BMJ Open

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035919
Article Type:	Protocol
Date Submitted by the Author:	21-Nov-2019
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Keywords:	Adult nephrology < NEPHROLOGY, Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY

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TITLE:

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

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Word count 3151

ABSTRACT

Introduction

Preserving Residual Kidney Function (RKF) may be beneficial to patients on haemodialysis (HD) and it has been proposed that commencing dialysis incrementally rather than three times a week may preserve RKF. In Incremental HD, target dose includes a contribution from RKF, which is added to HD dose, thus allowing individualisation of the HD prescription. We plan to conduct a feasibility randomised controlled trial (RCT) comparing incremental HD and conventional three times weekly treatments in incident HD patients. The study is designed also to provide pilot data to allow determination of effect size to power a definitive study.

Methods and Analysis

After screening to ensure native renal urea clearance >3ml/min/1.73m^2, the study will randomise 56 patients within 3 months of HD initiation to either conventional in-centre thrice weekly dialysis or incremental in-centre HD commencing two days a week. Subjects will be followed up for 12 months. The study will be carried out across 4 UK renal centres.

The primary outcome is to evaluate the feasibility of conducting a definitive RCT and to estimate the difference in rate of decline of RKF between the two groups at 6 and 12-month time points. Secondary outcomes will include the impact of dialysis intensity on vascular access events, major adverse cardiac events(MACE) and survival. The impact of dialysis intensity on patient reported outcomes measures, cognition and frailty will be assessed using EQ-5D-5L, PHQ-9, Illness intrusiveness rating score(IIRS), Montreal Cognitive assessment (MoCA), and Clinical Frailty Score(CFS).

The outcome of this study will be used to inform the design of a definitive study, adequately powered to determine whether RKF is better preserved after incremental HD initiation compared to initiation using conventional thrice weekly treatments.

Ethics and dissemination

Ethics approval has been granted by East of England – Cambridge South Research Ethics Committee, United Kingdom (REC17/EE/0311). Results will be disseminated via peer-reviewed publication.

Trial registration number NCT03418181

Key words: 3 -10 keywords

Residual Kidney Function -End stage renal disease – HD - RCT – Randomised Controlled Trial

Strengths and limitations of this study

- No existing published prospective studies comparing incremental HD and conventional three times weekly treatments in incident HD patients and this study will aim to address this gap.
- The study will provide pilot data to allow determination of effect size to power a definitive study.
- Impact and intrusiveness of dialysis intensity being compared between study groups.
- Study size will not permit to determine the rate of decline of RKF in incremental groups.

Background

Most end stage renal failure (ESRF) patients have a degree of native kidney function (Residual Kidney Function, RKF) remaining when they initiate HD. There has been recent interest in incremental HD, a method of individualising HD according to the level of RKF to permit dialysis to be commenced at a lower intensity than conventional approaches allow. Most patients commence dialysis using conventional three times weekly dialysis with RKF usually not accounted for in prescribing dialysis dose. In Incremental HD, RKF is combined with dialysis clearance to provide an overall measure of solute removal allowing the dose provided by dialysis to be individualised. Various algorithms are available to assist with this such as Standard Kt/V (Std Kt/V) which includes contributions from both Std Kt/V_{RKF} and Std $Kt/V_{dialysis}$ [1-3]. In this approach, reduction of dialysis dose may be considered provided that the combined urea clearance targets are met and other markers of dialysis adequacy such as blood pressure, inter-dialytic weight gains, anaemia, potassium, phosphate control, nutrition and general well-being are not compromised. The technique requires that the proportion of target dose provided by dialysis is increased as the RKF declines or if there are any other indicators for inadequate dialysis. The dialysis team and patients need to be aware of the importance of regular measurement of RKF 1 to 3 monthly [4]. This incremental approach may not be suitable for patients who are unable or unwilling to collect urine samples.

Traditionally RKF has been incorporated into peritoneal dialysis dosing but it has not been included in calculating HD dose due to limited practical experiences and outcome data from clinical studies. There are no RCTs that compare clinical outcomes of incremental HD and those of conventional thrice-weekly HD. A number of observational studies have compared clinical outcomes of twice-weekly HD and conventional thrice-weekly HD regimens [5-19]. These studies suggest that the mortality risks and survival outcomes are not inferior in those on the twice weekly dialysis regime compared and those treated conventionally, provided there is adequate RKF. Importantly, several non-randomised studies have suggested that RKF is better preserved in those dialysed twice weekly commencing soon after dialysis initiation [6,10, 11, 17, 18]. Preservation of RKF may provide clinical benefits to HD patients including

better fluid control, significant solute and fluid removal. It is also associated with improved quality of life and survival.

These findings indicate the need for a prospective RCT comparing RKF preservation following incremental and conventional initiation of dialysis. We are undertaking a study to determine the feasibility of conducting such a study. Our study will also provide pilot data to estimate differences in the rate of decline of RKF in the first year after commencing dialysis using either conventional or incremental approaches. The primary outcome of our study is to evaluate the feasibility of conducting a RCT in patients who have recently started HD. Patients will be randomised either to an incremental arm initiating with twice weekly dialysis or to a conventional three times weekly dialysis. Our study will explore key methodological, design, and safety issues, and also estimate an effect size. These findings will facilitate the design of a subsequent definitive study.

Methods/Design

Funding and governance

The study is funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme. The study received ethical approval from East of England – Cambridge South (REC reference 17/EE/0311; IRAS project ID 219032). The trial is sponsored by East and North Hertfordshire NHS Trust. The University of Hertfordshire Clinical Trial Support Network (CTSN) will provide independent support for randomisation and monitoring of the study. The conduct of the trial will be overseen by a Steering group which will meet regularly and will include an independent Chair and co-applicants. The CTSN will monitor compliance with the study protocol at 3 months following study initiation and then as required by sponsor scrutiny of data returns.

Setting

The study will take place in four NHS Trust renal units – East and North Hertfordshire, Royal Free Hospitals, Royal Berkshire Hospitals and University Hospitals of Leicester. The total number of participants from all centres will be 56. Recruitment commenced in January 2018 and completion of follow up will be in May 2020.

Study Objectives and End Points:

The study's primary objective is to determine the feasibility of conducting a definitive RCT of incremental HD initiation, compared with conventional thrice weekly in-centre HD initiation. There are a number of aspects to this primary objective which are summarised in Table 1. We will determine ease of recruitment (recruitability) and retention in the study(retainability), as well as fidelity to the protocol (protocol adherence) of patients in the study. The study will establish evidence for the safety of the incremental approach. It will also generate data allowing estimation of the effect size of the difference in rate of decline of RKF in the 6 months following randomisation between incremental and conventional HD arms.

Secondary objectives of the study are to determine whether there is a signal of benefit for incremental HD initiation for improving Quality of Life, mood, cognitive function, illness intrusiveness, functional status, frailty, risk of vascular access failure or interventions, major adverse cardiac events and survival. Specific tools used and methods to measure secondary outcomes related to these secondary objectives are detailed in Table 1. Illness intrusiveness will be measured with the Illness Intrusiveness Rating Scale, a validated tool to measure impact of the dialysis treatment and disease on physiologically meaningful activity and its psychosocial impact[20]. Quality of Life will be measured using EQ-5D-5L, a validated tool which will capture different dimensions of quality of life including anxiety/depression and pain/discomfort and can be used in health-economic evaluation[21]. Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA) which is a tool for assessment of cognitive function that has been validated in dialysis patients against detailed neurophysiological testing covering different domains of cognitive function and provides good sensitivity and specificity for identifying cognitive impairment in this population [22, 23]. Clinical frailty will be measured using the Clinical Frailty Score[24, 25].

