4-hour TT arm but was not significant, -0.89 p=0.17.

![Figure 7-4: Effect of treatment time on symptom score](image)

*Figure 7-4: Effect of treatment time on symptom score*
7.3.3 Effect of treatment time on KDQoL sub domain - burden of kidney disease

An increase in burden of kidney disease score reflects a lessening of burden. The burden of kidney disease score was found to increase with extended TT from $44.1 \pm 20.2$ to $51.0 \pm 19.4$, $p<0.05$.

The increase in the disease burden score $48.6 \pm 26.1$ to $45.8 \pm 24.0$ was not significant, $p=0.151$, Figure 7-5.

The burden of kidney disease score was also skewed and the natural logarithm of score was employed in the mixed model.

![Figure 7-5 Effect of treatment time on logarithm burden of kidney disease score](image)

*Figure 7-5 Effect of treatment time on logarithm burden of kidney disease score*
7.3.4 Effect of treatment time on domains of HRQoL

There was found to be no significant difference in physical health (SF-12 Physical) or mental health (SF-12 Mental) score on either treatment arm. Nor was there any change in effects of kidney disease domain score, Table 7-1.

Table 7-1: Effect of treatment time on domains of HRQoL

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pre 6 hour</th>
<th>Post 6 hour</th>
<th>p-value</th>
<th>Pre 4 hour</th>
<th>Post 4 hour</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of kidney disease</td>
<td>68.9 ± 23.2</td>
<td>70.3 ± 23.8</td>
<td>0.716</td>
<td>65.6 ± 23.2</td>
<td>66.8 ± 24.4</td>
<td>0.662</td>
</tr>
<tr>
<td>SF-12 Physical</td>
<td>33.8 ± 7.7</td>
<td>33.2 ± 7.6</td>
<td>0.586</td>
<td>38.5 ± 8.9</td>
<td>36.3 ± 9.1</td>
<td>0.122</td>
</tr>
<tr>
<td>SF-12 Mental</td>
<td>48.3 ± 11.7</td>
<td>50.9 ± 8.4</td>
<td>0.306</td>
<td>47.7 ± 11.1</td>
<td>50.1 ± 0.90</td>
<td>0.349</td>
</tr>
</tbody>
</table>
### 7.3.5 Tolerance to extended treatment time as measured by withdrawal from the study

The acceptability and tolerance to extended TT were gauged by withdrawal from the study.

Table 7-2 describes the reasons for the withdrawal. There were five “enforced” withdrawals on each treatment arm.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>6 Hour</th>
<th>4 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal clinical outcomes</td>
<td>Clearance (spKt/V or PO₄ control)</td>
<td>0</td>
<td>1†</td>
</tr>
<tr>
<td></td>
<td>Blood pressure control</td>
<td>0</td>
<td>1†</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Intra-dialytic cramp/hypotension</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Light-headed at end of HD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Discomfort/restlessness/</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Boredom</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Unrelated adverse event</td>
<td>Acute admission/event</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Change in modality</td>
<td>Cadaveric transplantation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>Patient changed mind</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

† At request of the consultant nephrologist

The withdrawals on the 6-hour arm were associated with non-clinical symptoms of boredom and restlessness on the HD chairs, with patients stating that the availability of beds would have altered their decision to exit the study. Two patients with clinical symptoms of light-headedness on the 6-hour arm withdrew at weeks 11 and 19. Both were diabetics with acceptable blood glucose levels.

Two of the withdrawals on the 4-hour arm were related to suboptimal clinical outcomes and were at the recommendation of the consultant nephrologist in charge of the patient’s clinical care. Another two withdrawals were related to fluid removal and UF. All four withdrawals were after week 10.

One withdrawal on each treatment arm took place in week 1. The patient on the 4-hour arm no longer wanted to be part of a clinical trial. The other patient on the 6-hour arm complained of boredom.
7.3.6 Narratives from semi-structured interviews

There were 11 semi-structured interviews conducted and these ranged from 20 to 45 minutes in duration depending on the patient’s individual physical and mental condition. Some patients were limited in their answers and others elaborated extensively. The characteristics of the recruits interviewed are outlined in Table 7-3.

Table 7-3: Characteristics of interviewees

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Male</th>
<th>Age&gt; 65 years</th>
<th>Age&gt; 75 years</th>
<th>HD vintage &gt;2 years</th>
<th>DM</th>
<th>Lives alone</th>
<th>Employed</th>
<th>Withdrawal on 4-hour arm</th>
<th>Withdrawal on 6-hour arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
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<td>M2</td>
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<td>M3</td>
<td>•</td>
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<td>M4</td>
<td>•</td>
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<td>F1</td>
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<td>M5</td>
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<td>M6</td>
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<td>M7</td>
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<td>M8</td>
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<tr>
<td>M9</td>
<td></td>
<td>•</td>
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<td>•</td>
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<tr>
<td>M10</td>
<td>•</td>
<td>•</td>
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<td>•</td>
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</tbody>
</table>

121
There was a general theme centred around their dependency on dialysis and recognition that it was a life-preserving treatment:

“Well, all I say is that from the time I’m on dialysis, well I think I would say it saved my life.” M3

But also some resentment around not being independent and that HD treatment, however valued, impinges upon their daily lives and heightened feelings of dependency:

“I find it cuts into my life too much, it’s like the focus of my life, of my day at least... and I wanted to minimise it or marginalise.” M9

“I don’t trust machines, I hate relying on other people for my health and happiness. I cannot do it. It’s not in my nature.” M5

Attendance for HD did however provide some routine human contact, which was not always undesired.

“I know I come out of the house at half-past-six three days a week, Tuesday, Thursday and Saturday. And it’s kind of regular with me.....it’s got to go with me throughout my life. Dialysis.....it becomes a part of you.” M10

“Dialysis gets me out of the house and keeps me active and I have to deal with people. I think that’s probably important to me.” M5

Unexpectedly the concept of a good dialysis was not interpreted as an intra-dialytic phenomenon but what it enabled the patient to do whilst away from the unit on non-dialysis days. Therefore a bad dialysis was defined by how they felt on leaving the centre.