Participants

Subjects meeting the inclusion criteria and not meeting the exclusion criteria will be eligible for screening and will be invited to participate in the study and asked to provide written informed consent prior to study screening. Eligibility criteria include having an inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA to ensure that only patients who are safe to potentially

randomise to incremental HD are consented. Where this is not available as part of routine care a pre-screening sample will be required.

Consent

Consent will be required prior to screening procedures and will include agreement to screening which includes confirmation of urea clearance ≥3ml/min/1.73m^2 BSA and an explicit consent to a protocol-driven dialysis regime and to randomisation to incremental HD or standard thrice weekly HD arms.

Inclusion Criteria:

- Age ≥ 18 years.
- Advanced kidney failure - established as a new starter on HD within the previous 3 months.
- RKF likely to permit twice weekly dialysis as defined by inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA measured routinely as part of standard care or as pre-screening.
- Sufficient understanding of the study procedures and requirements including capacity for explicit agreement to be randomised to standard or incremental HD regimens.

Exclusion Criteria:

- Planned organ transplantation within 3 months from study screening.
- Anticipated requirement for high-volume ultrafiltration on dialysis (e.g. subjects with daily enteral or parenteral nutrition)
- Blood-borne virus positivity.
- Subjects unable to comply with requirement for monthly inter-dialytic urine collection.
- Pregnancy.
- Prognosis <12 months as judged by the Principal Investigator.

Screening phase

At screening inclusion and exclusion criteria will be confirmed. Confirmation of inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will be performed. Pregnancy test will be performed in females of child-bearing age. Patients who, at screening, are eligible for study participation according to eligibility criteria, and who are confirmed to have a screening inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will eligible for randomisation. Subjects who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of dialysis initiation. At re-screening, a urea clearance ≥3ml/min/1.73m^2 BSA will be required for randomisation into the study.

Randomisation

Web-based randomisation will be carried out by each centre using Qualtrics, supported by the Clinical Trials Support Network, University of Hertfordshire. Subjects will be randomised on a 1:1 basis to each study arm and each subject allocated a unique study ID.

Study phase

Following randomisation, study subjects will be dialysed according to the protocol of their randomisation arm as per the schematic in Figure 1. Monthly quality assessment of dialysis in both arms will include a measure of dialysis clearance (Std Kt/$V_{Dialysis}$). RKF will be measured monthly by urea clearance in both arms and converted to Std Kt/V_{RKF}.

In the standard dialysis arm, dialysis adequacy will be assessed only using the Std Kt/$V_{Dialysis}$. In the incremental dialysis arm, the adequacy will be assessed using a composite of dialysis clearance (Std Kt/$V_{Dialysis}$) and RKF (Std Kt/V_{RKF}) as detailed below. This composite is termed Std Kt/$V_{Dialysis+RKF}$.

HD modes will remain standard throughout the study. Haemodiafiltration may be used where blood flow>250 ml/min, otherwise high-flux HD will be used.

Groups

Control Group: Standard HD arm

Subjects in the standard HD arm will be dialysed to target minimum Std $Kt/V_{Dialysis}$ of 2 per week. Subjects will be dialysed after randomisation initially for 3.5-4 hours thrice weekly. Dialysis dose will be adjusted using standard measures including maximising blood flow, dialysis time, membrane surface area and improving vascular access. Reduction in dialysis frequency will not be permitted.

Interventional Group: Incremental HD arm

Subjects randomised to the incremental HD arm will be dialysed to a target minimum Std Kt/V_{Total} (Std $Kt/V_{dialysis}$ + Std Kt/V_{RKF}) of 2 per week. Following randomisation dialysis will be initiated twice weekly, with a session duration of 3.5-4 hours. If Std Kt/V_{Total} exceeds the minimum target, clinicians will be permitted to reduce dialysis times provided the target level is still achieved. If Std Kt/V_{Total} does not meet the target, clinicians will be permitted to increase dialysis dose by optimising dialysis clearance (membrane selection, blood flow, vascular access, increasing dialysis time or frequency). Clinicians will be permitted to increase HD to thrice weekly or greater if required, and also to reduce frequency for these subjects should Std Kt/V_{Total} improve enough to allow target achievement. Subjects whose dialysis frequency is increased to thrice weekly or more will remain in the incremental HD arm.

Deviations to study protocol

If subjects are admitted to hospital, efforts will be made to adhere to the dialysis protocol. However, during admissions, modifications to the dialysis prescription, which include increasing dialysis frequency, are permitted in the interests of patient safety. These will be recorded as protocol deviations.

In the event of subjects in the incremental HD arm not providing inter-dialytic urine samples for calculation of Standard Kt/V_{Renal} for two consecutive months, the subject will be advised to dialyse thrice weekly and will remain in the study with target Standard $Kt/V_{Dialysis}$ >2 (i.e. assuming RRF is zero), until an inter-dialytic urine collection is provided. Additional study visits

may be performed if necessary following hospital admission, holiday or non-adherence to treatment schedule.

Procedures to avoid loss from follow up or study withdrawal

The patient information sheet and consent form will draw attention to the requirement for patients to agree that their dialysis regime and frequency will be adjusted according to the study protocol.

For patients wishing to withdraw consent, the investigator will explore with the patient the reasons for wishing to withdraw. In patients who wish to withdraw because they are unable to tolerate the intensity, frequency or duration of dialysis, the investigator will be permitted to offer to the patient to remain in the study with reduced dialysis intensity according to clinical judgement and record this as a protocol deviation (intention-to-treat approach). Patients who withdraw will be encouraged to remain in the study for the purpose of outcome data collection including measurement of RKF.

Data Collection

Data will be collected by the research team members at baseline and then monthly thereafter for 12 months. Table 2 summarises study assessments during the study and study time points.

Measurement of dialysis adequacy

Details of the method of measuring dialysis adequacy are provided in supplementary materials. The dialysis dosing adjustment will be carried out monthly using Std Kt/V calculated by this method.

Sample size

Retrospective studies suggest that decline of RKF may be attenuated in patients who receive twice weekly dialysis compared to thrice weekly, and that this effect occurs early such that a difference in RKF at 6 months is likely to be an optimal time point for the basis of a power analysis. Our initial power analysis, based on our own retrospective data[26], indicated an effect size (Cohen's d) of 0.37 calculated from mean and standard deviations of urea clearance

slopes in the first 6 months after HD initiation between two groups of patients, one initiating HD twice weekly and the other thrice weekly. Based on this, sample size for the proposed definitive RCT of 180 (90 each arm). A more accurate estimate for separation of RKF at 6 months between groups is desirable for the power analysis of a future prospective RCT.

Cocks and Torgerson [27] suggest a method to calculate the sample size for a pilot study from the estimated total sample size. Using this method, we find a required sample size of n=10 per arm to estimate mean and standard deviation of RKF at 6 months. However, Cocks and Torgerson advise a minimum sample size n=20 per arm. Allowing for 20% drop out at 6 months and 30% at 12 months an uplifted sample size of n=25 per arm at 6 months and n=18 per arm at 12 months requires randomisation of 50 subjects. During the initial few months of the study there were more patients than expected recovering dialysis independence so the sample size was increased to 56 to account for this. This is a feasibility study and a statistically significant difference in RKF decline between study groups is not expected. However, we anticipate that the sample size will be sufficient to provide an estimate of effect size.

Adverse events (AE) AND Serious Adverse Events (SAE)

All AE will be recorded in an AE log. SAEs will be reported to the CI and sponsors within 24 h of the research team becoming aware of the event. For the purpose of this study, SAE which result in death, hospitalisation, MACE, infections requiring antibiotic use, episodes of fluid overload needing resetting of dry weight, episodes of hyperkalemia (potassium level > 6.5 mmol/L), vascular access events (tunnelled line failures, tunnelled line infections, fistula thrombosis, fistula stenosis, false aneurysm) will be captured.

Data Analysis

The primary outcome is to evaluate the feasibility of conducting an RCT comparing the effect, on RKF decline, of incremental and conventional approaches to HD initiation. The study will be analysed as intention-to-treat. In order to estimate the study power for a future large scale RCT, estimates of change in RKF in the first 6 and 12 months after dialysis initiation will be determined.

Change in RKF will be determined using several methods. We will calculate, using regression analysis for individual subjects, rate of decline in GFR (mean of urea and creatinine clearance) for individual subjects and compare means between incremental and conventional HD groups. This effect size will be important in powering future definitive trials. In addition, we will estimate RKF (GFR) from monthly measured pre-dialysis middle molecule concentrations of β trace protein and β2-microglobulin converted to an equivalent GFR using the algorithm reported by Wong et al[28]. We will calculate rate of decline in GFR for individual patients from these middle molecule concentrations and using regression analysis for individual patient data to determine GFR slope and will compare mean slope between incremental HD and standard care groups.

Data from the EQ-5D-5L, PHQ-9, MoCA, IIRS and CFS will be compared between study arms with repeated measures parametric or non-parametric tests as appropriate (repeated measures ANOVA or Friedman tests). Comparison of MACE, vascular access events (access failure, access intervention, access related infections, fistula stenosis and fistula thrombosis), hyperkalaemic episodes, fluid overload episodes and lower respiratory tract infection episodes will be compared between groups using time-to-event analysis by the Nelson-Aalen approach.

Discussion

Clinical practise guidelines for HD adequacy, update 2006 [29] suggests that reduction of treatment frequency to less than thrice-weekly should only be considered in patients with inter-dialytic urea clearance >2ml/min/1.73m^2 since urea kinetic modelling simulations have shown that when residual urea clearance is less than this, it is not possible to achieve a weekly standard Kt/V of 2.0 with twice-weekly dialysis regimes. Hence in this study we have opted for a required inter-dialytic urea clearance (RKF) of ≥3ml/min/1.73m^2 BSA prior to randomisation as an inclusion criterion to provide a safety margin.

There are a large number of observational studies [5-18] that compare clinical outcomes of patients treated with twice-weekly HD with those on conventional thrice-weekly HD regimes but to date no RCT that compare clinical outcomes of incremental or infrequent HD versus

conventional thrice-weekly HD have been published. There are suggestions from observational studies that the rate of decline of RKF is slower using infrequent and incremental HD regimes but there is no prospective, randomised data. Hence it is unclear to what extent the benefits of incremental and infrequent HD are due to patient selection. Similarly, there are no comparative data on Quality of Life measures or on patient experience in conventional versus incremental HD. Mortality risk and survival outcomes have not been reported to be worse in patients treated with twice-weekly dialysis sessions [9, 13, 16] and a large US study found that mortality risk was lower in prevalent patients treated with twice-weekly HD, provide there was adequate RKF [5]. Hence there is a need for a definitive trial of incremental versus conventional dialysis initiation to define the effects on RKF preservation and patient–reported outcome and experience.

The outcome data of this current study will be used to inform the design of such a future definitive study. It is likely that the outcomes of a definitive study will be important, not only in defining the potential benefit of incremental HD for patients, but in establishing whether such an approach may allow optimization of resource use. If dialysis intensity can be reduced for patients with sufficient RKF with patient benefit, this will liberate dialysis resources that may permit other patients with high dialysis requirements to dialyse more frequently.

Competing interests

The authors declare that they have no competing interests. This report is independent research funded by BRS and BPKA. The views expressed in this publication are those of the authors.

Author's contributions

Design of the study and the development of the protocol: EV, RMKK, KF, SS
Trial set up and running of the study, trial governance, data integrity monitoring: EV, DW
Data analysis: EV, RMKK, KF, DW
Principal Investigators: EV, JB, AD, BA
All authors are involved in the steering group of the study and in the analysis and interpretation of the data.
All authors read and approved the final manuscript.

Abbreviations

AEs: Adverse Events
CFS: Clinical Frailty Score
CI: Chief Investigator
CRFs: Case Report Forms
EQ-5D-5L: EuroQol - 5D-5L
ESRD: End Stage Renal Disease
HD: Haemodialysis
IIRS: Illness Intrusiveness Rating Scale
Kt/V: Urea Clearance normalised to total body water
MACE: Major Adverse Cardiac Events
MoCA: Montreal Cognitive Assessment
PHQ-9: Patient Health Questionnaire 9
PI: Principal Investigator
RCT: Randomised Controlled Trial
RKF: Residual Kidney Function
SAEs: Serious Adverse Events
SUSAR: Suspected Unexpected Serious Adverse Reaction