“A good dialysis is not coming off feeling dizzy, cramp and able to walk straight without veering off to the left or right. And not going home to sleep as well.” F1

“A good dialysis is when I can walk everywhere and I’m not out of breath.” And when asked if that meant that the time away from dialysis was the more important aspect, the reply was “Oh yeah, I’m busy, I’m a very busy man.” M5

“A bad one is when you dialyse and go home and you’re too tired. You feel as if, what is the sense of doing it. A good one is when you go home you’re feeling alright.” M6

The common negative aspect frequently cited was, as expected, the heavy intrusion into their daily lives; time that would have previously been spent away from the unit.

“It didn’t affect anything greatly I think, on the 6 hours, I was on a ward, you know, a bit long.” M1
“I don’t mind coming in...” [as long as] “…it’s short” [even if] “it’s four or five times a week I don’t mind.....but short.” This led to the concept of weekly hours, “Six hours would be better if it means less days.” M10

But there were mixed feelings about how closely either of the two treatment arms aligned to the concept of a good dialysis. This was weighed up by contrasting how well they felt after dialysis and how well they tolerated the time intrusion.

“So I mean seriously I do not want to admit the six hours is better because that’s eighteen hours a week. But something is working.” M7

“Everybody will prefer the 4 hours because it is quick.” M10

“Overall I think it’s [6 hours] probably a good idea people have felt better.” M1

“I did feel the cleansing was good but it’s the amount of time that was hard to adjust to, I never adjusted to it really,” commented M5, a patient who completed the extended TT arm, and suggests that despite finding the extended TT challenging he was able to reconcile this with the benefit he may have felt from “cleansing”.

The increased intrusion into daily life had an impact on mood and frustration.

“Not tired .....more like fed up ....you don’t want to be in a hospital so long.” M1

But the standard 4-hour arm unexpectedly did not yield more time away from the centre once the time spent travelling to and from the centre was considered.

“The four hours was worst because they kept me here longer... [Commenting on waiting for transport] ...the only thing I felt was I should be home quicker.” M3

“The 6 hours was hard work sitting here” but when asked why they didn’t ask to exit the study, the response was “I was feeling alright”. M10

“Definitely the 6 makes me feel better than 4. I didn’t like to be on 4,” M8, commented one patient who was not overtly symptomatic on either arm.

It was also surprising that despite the bustle and noise of dialysis units with more than 20 stations and patients being treated in very close proximity, often only a metre from the next patient, one patient commented:

“It’s a long time alone...it is usually a solitary process.” M5
The perception that extended TT felt different when compared with the standard 4 hours was common. From a general feeling of well-being, patients experiencing extended TT appeared to increasingly comment on feelings of improved energy.

“Ah yes ... I think the difference is until now...” suggesting that the benefit in one individual appeared to be sustained “since I’ve done the 6 hours, yes I feel a lot better”. M10

“Definitely the 6 makes me feel better than 4. I didn’t like to be on 4.” M8

“On the 6 hours I was a lot energised. I didn’t go home and sleep as I do now. And also I found that I could go home and do something, where now I can’t go home and do anything. On 4 hours I just don’t have the energy to do it. Sometimes I have to knock my neighbours daughter to open a tin of something so that I can eat ... you can’t always stand in front of the cooker. On the 6 hour I used to go home and cook.” F1

“Well general energy level” and “I had more energy [on 6 hours].” M8

Some did not feel any different, “To be honest I didn’t feel any difference.” M3

But extended TT had an impact on clinical measures which may have contributed to the experiences reported on each arm:

“....the thing is with the 6 hour, my sugar it come down... and I’m taking nearly half insulin.” M4

“Sometimes go low on the dialysis but mostly its high 165” [blood pressure on 4 hours] and “blood pressure make the headache more”. M4

“I didn’t seem to get cramp on the 6 hours, which I do from time to time, even after I go home on the 4 hour.” M2

“The first day I went back to 4 hours I was sick on the machine and it took about 2 weeks for my body to settle. I’m still not achieving a lower blood pressure as I did on 6 hours.” F1

But it was speculated that an associated factor may be the impact of extended TT on other dialysis parameters, for example BFR.

“I normally do 500 here but they wouldn’t do 500 because their regime only does 350” [regarding BFR on dialysis at the base unit and a unit he visited on holiday in Austria where he reports feeling better]. He pointed out that his pump speed on the 6-hour arm was 290ml/min and commented “...well a lower pump speed may suit me”. M2
The most commonly reported experience aside from post dialysis fatigue was the impact on sleep patterns.

“I sleep better...I don’t have problems.....before the 6 hours I don’t sleep very well.” M10

“Also harder to sleep on 4 hours... I’m so tired but I can’t get to sleep... I can lie down for 2 hours, even if I close my eyes and turn everything off, I still can’t get to sleep.” M7

“On 6 hours slept better, especially through the night. I was up longer [on getting home from dialysis] “When it got to 8 or 9 o’clock that’s when I fancied sleeping, but I would sleep through. Like now [back on 4 hours] I’m waking up three times in the night, sometimes even more.” F1

It was also felt that the perception of increased energy levels gave rise to increased social activity and interaction.

“I was able to go home and get to my church at 7 o’clock for prayer meeting or functions.” F1

“Sometimes I used to pick my grandson up. I used to have him because his mum used to work part-time. I am back on 4 hours I don’t pick him anymore. I used to look after him and now I can’t - so that’s one drawback,” [to being back on 4 hours]. F1

“I feel more energetic, basically I’m more aware earlier in the day, and I ’m capable of doing a lot more. Something is working. I can drive more easily now. But I never felt like driving before, I literally stayed within Watford,” commented a patient who drove to another city to visit his daughter for the first time since starting HD. M7

There were comments on the lack of facilities available to patients to combat the boredom of dialysis, which was more marked with increased TT.