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Table 1: Study Objectives

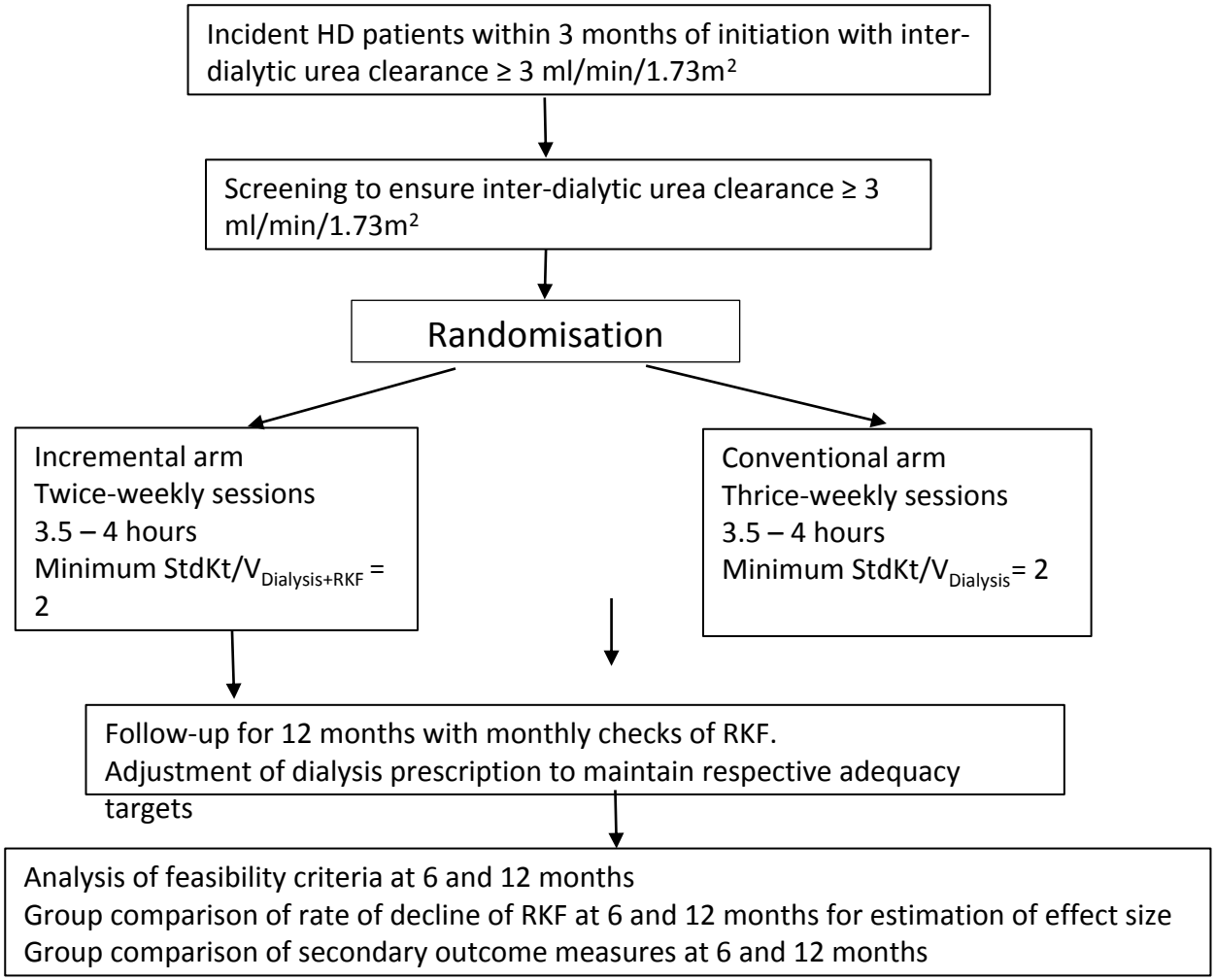
Primary Objective	Primary Outcome
The number of subjects agreeing to participate in the study – **Recruitability**	*Number of patients potentially eligible for screening during the study period at each study centre *Proportion of screened patients who fulfil study criteria *Proportion of patients approached who agree to participate in the study
The number of subjects who remain in the study – **Retainability**	Proportion of patients randomised who withdraw from the study and the reasons for their withdrawal
The proportion of subjects who adhere to protocol-driven changes in dialysis frequency - **Protocol adherence**	Proportion of patients who adhere to protocol dialysis frequency
The number of adverse and serious adverse events - **Safety of the study**	Frequency of hospital admission due to hyperkalemia and fluid overload, and lower respiratory tract infection (LRTI)
An estimate of the effectiveness of the intervention - **Effect size**	*Dialysis dose and residual kidney function as measured by Std Kt/V *Rate of change (mean) of RKF in the first 6 and 12 months after randomisation.
Secondary Objectives	**Secondary Outcome**
Quality of life (QOL)	QOL is assessed using EQ-5D-5L questionnaire
Mood – Depression	Depression assessed using PHQ-9 questionnaire.
Cognitive function	Change in cognitive function as assessed by MOCA tool
Illness intrusiveness	Illness intrusiveness is assessed using Illness intrusiveness rating scale
Functional status /Frailty	Functional status assessed by Clinical Frailty Score (CFS)
Vascular access failures or problems	Frequency of vascular access failures and interventions
Major Adverse Cardiac Events (MACE)	MACE is assessed by recording of the frequency of the events.
Survival	Survival is measured by all-cause mortality

Table 2: Schedule of Events

	Study Period		
	Pre-screening	**Baseline/Screening**	**Visit 1-12**
Months	**-12 to 0**	**0**	**1-12**
Study Procedures/Assessments			
Consent		**X**	
Inclusion/Exclusion Criteria	**X**	**X**	
Demographics, Medical History, Physical examination, Height		**X**	
Randomisation		**X**	
Rescreening*		**X**	
Concomitant medications -Diuretics, Erythropoietin Stimulating Agents, Antihypertensive, Phosphate Binders		**X**	**X**
Monthly dialysis blood tests		**X**	**X**
Monthly dialysis Adequacy assessments		**X**	**X**
Pre HD1 Urea, Post HD1 Urea, Pre HD2 Urea, Post HD2 Urea**	**X**	**X**	**X**
Inter-dialytic urine collection for Urea & Creatinine Clearance measurement		**X**	**X**
Frozen samples for β-2 Microglobulin & β Trace Protein		**X**	**X**
Bioimpedence measurement		**X**	**X**
Safety Assessments			
Adverse Events, Serious Adverse Events, MACE, End points			**X**
Questionnaires			
EQ-5D-5L, IIRS, PHQ9, MoCA, CFS		**Months 0, 6, 12**	

*Patients who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of HD initiation

** Dialysis adequacy can be calculated using either PostHD1 Urea, PreHD2 Urea, PostHD2 Urea or optionally using PreHD1 Urea, PostHD1 Urea, PreHD2 Urea.


Incident HD patients within 3 months of initiation with inter-dialytic urea clearance ≥ 3 ml/min/1.73m2
Screening to ensure inter-dialytic urea clearance ≥ 3 ml/min/1.73m2
Randomisation
Incremental arm
Twice-weekly sessions
3.5 – 4 hours
Minimum StdKt/VDialysis+RKF = 2
Conventional arm
Thrice-weekly sessions
3.5 – 4 hours
Minimum StdKt/VDialysis= 2
Follow-up for 12 months with monthly checks of RKF.
Adjustment of dialysis prescription to maintain respective adequacy targets
Analysis of feasibility criteria at 6 and 12 months
Group comparison of rate of decline of RKF at 6 and 12 months for estimation of effect size
Group comparison of secondary outcome measures at 6 and 12 months

CALCULATION PROCESS FOR DIALYSIS STANDARD Kt/V TAKING INTO ACCOUNT ULTRAFILTRATION WEIGHT (DAUGIRDAS METHODOLOGY)

STEP 1: Calculate spKt/V not taking into account fluid removal

$$spKt/V = \ln\left(\frac{Cpre}{Cpost}\right) \qquad \textit{(EQUATION 1)}$$

Where Cpre s urea concentration pre-dialysis and Cpost is urea concentration post dialysis

STEP 2: Calculate eKt/V not taking into account fluid removal using Tattersall transformation

In this calculation the Tattersall time constant is modified from 35 mins to 30.7mins as per modifications recommended by Daugirdas (Kidney International (2010) 77, 637–644)

eKt/V=spKt/V from step 1* $\frac{\left(\frac{Td}{60}\right)}{(Td \times 60 + 30.7)}$ ***(EQUATION 2)***

Where Td is dialysis duration expressed in hours

STEP 3: Calculate Adjusted Watson Volume

Watson V needs to be downsized by 10% to account for higher modelled V compared to anthropometric Watson V (Daugirdas Kidney International (2010) 77, 637–644).