“And honestly I’m lying here, you know often I’m just bored out of my tree even if I’ve got a book to read or something, there’s no choice of what you can do.” M9

“Getting through the last couple of hours stresses your brain.” When asked to clarify the term stresses your brain, the patient replied, “Boredom mostly but uncomfortable too, my back plays up a bit.” M7

“I couldn’t always get on the machine...[on time] that would be annoying.” M9

“We were supposed to get wifi, new technology would help.” M7
Some patients commented on the workload of staff, therefore making requests to relieve boredom and improve dialysis experience may have felt inconsequential and so were not made.

“They’re all so busy! But the TV subtitles weren’t on but ...” M7

There were repeated discussions about provision of home dialysis therapies, particularly around the flexibility of dialysing when it suited the individual.

“You could do it when you want.” M2

“I wouldn’t mind having 6 hours at home, and I’ve been thinking about the pros and cons. And I felt that doing it at home I’d be better off.” M1

Although the flexibility was desirable the concomitant responsibility was less so.

“I wasn’t really thinking of doing it myself... I would have if I had somebody to help... if you became unwell or anything, you know, I would be really terrified.” M1

“Everyone here knows what they are doing. And so if you do get an issue...”, M2, suggests that a feeling of safety is afforded by in-centre care.

But the contrasting individualised care and attention observed at significantly smaller holiday units was noted.

“The unit had only 10 beds and the “boss” [consultant] comes round once a week and doctor comes every day.” M2

“I find it strange. I’ve been a professional performing artist for 50 years so I’ve got an idea of what professional is. There is no consistency, every nurse is different, the concentration is different the attitude is different the approach is different.” M5

On being asked if there was a point at which there was a balance between the negative aspects of dialysis and the benefits or even if there were a point at which the negatives outweighed the benefits.

“I can’t give it up because I get very short of breath without it.” M4

“There’s a trade-off between the benefit and the extra 2 hours. As I say I am achieving more and that’s not a word I would ever have used before.” M7
Some were able to suggest a maximal point at which the clinical benefit was of value countered by increased time on dialysis, "...a little bit more time yes. Yes I would say five and a half." M1

“When I was on 6 hours my grandchildren worry a lot - why are you out so late they ask. If I don’t get home by 2 o’clock....” M11, explaining that they wait for him to get back from dialysis to play. The cost here appeared to be high as the time with family particularly children, was greatly valued.

In terms of motivating factors to accept extended TT, patients considered conditions that could be alleviated with extended TT.

“The thought that you would have a better heart condition.... that’s just the price you’ve got to pay...” commenting on the pros and cons of longer TT. Adding that it may be more acceptable later in life, “maybe when I’m older.... and it wouldn’t really bother me as much to be lying here ... I haven’t got to that state of you know immobility yet. I’ve got a few things that I want to do”. M9

But it was also a case of being accustomed to routine and receptive to a scheduled day.

“I think it was worth it... I knew I was coming for 6 hours and I planned my life around that.” M8

But some patients felt very limited by the constraints of HD, specifically around travel and the lack of spontaneity that results from in-centre care.

“If I got transplant then I can go,” [to Pakistan to visit siblings] on being able to travel without planning and making arrangements for dialysis. M4

Two patients elected to permanently switch to extended TT but there were significant issues with service provision as discussed previously in Chapter 3.

“I wanted to do it [6 hours] after the trial but was told... well there’s no provision for me to do it - unless I go to afternoons,” F1, underlines the extent to which life is tailored around dialysis and therefore switching to a different treatment schedule, involving a delay of 3 or 4 hours, is almost incomprehensible.

7.4 Discussion

This study demonstrates very clearly that extended TT results in significant reduction in post dialysis fatigue as evidenced by a reduced time to recovery. This may have been, at least in part, an underlying factor in the significant reduction in burden of kidney disease, although on initial inspection this seems rather counterintuitive. The dialysis symptom score also decreased
significantly and this is likely to be related to the decrease in UFR on the extended TT arm. The alleviation of PDF symptoms were substantiated by narratives from semi-structured interviews.

Fatigue in HD patients is indicated by a chronic lack of energy that is more severe on dialysis days and affects both physical and mental function and ability (Horigan 2012). It is thought to differ from PDF in that it is more likely to be related to the removal of fluid during dialysis and associated with other symptoms such as cramp, headache and nausea (Sklar, Newman et al. 1999). We found PDF to reduce significantly with extended TT and this may be associated with the reduced UFR, although we also found phosphate and urea clearance to improve significantly with extended TT. However, serum phosphate and dialysis adequacy, as measured by Kt/V, have not been found to be associated with reduction in PDF (Leinau, Murphy et al. 2009). This further reiterates the limitations of Kt/V as a universal measure of adequate dialysis.

Symptoms of fatigue have also been found to correlate with poor sleep patterns (Jhamb, Argyropoulos et al. 2009) but this is likely to be related to a constant lack of energy associated with chronic sleep deprivation than specifically PDF.

From our interviews it is suggested that some patients experienced improved sleep on the 6-hour arm, the underlying cause is unclear but may be associated with altered circadian rhythm and daytime activity. We have reported dietary calorie intake to increase with extended TT and this may be related to improvement in sleep. This has also been suggested by secondary analysis of HEMO data demonstrating sleep quality has a linear association with appetite, decreasing significantly as appetite decreases from very good to very poor (Burrowes, Russell et al. 2012). Sleep quality has also been associated with time to recovery by the FHN group who found those with poor sleep quality experienced significantly longer TTR (Unruh, Kurella Tamura et al. 2011)

However, as described in Chapter 4, extended TT does facilitate better clearance of larger molecules such as phosphate and it may be that there is improved clearance of larger compounds which have increased volumes of distribution which in turn impact on PDF.

The changes in symptom score with extended TT were not surprising but the decrease in burden of kidney disease was unexpected and may be an effect of the reduced time to recover and PDF, leading to increased functional ability away from dialysis.

We have evidenced through our narratives that the increased functional ability is aligned to social interaction and so in a sense individual patients may have felt less restricted and controlled by their dialysis treatment despite it being of longer duration. This seems plausible as the physical and
mental health scores weren’t appreciably different on either treatment arm. So in effect there appears to be a settlement between hours lost on dialysis and hours gained spent in activity rather than sleeping.