Calculate Watson Volume by standard equation and downgrade by 10%

Adjusted Watson V=Watson V * 0.9 ***(EQUATION 3)***

STEP 4: Calculate Leypoldt standard Kt/V

In this we employ eKt/V from equation 2. This equation for standard Kt/V does not account for UF volume. Leypoldt equation is as below (Leypoldt JK. Hemodial Int 2004; 8: 193–197. and Daugirdas Kidney International (2010) 77, 637–644):

$$\mathrm{stdKt}/V = \frac{10,080\,\frac{1-e^{-eKt/V}}{t}}{\frac{1-e^{-eKt/V}}{eKt/V} + \frac{10,080}{Ft}} - 1$$

(EQUATION 4)

Where f=frequency, t=dialysis time, eKt/V is results from **Equation 2**

STEP 5: Calculate Standard Kt/V taking into account UF weight using Daugirdas methodology:

$$\mathrm{stK_dt}/V = S/(1 - (0.74/F) \cdot \mathrm{UFw}/V) \quad \textit{(EQUATION 5)}$$

(equation 2 from Daugirdas et al, Kidney International (2010) 77, 637–644)

where S=StdKt/V from EQUATION 4, F=frequency (sessions/week), UFw=weekly fluid gain between HD sessions, V=adjusted Watson V from **Equation 3**

CALCULATION OF RESIDUAL RENAL FUNCTION STANDARD Kt/V

STEP 1: Calculate Urea clearance

$$\textbf{Urea clearance} = \frac{\boldsymbol{UrineVol \times 1000 \times UreaUrea}}{\dfrac{(\boldsymbol{UrineDuration \times 24 \times 60 - (Td \times 60)})}{\left(\dfrac{(\boldsymbol{PostUrea + PreUrea})}{\boldsymbol{2}}\right)}} \quad \textbf{(EQUATION 6)}$$

Where urea clearance units are ml/min, UrineVol=urine volume (L), UrineUrea=urine urea concentration (mmol/L), UrineDuration=Urine collection duration (whole days between HD session), Td=dialysis duration (hours), PostUrea=Blood urea concentration at end of HD when urine collection starts (mmol/L), PreUrea= Blood urea concentration at start of HD when urine collection ends (mmol/L).

This equation assumes that dialysis is occurring at regular time points and utilises duration of urine collection as days between HD sessions minus dialysis duration.

Step 2: Calculate urea clearance corrected for body surface area (used for screening process of study but not for calculation of Std Kt/V which uses unadjusted urea clearance

BSA=Dubois BSA (m^2)

BSA = 0.007184* Height in $cm^{0.725}$ * Weight in $Kg^{0.425}$ **(EQUATION 7)**

Urea clearance adjusted for BSA=Urea clearance *1.73/BSA **(EQUATION 8)**

Step 3: Calculate Adjustment factor needed to downgrade urea clearance so it can be used to calculate Standard Kt/V

This method applies a multiplier to Urea Clearance to downgrade it so that it is appropriately incorporated into the Standard Kt/V calculation (fKru=approximately 0.7, or 70%)

$$\mathrm{fKrU} = \frac{0.974}{(spKt/V + 1.62) + 0.4} \quad \textbf{(EQUATION 9)}$$

(from Daugirdas Kidney International (2010) 77, 637–644). SpKt/V is that from **Equation 1**

Step 4: Adjust Urea clearance for incorporation into Standard Kt/V

Adjusted KrU=Urea clearance * fKrU **(EQUATION 10)**

Where Urea clearance is from equation 6 and fKrU is from **equation 9**

From equation 4 in Daugirdas, Kidney International (2010) 77, 637–644

Step5: Calculate Residual Renal Function equivalent Standard Kt/V

This is calculated as K*t/V where K=adjusted KrU, t=minutes in 7 days, V=Adjusted Watson Volume

$$\textbf{Residual Renal Standard Kt/V} = \frac{\boldsymbol{Adjusted\ KrU} \times \mathbf{10080}}{\boldsymbol{Adjusted\ Watson\ Volume} \times \mathbf{1000}}$$

(EQUATION 11)

from equation 5 in Daugirdas Kidney International (2010) 77, 637–644

Where Adjusted KrU is from equation 10 (ml/min) and Adjusted Watson Volume (L) is from **Equation 3** above.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	5
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	13
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, Table 1
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect	8

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6, 7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 2

Notes:

- 13: Table 2, Figure 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 21. November 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035919.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2020
Complete List of Authors:	KAJA KAMAL, RAJA MOHAMMED; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Farrington, Ken; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Wellsted, David; University of Hertfordshire Sridharan , Sivakumar; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Alchi, Bassam; Royal Berkshire NHS Foundation Trust, Renal Unit Burton, James; University Hospitals of Leicester NHS Trust, Renal Unit Davenport, Andrew; Royal Free Hospital, Renal Unit Vilar, Enric; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine
Keywords:	Adult nephrology < NEPHROLOGY, Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY

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TITLE:

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

Author:

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Word count 3151

ABSTRACT

Introduction

Preserving Residual Kidney Function(RKF) may be beneficial to patients on haemodialysis (HD) and it has been proposed that commencing dialysis incrementally rather than three times a week may preserve RKF. In Incremental HD, target dose includes a contribution from RKF, which is added to HD dose, allowing individualisation of the HD prescription. We will conduct a feasibility randomised controlled trial(RCT) comparing incremental HD and conventional three times weekly treatments in incident HD patients. The study is designed also to provide pilot data to allow determination of effect size to power a definitive study.

Methods and Analysis

After screening to ensure native renal urea clearance >3ml/min/1.73m^2, the study will randomise 54 patients within 3 months of HD initiation to conventional in-centre thrice weekly dialysis or incremental in-centre HD commencing two days a week. Subjects will be followed up for 12 months. The study will be carried out across 4 UK renal centres.

The primary outcome is to evaluate the feasibility of conducting a definitive RCT and to estimate the difference in rate of decline of RKF between the two groups at 6 and 12-month time points. Secondary outcomes will include the impact of dialysis intensity on vascular access events, major adverse cardiac events(MACE) and survival. Impact of dialysis intensity on patient reported outcomes measures, cognition and frailty will be assessed using EQ-5D-5L, PHQ-9, Illness intrusiveness rating score(IIRS), Montreal Cognitive assessment(MoCA), and Clinical Frailty Score(CFS). Safety outcomes include hospitalisation, fluid overload episodes, hyperkalaemia events and vascular access events.

This study will inform the design of a definitive study, adequately powered to determine whether RKF is better preserved after incremental HD initiation compared to conventional initiation.

Ethics and dissemination

Ethics approval has been granted by Cambridge South Research Ethics Committee, United Kingdom(REC17/EE/0311). Results will be disseminated via peer-reviewed publication.

Trial registration number:NCT03418181

Key words: 3 -10 keywords

Residual Kidney Function -End stage renal disease – HD - RCT – Randomised Controlled Trial

Strengths and limitations of this study

- There are no randomised studies comparing incremental HD and conventional three times weekly treatments in incident HD patients. This study will address this gap.
- It will provide data on feasibility of recruitment to a definitive study together with an estimate of the effect size of group differences in rate of loss residual kidney function allowing sample size calculation.
- Impact and intrusiveness of dialysis intensity will also be compared between groups.
- The sample size will not permit definitive determination of differences in the rate of decline of RKF between groups.

Background

Most end stage renal failure (ESRF) patients have a degree of native kidney function (Residual Kidney Function, RKF) remaining when they initiate HD. There has been recent interest in incremental HD, a method of individualising HD according to the level of RKF to permit dialysis to be commenced at a lower intensity than conventional approaches allow. Most patients commence dialysis using conventional three times weekly dialysis with RKF usually not accounted for in prescribing dialysis dose. In Incremental HD, RKF is combined with dialysis clearance to provide an overall measure of solute removal allowing the dose provided by dialysis to be individualised. Various algorithms are available to assist with this such as Standard Kt/V (Std Kt/V) which includes contributions from both Std Kt/V_{RKF} and Std $Kt/V_{dialysis}$ [1-3]. In this approach, reduction of dialysis dose may be considered provided that the combined urea clearance targets are met and other markers of dialysis adequacy such as blood pressure, inter-dialytic weight gains, anaemia, potassium, phosphate control, nutrition and general well-being are not compromised. The technique requires that the proportion of target dose provided by dialysis is increased as the RKF declines or if there are any other indicators for inadequate dialysis. The dialysis team and patients need to be aware of the importance of regular measurement of RKF 1 to 3 monthly [4]. This incremental approach may not be suitable for patients who are unable or unwilling to collect urine samples.

Traditionally RKF has been incorporated into peritoneal dialysis dosing but it has not been included in calculating HD dose due to limited practical experiences and outcome data from clinical studies. There are no RCTs that compare clinical outcomes of incremental HD and those of conventional thrice-weekly HD. A number of observational studies have compared clinical outcomes of twice-weekly HD and conventional thrice-weekly HD regimens [5-19]. These studies suggest that the mortality risks and survival outcomes are not inferior in those on the twice weekly dialysis regimen compared and those treated conventionally, provided there is adequate RKF. Importantly, several non-randomised studies have suggested that RKF is better preserved in those dialysed twice weekly commencing soon after dialysis initiation [6,10, 11, 17, 18]. Preservation of RKF may provide clinical benefits to HD patients including

better fluid control, significant solute and fluid removal. It is also associated with improved quality of life and survival.

These findings indicate the need for a prospective RCT comparing RKF preservation following incremental and conventional initiation of dialysis. We are undertaking a study to determine the feasibility of conducting such a study. Our study will also provide pilot data to estimate differences in the rate of decline of RKF in the first year after commencing dialysis using either conventional or incremental approaches. The primary outcome of our study is to evaluate the feasibility of conducting a RCT in patients who have recently started HD. Patients will be randomised either to an incremental arm initiating with twice weekly dialysis or to a conventional three times weekly dialysis. Our study will explore key methodological, design, and safety issues, and also estimate an effect size. These findings will facilitate the design of a subsequent definitive study.

Methods/Design

Funding and governance

The study is funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme, grant number 16-020. The study received ethical approval from East of England – Cambridge South (REC reference 17/EE/0311; IRAS project ID 219032). The trial is sponsored by East and North Hertfordshire NHS Trust. The University of Hertfordshire Clinical Trial Support Network (CTSN) will provide independent support for randomisation and monitoring of the study. The conduct of the trial will be overseen by a Steering group which will meet regularly and will include an independent Chair and co-applicants. The CTSN will monitor compliance with the study protocol at 3 months following study initiation and then as required by sponsor scrutiny of data returns.

Patient and public involvement

A summary of the initial protocol was shared with ten patients who were asked to comment on the study design, the potential willingness of patients to participate in the study, and the burden of study procedures and interventions. Their comments were taken account of in preparing the final version of the protocol. Patients will be involved in interpreting study finding and in design of definitive study.

We will report a summary of results to patients in a personal communication by mail. We will also summarise results to local patient association newsletters.

Setting

The study will take place in four NHS Trust renal units – East and North Hertfordshire, Royal Free Hospitals, Royal Berkshire Hospitals and University Hospitals of Leicester. The total number of participants from all centres will be 54. Recruitment commenced in January 2018 and completion of follow up will be in May 2020.

Study Objectives and End Points:

The study's primary objective is to determine the feasibility of conducting a definitive RCT of incremental HD initiation, compared with conventional thrice weekly in-centre HD initiation. There are a number of aspects to this primary objective which are summarised in Table 1. We will determine, at each study site, the proportion of incident HD patients it is practical to approach, who pre-screen as suitable for formal study screening (eligibility for screening). We will determine the proportion of those patients who consent undergo formal screening, pass the screening test and are randomised (recruitability). We will also determine the study retention rate (retainability) as well as fidelity to the protocol (protocol adherence) of patients in the study. Numerators and denominators for these parameters are shown in Figure 1. The study will establish evidence for the safety of the incremental approach. It will also generate data allowing estimation of the effect size of the difference in rate of decline of RKF in the 6 months following randomisation between incremental and conventional HD arms.

Secondary objectives of the study are to determine whether there is a signal of benefit for incremental HD initiation for improving Quality of Life, mood, cognitive function, illness intrusiveness, functional status, frailty, risk of vascular access failure or interventions, major adverse cardiac events and survival. Specific tools used and methods to measure secondary outcomes related to these secondary objectives are detailed in Table 1. Illness intrusiveness will be measured with the Illness Intrusiveness Rating Scale, a validated tool to measure impact of the dialysis treatment and disease on physiologically meaningful activity and its psychosocial impact[20]. Quality of Life will be measured using EQ-5D-5L, a validated tool which will capture different dimensions of quality of life including anxiety/depression and

pain/discomfort and can be used in health-economic evaluation[21]. Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA) which is a tool for assessment of cognitive function that has been validated in dialysis patients against detailed neurophysiological testing covering different domains of cognitive function and provides good sensitivity and specificity for identifying cognitive impairment in this population [22, 23]. Clinical frailty will be measured using the Clinical Frailty Score[24, 25].

Table 1 Study objectives

Primary Objective	Primary Outcome
The proportion of eligible subjects agreeing to participate in the study – **Recruitability**	* Proportion incident HD patients it is practical to approach, who pre-screen as suitable for screening (eligibility for screening) *Proportion of screened patients who fulfil all eligibility criteria for participation in the study *Proportion of these patients who agree to participate in the study
The proportion of randomised subjects who remain in the study – **Retainability**	Proportion of patients randomised who remain in the study excluding study withdrawals, and reasons for withdrawals
The proportion of subjects who adhere to protocol-driven changes in dialysis frequency - **Protocol adherence**	Proportion of patients who adhere to protocol dialysis frequency
The number of adverse and serious adverse events - **Safety of the study**	Frequency of hospital admission due to hyperkalemia and fluid overload, and lower respiratory tract infection (LRTI)
An estimate of the effectiveness of the intervention - **Effect size**	*Dialysis dose and residual kidney function as measured by Std Kt/V *Rate of change (mean) of RKF in the first 6 and 12 months after randomisation.
Secondary Objectives	**Secondary Outcome**
Retention of RKF	Proportion of patients with interdialytic urea clearance ≥2 and ≥3 ml/min/1.73m^2 at 6 months.
Quality of life (QOL)	QOL is assessed using EQ-5D-5L questionnaire
Mood – Depression	Depression assessed using PHQ-9 questionnaire.
Cognitive function	Change in cognitive function as assessed by MOCA tool
Illness intrusiveness	Illness intrusiveness is assessed using Illness intrusiveness rating scale
Functional status /Frailty	Functional status assessed by Clinical Frailty Score (CFS)
Vascular access failures or problems	Frequency of vascular access failures and interventions
Major Adverse Cardiac Events (MACE)	MACE is assessed by recording of the frequency of the events.
Survival	Survival is measured by all-cause mortality

Participants

All adult patients who have commenced HD in the previous 3 months will be considered for the study. Those who potentially meet the eligibility criteria after pre-screening by review of medical records including the requirement for a standard of care inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will eligible for study screening. Those consenting for the study will undergo formal screening to include confirmation of their meeting the eligibility criteria including having an inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA on retesting.