This concept of “trading” of benefit and drawback with respect to TT is very interesting and suggests patients see TT as being a negotiable parameter. This has been examined in relation to fluid intake in a cross-sectional study that demonstrated patients readiness to dialyse for an extra 15 minutes in “exchange” for a more liberal fluid allowance (Flythe, Mangione et al. 2014). This again reiterates the shortcomings of a dialysis delivery framework which assumes 4 hours thrice weekly suits all, when in reality individual patients may be willing to do more if it is accompanied by a benefit that they value.

The tolerance to both treatment arms were judged primarily by the numbers of withdrawals. There were six voluntary withdrawals on the extended TT arm and four on the standard 4-hour arm. However, the timing of the withdrawals on the 6-hour arm secondary to feelings of general unwell at the end of dialysis and more than half way through the allocated 24 weeks, may allude to dehydration and a need for increase in target weight. But we note that accounting for travelling time, patients are more likely to be away from their homes for an extended period and so may experience delayed meals. Despite intra-dialytic blood glucose monitoring to be normal we cannot rule out that the diabetic patients may well have been symptomatic due to glucose levels outside of their normal range. This is another consideration in the assessment of feasibility of extended TT because patients with different co-morbidities may need extra support and clinical monitoring.

The narratives generated enable the understanding of how individuals make sense of the HD treatment, how they incorporate it into their daily lives highlighting how their individual personalities alter the experience. Studies examining HD patients experiences of their life situation have demonstrated similar themes to those reported here, the struggle with a time-consuming treatment and having a sense that life is restricted (Hagren, Pettersen et al. 2005). The adversity of dialysis relates to the dependence on a life-sustaining treatment with a sense of loss of freedom. This was mentioned extensively in our communications, dialysis was inextricably linked to life itself and there was the perception that the HD machine and their body were one unit. Restrictions are noted to affect functional ability and performance which then infiltrates all aspects of life including social interaction (Hagren, Pettersen et al. 2001). So the association made by patients during their narratives between extended TT and increased functional ability, experiencing less fatigue, and improved social activity, attending church social functions and travelling to meet relatives, was not anticipated.
We had limited comments relating to dialysis staff and this may have been influenced by some patients requesting that interviews be conducted on the dialysis unit within hearing distance of their nursing carers. The narratives may also have been biased by the interviewer in that patients were interviewed by a single clinical investigator who was also responsible for recruitment and data collection and so patients may have been less likely to report negative aspects of extended TT.

7.5 Conclusion

Extended TT of 6 hours is associated with a significantly reduced TTR and improvement in symptom and disease burden. The main themes identified from the patients’ narratives were: dependency on dialysis; intrusion of dialysis into daily life; functional and social ability. The concept of good or bad dialysis is not defined by intra-dialytic phenomenon but rather functional ability on non-dialysis days that facilitates social interaction and feelings of “normality”.
8 EFFECT OF BLOOD FLOW RATE ON TIME TO RECOVERY

8.1 Introduction

Our findings suggest a significant effect of extended TT on time to recovery. But this may have been confounded by the simultaneous reduction in BFR, which was introduced to ensure that an equivalent quantity or dose of dialysis was delivered on both treatment arms. We decreased BFR so that the blood volumes processed on both the standard and extended treatment time arms were not significantly different. Although we achieved this aim; by altering BFR we were unable to negate the potential effect that this could have had on the reduction observed in the time to recovery. It may be argued that the improvement in TTR could have been attributed to the reduction in BFR rather than extending TT. This was alluded to in a narrative reported in Chapter 7 from a patient who commented that a gentle, slow dialysis with reduced BFR “may suit me” as he felt better. In order to exclude the role of BFR on the reduced TTR observed in the main study we conducted a second study at a satellite dialysis centre not participating in the main trial where TT remained the same and BFR was the only variable altered.

8.2 Study flow diagram

![Study flow diagram](image)

*Figure 8-1: Study flow diagram*
All patients at the unit on the day-time shifts were invited to enrol and provide written consent. The inclusion criteria were that their usual TT was 4 hours and that they had been stable on HD for at least 90 days. After providing written consent patients were asked what their usual TTR was and this was recorded. They were then prescribed a study BFR that was 66% of their usual. This served to mimic the reduction in BFR undertaken on the main study. As the patient-reported response in the main study was felt to be relatively early we maintained the reduced BFR for a period of 4 weeks and then re-assessed TTR. All BFR used for results analysis were calculated from blood volumes processed and so these represented actual flow rates rather than prescribed.

### 8.3 Patient demographics

All 29 patients from day-time shifts were enrolled and their demographic characteristics are described in Table 8-1 below.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>22 (75.8%)</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>66.0 ± 11.2</td>
</tr>
<tr>
<td>Dialysis vintage (Mean years ± SD)</td>
<td>7.3 ± 6.1</td>
</tr>
<tr>
<td>CVC as vascular access (%)</td>
<td>26 (89.7%)</td>
</tr>
<tr>
<td>Diabetes as cause of ESRD (%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td>Ethnicity (% White)</td>
<td>12 (41.4%)</td>
</tr>
</tbody>
</table>

### 8.4 Ethical considerations

An ethics amendment was applied for the introduction of a second “control” group and this was received from the Stanmore Ethics committee (Appendix 4).
8.5 Statistical methodology

The descriptive statistics are expressed as the mean ± standard deviation. The difference in TTR was assessed using Wilcoxon Signed rank test using Statistical Package for Social Sciences (SPSS) version 22. Statistical significance was defined as p<0.05.

8.6 Results

As intended the achieved BFR was significantly lower 263ml/min ± 16ml/min, equating to a 66% reduction as prescribed, of the cohorts usual BFR of 395ml/min ± 25ml/min, p<0.001, Figure 8-2.

![Figure 8-2: Variation in blood flow rate from usual](image-url)
8.6.1 Effect of reduced blood flow rate on time to recovery and spKt/V

The reduction in BFR, in the absence of a simultaneous extension to TT, resulted in minimal change in time to recovery, mean 366.1ml/min ± 311min to 358.7ml/min ± 314min, p=0.60, Figure 8-3.