Consent

Consent will be required prior to screening procedures and will include agreement to screening which includes confirmation of urea clearance ≥3ml/min/1.73m^2 BSA and an explicit consent to a protocol-driven dialysis regimen and to randomisation to incremental HD or standard thrice weekly HD arms.

Inclusion Criteria:

- Age ≥ 18 years.
- Advanced kidney failure - established as a new starter on HD within the previous 3 months.
- RKF likely to permit twice weekly dialysis as defined by inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA measured routinely as part of standard care or as pre-screening.
- Sufficient understanding of the study procedures and requirements including capacity for explicit agreement to be randomised to standard or incremental HD regimens.

Exclusion Criteria:

- Planned organ transplantation within 3 months from study screening.
- Anticipated requirement for high-volume ultrafiltration on dialysis (e.g. subjects with daily enteral or parenteral nutrition)
- Blood-borne virus positivity.
- Subjects unable to comply with requirement for monthly inter-dialytic urine collection.

- Pregnancy.
- Prognosis <12 months as judged by the Principal Investigator.

Screening phase

At screening inclusion and exclusion criteria will be confirmed. Confirmation of inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will be performed. Pregnancy test will be performed in females of child-bearing age to reduce chance of unexpected pregnancy occurring during the study which would require study withdrawal. Patients who, at screening, are eligible for study participation according to eligibility criteria, and who are confirmed to have a screening inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will eligible for randomisation. Subjects who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of dialysis initiation. At re-screening, a urea clearance ≥3ml/min/1.73m^2 BSA will be required for randomisation into the study.

Randomisation

Web-based randomisation will be carried out by each centre using Qualtrics, supported by the Clinical Trials Support Network, University of Hertfordshire. Subjects will be randomised on a 1:1 basis to each study arm and each subject allocated a unique study ID.

Study phase

Following randomisation, study subjects will be dialysed according to the protocol of their randomisation arm as per the schematic in Figure 1. Monthly quality assessment of dialysis in both arms will include a measure of dialysis clearance (Std Kt/$V_{Dialysis}$). RKF will be measured monthly by urea clearance in both arms and converted to Std Kt/V_{RKF}.

In the standard dialysis arm, dialysis adequacy will be assessed only using the Std Kt/$V_{Dialysis}$. In the incremental dialysis arm, the adequacy will be assessed using a composite of dialysis clearance (Std Kt/$V_{Dialysis}$) and RKF (Std Kt/V_{RKF}) as detailed below. This composite is termed Std Kt/$V_{Dialysis+RKF}$. HD modes will remain standard throughout the study. Haemodiafiltration may be used where blood flow>250 ml/min, otherwise high-flux HD will be used.

Assessment of residual kidney function

There are two main methods of including residual kidney function in HD prescription. The first converts residual urea clearance to an equivalent dialysis sessional clearance[7]. The second converts sessional Kt/V to a weekly equivalent clearance. Both these allow the addition of dialysis and renal clearances. There are two variants of the second method: standard Kt/V[26] and the Casino-Lopez Equivalent renal urea clearance (EKR)[27]. Both these are urea clearance based. The ERBP guidelines recommend use of GFR (mean of urea and creatinine clearance) in the EKR equation rather than urea clearance which was intrinsic to originally derived equation. We have used standard Kt/V which takes a more conservative view of RKF since urea clearance is around 30% lower than GFR. Further details of the methodology for assessment of residual kidney function can be found in Supplementary Materials.

Groups

Control Group: Standard HD arm

Subjects in the standard HD arm will be dialysed to target minimum Std $Kt/V_{Dialysis}$ of 2 per week. Subjects will be dialysed after randomisation initially for 3.5-4 hours thrice weekly. Dialysis dose will be adjusted using standard measures including maximising blood flow, dialysis time, membrane surface area and improving vascular access. Reduction in dialysis frequency will not be permitted.

Interventional Group: Incremental HD arm

Subjects randomised to the incremental HD arm will be dialysed to a target minimum Std Kt/V_{Total} (Std $Kt/V_{dialysis}$ + Std Kt/V_{RKF}) of 2 per week. Following randomisation dialysis will be initiated twice weekly, with a session duration of 3.5-4 hours. If Std Kt/V_{Total} exceeds the minimum target, clinicians will be permitted to reduce dialysis duration provided the target level is still achieved. If Std Kt/V_{Total} does not meet the target, clinicians will be permitted to increase dialysis dose by optimising dialysis clearance (membrane selection, blood flow, vascular access, increasing dialysis time or frequency). Clinicians will also be permitted to increase the dialysis frequency to thrice-weekly or greater if required. The main trigger for

this will be failure to meet minimum adequacy targets but clinicians will have the freedom to make this transition on other clinical grounds including hyperkalaemia and fluid overload. The reasons for switching from twice to thrice weekly will be recorded. Hyperkalaemia and fluid overload are also captured as Serious Adverse Events.

Deviations to study protocol

If subjects are admitted to hospital, efforts will be made to maintain adherence to the dialysis protocol. However, during admissions, modifications to the dialysis prescription, which include increasing dialysis frequency, are permitted in the interests of patient safety. These will be recorded as protocol deviations.

In the event of subjects in the incremental HD arm not providing inter-dialytic urine samples for calculation of Standard Kt/V_{Renal} for two consecutive months, the subject will be advised to dialyse thrice weekly and will remain in the study with target Standard $Kt/V_{Dialysis}$ >2 (i.e. assuming RRF is zero), until an inter-dialytic urine collection is provided. Additional study visits may be performed if necessary following hospital admission, holiday or non-adherence to treatment schedule.

Procedures to avoid loss from follow up or study withdrawal

The patient information sheet and consent form will draw attention to the requirement for patients to agree that their dialysis regimen and frequency will be adjusted according to the study protocol.

For patients wishing to withdraw consent, the investigator will explore with the patient the reasons for wishing to withdraw. In patients who wish to withdraw because they are unable to tolerate the intensity, frequency or duration of dialysis, the investigator will be permitted to offer to the patient to remain in the study with reduced dialysis intensity according to clinical judgement and record this as a protocol deviation (intention-to-treat approach). Patients who withdraw will be encouraged to remain in the study for the purpose of outcome data collection including measurement of RKF.

Data Collection

Data will be collected by the research team members at baseline and then monthly thereafter for 12 months. Table 2 summarises study assessments during the study and study time points.

Table 2 Schedule of events.