*Figure 8-3: Effect of reduced blood flow rate on time to recovery*
But dialysis adequacy, as measured by spKt/V, although still meeting local and national standards, decreased significantly from $1.82 \pm 0.5$ to $1.58 \pm 0.5$, $p<0.01$, Figure 8-4.

**Figure 8-4: Effect of reduced blood flow rate on spKt/V**

### 8.7 Discussion

This simple interventional study demonstrates that reduction in BFR alone does not have a significant effect on TTR. We are limited in that the outcomes observed in the main cross-over study are not applicable to other cohorts with different demographics. Indeed this cohort was older and of longer dialysis vintage with more patients of white ethnicity which was reflected in the lower proportion of patients with diabetes as their cause of ESRD. Older white patients on HD are reported to have longer TTR and more likely to experience symptoms of fatigue than older black patients (Kutner, Brogan et al. 2000). This may have biased our results as there were half as many whites in the main study, 21%, compared to this cohort, of whom 41% were white. But a quarter of the main study cohort were of Indo-asian origin and this group are demonstrated to have a significantly lower perceived quality of life compared to their white age-matched counterparts (Bakewell, Higgins et al. 2001).

However, analyses of data from incident HD patients suggest little difference in perception of QoL and health status (Kutner, Zhang et al. 2005). Therefore it may be that dialysis vintage has a variable effect on HRQoL in different ethnic groups.
The symptoms of PDF are suggested to be associated with reduced myocardial blood flow (Dubin, Teerlink et al. 2013). Repeated incidences of myocardial ischaemia during routine dialysis result in myocardial stunning and eventual cardiac fatigue (Barnes, Dutka et al. 2002). It raises the possibility that post dialysis fatigue, which influences the time taken to recover from dialysis, may be a clinical manifestation of severe cardiac fatigue (Covic, Siriopol et al. 2013). However, the incidence of myocardial stunning increases with raised UFR. By not altering TT we did not affect UFR and therefore the absence of change in TTR may not be altogether unexpected.

There is a paucity of published data on the effect of changing BFR without altering TT on symptoms and clinical outcomes. In a small study of young HD patients investigating the effects of BFR, 250ml/min, 350ml/min and 450ml/min on cardiac parameters, including ejection fraction, using echocardiography and found no difference, either before, during, and at the end of dialysis (Alfurayh, Galal et al. 1993). This further supports the theory that impact of BFR per se is limited unless accompanied by changes in TT which affect other dialysis parameters such as UFR.

But BFR does play a part in achievement of dialysis adequacy targets (Ward 1999) and this was evidenced in this cohort where we observed a significant decrease in achieved spKt/V. We are unable to dissociate the negative confounding effect of reduced spKt/V from our findings, the positive effect of BFR reduction may have been tempered by the effects of reduced clearance. But we note that patients were not under-dialysed by either local or national standards.

8.8 Conclusion

Reducing blood flow rate without elongation of TT has no significant effect on time to recovery from HD and maybe related to the absence of any reduction in UFR. The ethnic mix of this cohort may have played a role in our findings.
CHAPTER 9

9 SUMMARY AND FUTURE WORK

9.1 Summary of findings and conclusion

Patient outcomes on HD remain sub-optimal. A number of observational studies and international registry reports suggesting beneficial effect of extended TT have reinforced the message from Tassin, a centre renowned for advocating extended TT over three decades. However, there is no consensus within the HD community regarding treatment duration and this has not been investigated within in-centre HD in a prospective randomised trial.

This thesis set out to find evidence of the potential clinical effects of extended TT on HD in a scientifically robust manner by exploring the impact on nutritional status, biomarkers of cardiac function and inflammation as well as dialysis treatment variables. In order to encapsulate the question of feasibility of extended treatment duration, the impact on service provision and patient experience was also examined. This chapter aims to provide an overview of the findings as well as suggestions for areas of future research. A summary of significant findings are tabulated below.
Table 9-1: Summary of study findings

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutritional</strong></td>
<td>Reduction in malnutrition inflammation score</td>
</tr>
<tr>
<td>Improvement in hand grip strength</td>
<td>No change in serum albumin</td>
</tr>
<tr>
<td>Reduction in serum phosphate levels</td>
<td></td>
</tr>
<tr>
<td>Increased calorie intake</td>
<td></td>
</tr>
<tr>
<td><strong>Dialysis related</strong></td>
<td>Reduction in mean arterial blood pressure</td>
</tr>
<tr>
<td>Reduction in systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Reduction in anti-hypertensive agents</td>
<td></td>
</tr>
<tr>
<td>Increase in achieved spKt/V</td>
<td></td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td>No change in BNP</td>
</tr>
<tr>
<td>No change in Troponin</td>
<td></td>
</tr>
<tr>
<td>No change in high sensitivity -CRP</td>
<td></td>
</tr>
<tr>
<td><strong>Patient Experience</strong></td>
<td>Improvement in time to recovery</td>
</tr>
<tr>
<td>Improvement in symptom score</td>
<td>No change in SF-12 physical</td>
</tr>
<tr>
<td>Improvement in burden of kidney disease</td>
<td>No change in SF-12 Mental</td>
</tr>
</tbody>
</table>

The study was able to demonstrate that extended TT of 6 hours on HD has a positive effect on blood pressure control with significantly reduced MAP achieved with decreased reliance on anti-hypertensive agents. These findings are consistent with those from studies of frequent HD, although, the decrease in systolic blood pressure in this study was of a greater magnitude (Kotanko, Garg et al. 2015). The reason and mechanism for this is not clear. If the underlying cause of better blood
pressure control was volume related and extended HD had allowed for achievement of a more accurate dry weight this would have been indicated by a reduction in ECW standardised by weight. The results do not substantiate this theory. However, the limitations of whole body BIA measurement may have influenced the ability to detect change in %ECW, using segmental BIA may have more accurately identified the disproportionate changes in ECW in the trunk and lower limbs (Davies and Davenport 2014). Also single BIA measurements were made when in hindsight serial measurements would have improved accuracy and reliability, therefore limiting the assertions that can be made regarding the mechanism for decrease in blood pressure on the extended TT arm.

A significant decrease in BNP levels with extended TT may also have served to clarify the role of volume status in blood pressure reduction but there was no significant change in this biomarker and may indicate an absence of worsening cardiac function rather than imply volume status was unchanged (Block and Isakova 2015).

The extended treatment duration also facilitated increased clearance of larger molecules such as phosphate with serum levels being significantly reduced compared to the standard treatment 4-hour arm. This finding has serious implications for reduction of vascular calcification and in turn arterial stiffness and LVH, which relate to cardiovascular events and mortality (Block, Hulbert-Shearon et al. 1998, Ganesh, Stack et al. 2001). Improved phosphate clearance may serve to allow a more liberal dietary restriction, particularly protein, which increases the likelihood of better nutritional status.

This study demonstrates that extended TT has potentially induced very positive changes in two risk factors of cardiovascular disease: improved blood pressure; and better control of serum phosphate. Both these beneficial end points were linked with reduced reliance on anti-hypertensive and phosphate binding agents, the latter in particular would represent significant cost efficiency.

Extended TT was found to significantly increase HGS, improve MIS, and increase dietary energy intake. These three markers all imply improved nutritional status. The study cohort had acceptable BMI at baseline which would indicate that they were not overtly malnourished and so profound changes in dry weight were not expected. However, the improved functional ability may have resulted in increased energy expenditure. The narratives from patients support this argument.

The amelioration of post-dialysis fatigue is considered a pivotal finding of this study. Lowered time to recovery together with improved HRQoL sub-domain, burden of kidney disease facilitated an enhanced patient experience where they were able to attain a level of ‘normality’ in everyday life, with increased opportunity for social interaction. This further strengthens the case that patients were very likely more active whilst on the extended TT arm and so expended more energy. With
respect to time to recovery, patients were effectively trading a loss of 120 minutes on HD with 295 minute gain in recovery time. The vehicle for reduced time to recovery is considered to be lowered UFR facilitating reduced intra-dialytic symptoms, including intra-dialytic hypotension. The reduction in BFR is not thought to be a factor as proven by the stability in time to recovery in patients who received lowered BFR without change in TT.

The study is limited by its small patient numbers and also that for some patients the standard arm was a reduction in TT and this may have had an effect on the ability to detect an effect on biomarkers of inflammation and cardiac disease, although, cTNI was found to increase significantly on the standard 4-hour treatment arm. This further underlines the possible detrimental effects of currently prescribed standard treatment duration of 4 hours based on a Kt/V which exceeds national and international standards.

Current HD prescription in the UK is based largely on achieving target dialysis dose as measured by Kt/V and this is one of the important issues clarified in this study. The accepted method of quantifying dialysis adequacy with a single measure, Kt/V, is wholly inappropriate. The reliance on a lone marker of quality may have reassured the dialysis community into concluding that dialysis provision was meeting standards, when in fact review of other factors, blood pressure control, nutritional status and patient experience, all examined in this study suggest otherwise. This culture may be partially responsible for impeding the introduction of alternative prescription regimens which may more readily accommodate extended TT.

This study provides evidence to substantiate the clinical patient benefits of extended TT, suggested in observational studies, within in-centre HD. But the examination of feasibility of extended TT has been less convincing. Nursing staff found significant impact on service provision with limited numbers of HD slots. This study brings to light evidence that although extended TT may be clinically beneficial the constraints placed on service provision make it a challenging proposition to implement in UK HD centres operating within a framework of two or three daily shifts over a 12 to 15 hour time period. The domino effect on nursing working practices and hours are thought to be extensive.

But the historical design of HD delivery is not based on patient outcomes. Supporters of other intensive HD delivery models have suggested the use of alternate day HD, removing the long weekend two-day inter-dialytic period which is associated with increased cardiovascular events and mortality (Georgianos and Sarafidis 2015). But more frequent HD is reported to be associated with increased complications of vascular access and daily nocturnal HD was related to increased perceived burden (Labriola, Morelle et al. 2015). The latter is an important parameter raised by the
recruits in this study suggesting treatment burden may be reduced by moving away from the inflexibility of in-centre HD to home HD.

Systematic review of home HD including daily and nocturnal modalities has demonstrated provision may be cost neutral or cost saving in comparison to in-centre HD, primarily due to reduced staffing costs (Walker, Marshall et al. 2014). In an international survey of nephrologists, including those in the UK, more than a third felt that improving QoL was more important than helping patients to live longer with approximately 60% agreeing that home HD would provide a better QoL than in-centre HD (Fluck, Fouque et al. 2014). But despite these beliefs and proven cost efficiency there continues to be only a small minority of patients on home HD.

The uptake of home HD is not limited by service providers alone. Many patients despite being viable candidates for this modality are reluctant, as our patient narratives demonstrate, due to fear of ‘operating’ a dialysis machine and safety concerns. This has also been echoed by patients already on home HD likening it to being a novice driver, with time, the procedures becomes second nature. The autonomy and flexibility afforded by home HD encourages patients despite relative ‘cost’ of early anxieties and logistical issues (Rajkomar, Farrington et al. 2014).

The findings of this study have implications for policy and service provision. The current structure of HD provision in shift format was designed by service providers to maximise throughput at a time when the detrimental effects of lowering TT were not fully appreciated. Setting aside the non-significant effect of TT from the NCDS study findings in favour of small molecule clearance may have been justified; the significant findings of this prospective randomised cross-over study, albeit limited in power, indicates a need for TT to be considered in quality standards. Modalities such as home HD may initially be more accommodating of extended TT than in-centre HD.

9.2 Future work

The avenues for future work lie in studies with sufficient power to detect effects of longer TT using outcomes such as hospitalisation rates. Improved clinical outcomes should logically result in reduced admission rates and length of stay, and therefore result in cost efficiency. Evidencing improvements in the health economics may serve to empower and motivate those that plan and deliver HD services to be more innovative in providing extended TT to those patients that may benefit.

There is also a need to foster a more patient-centred approach to HD delivery and this must stem from patients and their carers being involved in setting the research agenda and outcome criteria. If we are to provide HD treatment that benefits patients we need to ensure that what we term to be a
benefit is perceived as such by our patients. Three days spent clearing uraemic toxins may be viewed as three days of not seeing children, grandchildren or being able to function and interact normally in society. Patient survival rates are paramount to service providers and are a pragmatic choice of endpoints to studies and allow ease of statistical analysis (Bargman 2007). But survival in the absence of improvement in functional ability and quality of life may not always be desired by our patients, therefore this should be reflected in choice of endpoints in future studies of intensive HD.
REFERENCES

"<NUTRITION STATUS HD pt audit FULL REPORT Feb 2007.pdf>..


treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS." Kidney Int 69(7): 1222-1228.


APPENDIX 1: ETHICS APPROVAL

National Research Ethics Service
NRES Committee London - Stanmore
Northwick Park Hospital
Room 019, Level 7 Maternity Block
Watford Road
Harrow
Middlesex
HA1 3UJ

Telephone: 020 8989 3020
Facsimile: 020 8989 5222

08 June 2011

Dr Peter Choi
Consultant and Honorary Senior Lecturer
Imperial College Healthcare NHS trust
Renal Services, 4th floor Ham House
Hammersmith Hospital,
Du Cane road, London
W12 0HS

Dear Dr Choi

Study title: Feasibility and physiological and nutritional effects of extended treatment duration in patients with end-stage renal disease on haemodialysis

REC reference: 11/LO/0505

Thank you for your letter of 27 May 2011, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC on 8th June 2011. A list of the sub-committee members is attached.

Confirmation of ethical opinion

In relation to the adverse events the Sub-committee noted that the section had been much improved in the protocol. However it was felt that this could be made fuller and by way of suggestion only you could use wording from the MHRA website:

'Serious adverse event or serious adverse drug reaction or unexpected serious adverse reaction: any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.'

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the

This Research Ethics Committee is an advisory committee to London Strategic Health Authority.
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.
above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

**ADDITIONAL CONDITION**

**Participant Information Sheet:**

The name of the REC ought to be put under the heading ‘Who has reviewed the study?’ and not as part of the footer. Currently the incorrect REC is named (Hammersmith...).

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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</thead>
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<td>Advertisement</td>
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<td>Covering Letter</td>
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<td>GP/Consultant Information Sheets</td>
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<tr>
<td>Investigator CV</td>
<td>Dr Peter Choi</td>
<td>04 April 2011</td>
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<td>Other: CV: Seema Singh</td>
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<tr>
<td>Response to Request for Further Information</td>
<td>Letter from Chief Investigator</td>
<td>27 May 2011</td>
</tr>
</tbody>
</table>

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
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<td>Other: CV: Seema Singh</td>
<td></td>
<td>05 April 2011</td>
</tr>
<tr>
<td>Other: CV: Dr N Duncan</td>
<td></td>
<td>07 April 2011</td>
</tr>
<tr>
<td>Other: CV: Virginia Proust</td>
<td></td>
<td>06 April 2011</td>
</tr>
<tr>
<td>Participant Consent Form</td>
<td>1.0</td>
<td>05 April 2011</td>
</tr>
<tr>
<td>Participant Information Sheet</td>
<td>2.0</td>
<td>25 May 2011</td>
</tr>
<tr>
<td>Protocol</td>
<td>2.0</td>
<td>25 May 2011</td>
</tr>
<tr>
<td>REC application</td>
<td></td>
<td>05 April 2011</td>
</tr>
<tr>
<td>Response to Request for Further Information</td>
<td>Letter from Chief Investigator</td>
<td>27 May 2011</td>
</tr>
</tbody>
</table>

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments  
Adding new sites and investigators  
Progress and safety reports  
Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/LO/0505 Please quote this number on all correspondence
With the Committee’s best wishes for the success of this project

Yours sincerely

[Signature]

Mrs Rosemary Hill
Chair

Email: uzma.chaudhry@nwlh.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to:

Mrs Seema Singh
Imperial College Healthcare NHS trust
Renal Services, 4th floor Ham House
Hammersmith Hospital,
Du Cane road, London
W12 0HS

Ms Becky Ward
(Sponsor contact & R&D Contact)
St. Mary’s Hospital
Room GM14, Ground mezzanine floor,
Praed Street Wing
London W2 1PG
APPENDIX 2: LOCAL R&D APPROVAL

10 July 2012

Dr Peter Choi
Consultant and Honorary Senior Lecturer
Imperial College Healthcare NHS Trust
Renal Services, 4th Floor Hammersmith House
Hammersmith Hospital
DuCane Road
London, W12 0HS

Dear Dr Choi

Project Title: Feasibility and physiological and nutritional effects of extended treatment duration in patients with end-stage renal disease on haemodialysis

Joint Research Office Reference number: JROHH0241

Ethics reference number: 11/LO/0505

Principal Investigator: Dr Peter Choi

I confirm that this project has now been approved by the Joint Research Compliance Office. The project may now start at Imperial College Healthcare NHS Trust sites. Please note that the start date of the project is the date of this letter and the duration is the same as that provided in your application form.

The list of documents reviewed and approved by the Joint Research Compliance Office under requirements of the Research Governance Framework are as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRES Committee London - Stanmore ethical approval letter</td>
<td></td>
<td>08 Jun 2011</td>
</tr>
<tr>
<td>NRES Committee London - Stanmore letter lifting suspension of favourable opinion</td>
<td></td>
<td>20 Apr 2012</td>
</tr>
<tr>
<td>NRES Committee London - Stanmore amendment approval letter</td>
<td>Amendment dated 04 May 2012</td>
<td>09 May 2012</td>
</tr>
<tr>
<td>Notice of substantial amendment</td>
<td></td>
<td>04 May 2012</td>
</tr>
<tr>
<td>Advertisement</td>
<td>1</td>
<td>April 2011</td>
</tr>
<tr>
<td>GP/Consultant Information Sheet</td>
<td>1</td>
<td>05 Apr 2011</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>Dr Peter Choi</td>
<td>01 Aug 2010</td>
</tr>
</tbody>
</table>

R&D ref: JROHH0241

Page 1 of 3

REC ref: 11/LO/0505
Before you commence your research, please note that you must be aware of your obligations to comply with the minimum requirements for compliance with the Research Governance indicators 17 (Data Protection); 25 (Health and Safety) and 22 (Financial Probity). Details of the requirements to be met can be found in the Research Governance Framework available on www.dh.gov.uk.

Under the Research Governance regulations, Serious Adverse Event Reports, Adverse Reactions and amendments to the protocol or other supporting documents must be forwarded to the Joint Research Office and Ethics Committee.

In accordance with the Research Governance Framework, research projects carried out in the Trust will be randomly chosen by the Joint Research Office for auditing. Please see the attached checklist for documentation that will be required during the audit.

I wish you well in your research.

Yours sincerely,

Ms Becky Ward
Research Governance Manager
Academic Health Science Centre
Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
# Joint Research Office Audit Checklist

<table>
<thead>
<tr>
<th>No</th>
<th>Documentation</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Master File</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Joint Research Office approval letter</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ethics committee approval letter</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Investigator's brochure</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Protocol and amendment if any</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Any revision to consent form</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Patient information sheet</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Signed informed consent</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Subject screening log</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Financial agreement document</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Insurance statements, subjects' compensation where required</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sponsorship agreement</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Relevant communications other than site visits</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Regulatory authority (ies) authorisation / approval</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and/or supporting staff in the study</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>GCP training</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Medical/laboratory/technical procedure/tests</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Sample label (s) attached to investigational medicinal product container (s)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Instructions for handling of investigational medicinal product (s) and trial related materials</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Distribution records for investigational medicinal product (s) and trial related materials</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Master randomisation list</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Pre-trial monitoring report</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Notification on safety information</td>
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</tr>
<tr>
<td>23</td>
<td>Documentation on external monitoring</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Subject enrolment log</td>
<td></td>
</tr>
<tr>
<td>Medical Record</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Entry to trial confirmed on the cover of patient’s medical notes</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Original consent form signed and dated by both patients and researchers filed in patient’s medical notes</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Details of the research assessments/treatments recorded in the patient’s medical notes</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 3: ETHICS APPROVAL FOR ADDITION OF WITHDRAWAL QUESTIONNAIRE

Health Research Authority

NRES Committee London - Stanmore
Skipton House
Ground Floor
NRES/HRA
80 London Road
London
SE1 6H
Tel: 020 797 22560

06 February 2013

Becky Ward
Imperial College London
AHSC Joint Research Office
510A, 5th Floor Lab Block, Charing Cross Hospital,
Fulham Palace Road, London,
W6 8RF

Dear Becky Ward

Study title: Feasibility and physiological and nutritional effects of extended treatment duration in patients with end-stage renal disease on haemodialysis

REC reference: 11/LO/0505
Amendment number: 3
Amendment date: 14 January 2013
IRAS project ID: 29801

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

There were no ethical issues discussed.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire: Questionnaire about Withdrawal from the Treatment Time Study</td>
<td>1.0</td>
<td>04 January 2013</td>
</tr>
<tr>
<td>Protocol</td>
<td>3.0</td>
<td>14 January 2013</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>29801/410014/13/652/15902</td>
<td>04 February 2013</td>
</tr>
<tr>
<td>Covering Letter: Email from Seema Singh to Julie Kidd</td>
<td></td>
<td>05 February 2013</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

11/LO/0505: Please quote this number on all correspondence

Yours sincerely

pp

Mrs Rosemary Hill
Chair

E-mail: NRESCommittee.London-Stanmore@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Professor Charles Pusey, Imperial College London

NRES Committee London - Stanmore

Attendance at Sub-Committee of the REC meeting on 14 February 2013

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Geraldine Edge</td>
<td>Consultant Anaesthetist</td>
<td>Expert</td>
</tr>
<tr>
<td>Mrs Rosemary Hill</td>
<td>Statistician</td>
<td>Expert</td>
</tr>
</tbody>
</table>
APPENDIX 4: ETHICS APPROVAL FOR ADDITION OF BLOOD FLOW RATE CONTROL GROUP

Health Research Authority
NRES Committee London – Stanmore
Skipton House
Ground Floor
NRES/HRA
30 London Road
London
SE1 9LH
Tel: 020 7972 2552

21 February 2014
Ms Seema Singh
NIHR Clinical Doctoral Research Fellow
Renal Dietitian
4th Floor Ham House
Hammersmith Hospital
Imperial College London NHS Trust
Du Cane Road
W12 0HS

Dear Ms Singh

Study title: Feasibility and physiological and nutritional effects of extended treatment duration in patients with end-stage renal disease on haemodialysis

REC reference: 11/LO/0585
Amendment number: Version 5, 28/01/2014 - 25801/560384/13/715/26357
Amendment date: 07 February 2014
IRAS project ID: 29801

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP/Consultant Information Sheets</td>
<td>GP Letter V2.0</td>
<td>21 November 2013</td>
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<tr>
<td>Protocol</td>
<td>5.0</td>
<td>29 January 2014</td>
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<tr>
<td>Covering Letter</td>
<td>Email from Seema Singh</td>
<td>07 February 2014</td>
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<tr>
<td>Participant Information Sheet</td>
<td>4.0</td>
<td>21 November 2013</td>
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</tbody>
</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days — see details at http://www.hra.nhs.uk/nra-training/

Yours sincerely

Mrs Rosemary Hill
Chair

E-mail: Julie.kidd@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Becky Ward, Imperial College London and Imperial College Healthcare NHS Trust
Professor Charles Pusey, Imperial College London
## NRES Committee London - Stanmore

### Attendance at Sub-Committee of the REC meeting on 14 February 2014

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs Rosemary Hill</td>
<td>Statistician</td>
<td>Lay</td>
</tr>
<tr>
<td>Mrs Shirley Williams</td>
<td>Retired</td>
<td>Lay</td>
</tr>
</tbody>
</table>

### Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Kate Donaldson</td>
<td>Assistant Coordinator</td>
</tr>
</tbody>
</table>