*Patients who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of HD initiation.

** Dialysis adequacy can be calculated using either PostHD1 Urea, PreHD2 Urea, PostHD2 Urea or optionally using PreHD1 Urea, PostHD1 Urea, PreHD2 Urea.

	Study Period		
	Pre-screening	**Baseline/Screening**	**Visit 1-12**
Months	**-12 to 0**	**0**	**1-12**
Study Procedures/Assessments			
Consent		**X**	
Inclusion/Exclusion Criteria	**X**	**X**	
Demographics, Medical History, Physical examination, Height		**X**	
Randomisation		**X**	
Rescreening*		**X**	
Concomitant medications -Diuretics, Erythropoietin Stimulating Agents, Antihypertensive, Phosphate Binders		**X**	**X**
Monthly dialysis blood tests		**X**	**X**
Monthly dialysis Adequacy assessments		**X**	**X**
Pre HD1 Urea, Post HD1 Urea, Pre HD2 Urea, Post HD2 Urea**	**X**	**X**	**X**
Inter-dialytic urine collection for Urea & Creatinine Clearance measurement		**X**	**X**
Frozen samples for β-2 Microglobulin & β Trace Protein		**X**	**X**
Bioimpedence measurement		**X**	**X**
Safety Assessments			
Adverse Events, Serious Adverse Events, MACE, End points			**X**
Questionnaires			
EQ-5D-5L, IIRS, PHQ9, MoCA, CFS		**Months 0, 6, 12**	

Measurement of dialysis adequacy

Details of the method of measuring dialysis adequacy are provided in supplementary materials. The dialysis dosing adjustment will be carried out monthly using Std Kt/V calculated by this method. For patients dialysing thrice weekly (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday) the Monday/Tuesday session is considered to be session 1 of the week (HD1) and the Wednesday/Thursday session is considered session 2 of the week (HD2). For patients dialysing twice weekly (Monday/Friday or Tuesday/Saturday) the Friday/Saturday is considered HD1 and the Monday/Tuesday HD2. Blood and urine samples to be taken are shown in Table 2 (Schedule of Events) and in Figure 2. The urine collection and measurement of RKF is performed from HD1 to HD2 and will be calculated from post-HD1 and pre-HD2 serum urea/creatinine, urine volume and urine urea/creatinine concentration as per the equations in the Supplementary Material. The measurement of dialysis dose is calculated from dialysis session data (pre- and post-weight HD2 weight, Watson Volume, pre- and post HD2 urea and dialysis session duration (Td) (see Supplementary Material for calculation procedure).

Urine collection will consequently be over approximately three days for twice weekly patients and two days for thrice weekly patients. Although there is a small risk of bias due to longer duration urine collections for twice weekly HD patients, this is likely to be balanced by the incentive for these patients to provide complete urine collections to ensure their dialysis intensity is not increased.

Sample size

Retrospective studies suggest that decline of RKF may be attenuated in patients who receive twice weekly dialysis compared to thrice weekly, and that this effect occurs early such that a difference in RKF at 6 months is likely to be an optimal time point for the basis of a power analysis. Our initial power analysis, based on our own retrospective data[28] indicated an effect size (Cohen's d) of 0.37 calculated from mean and standard deviations of urea clearance slopes in the first 6 months after HD initiation between two groups of patients, one initiating

HD twice weekly and the other thrice weekly. Based on this, the sample size for the proposed definitive RCT would be 180 (90 each arm). If the definitive study were to be carried out using the same 4 centres, the available incident HD population would be around 600 annually or 1200 over a proposed 2 year recruitment period. We anticipate that 40% of these patients will meet the eligibility criteria ie 480 patients. To achieve 180 analysable patients at 6 months following randomisation we will need to recruit 50% of eligible patients assuming a retention rate of 75% over 6 months.

This feasibility study will test these assumptions on effect size, the proportion of incident patients who can be pre-screened who are eligible to be approached for study consent, the proportion of patients approached for screening who consent, pass formal screening and undergo randomisation (recruitability), and the retention rate during the 6 months after randomisation (retainability). Sample sizes between 24 and 50 have been recommended for feasibility studies [29, 30]. Initially we chose a sample size of 50 but, because of a higher than anticipated recovery of renal function in the first few weeks of recruitment, increased this to 54. A sample of this size will enable us to estimate eligibility, recruitability, screen-failure rate and retainabililty rate to within a 95% confidence interval of +/- 11-14%.

Adverse events (AE) and Serious Adverse Events (SAE)

All AE will be recorded in an AE log. SAEs will be reported to the CI and sponsors within 24 h of the research team becoming aware of the event. For the purpose of this study, SAE which result in death, hospitalisation, MACE, infections requiring antibiotic use, episodes of fluid overload needing resetting of dry weight, episodes of hyperkalemia (potassium level > 6.5 mmol/L), vascular access events (tunnelled line failures, tunnelled line infections, fistula thrombosis, fistula stenosis, false aneurysm) will be captured.

Data Analysis

The primary outcome is to evaluate the feasibility of conducting an RCT comparing the effect, on RKF decline, of incremental and conventional approaches to HD initiation. The study will be analysed as intention-to-treat. In order to estimate the study power for a future large scale RCT, estimates of change in RKF in the first 6 and 12 months after dialysis initiation will be determined.

Change in RKF will be determined using several methods. We will calculate, using linear regression analysis for individual subjects, rate of decline in GFR (mean of urea and creatinine clearance) for individual subjects and compare means of these rates between incremental and conventional HD groups with a t test if normally distributed. This effect size will be important in powering future definitive trials. Using a previously described method we will employ a mixed effects model to compare rate of decline in GFR between randomisation groups[28]. As an indicator of RKF, we will compare urine volume data between groups using similar statistical techniques to the above. We will also compare proportions of patients in the two groups who have a residual interdialytic urea clearance ≥ 2 and ≥ 3 ml/min/1.73m^2 at 6months. In addition, we will estimate RKF (GFR) from monthly measured pre-dialysis middle molecule concentrations of β trace protein and β2-microglobulin converted to an equivalent GFR using the algorithm reported by Wong et al[31]. We will calculate rate of decline in GFR for individual patients from these middle molecule concentrations and using regression analysis for individual patient data to determine GFR slope and will compare mean slope between incremental HD and standard care groups..

Data from the EQ-5D-5L, PHQ-9, MoCA, IIRS and CFS will be compared between study arms with repeated measures parametric or non-parametric tests as appropriate (repeated measures ANOVA or Friedman tests). Comparison of MACE, vascular access events (access failure, access intervention, access related infections, fistula stenosis and fistula thrombosis), hyperkalaemic episodes, fluid overload episodes and lower respiratory tract infection episodes will be compared between groups using time-to-event analysis by the Nelson-Aalen approach.

Discussion

Clinical practise guidelines for HD adequacy, update 2006 [32] suggests that reduction of treatment frequency to less than thrice-weekly should only be considered in patients with inter-dialytic urea clearance >2ml/min/1.73m^2 since urea kinetic modelling simulations have shown that when residual urea clearance is less than this, it is not possible to achieve a weekly standard Kt/V of 2.0 with twice-weekly dialysis regimens. Hence in this study we have opted

for a required inter-dialytic urea clearance (RKF) of ≥3ml/min/1.73m^2 BSA prior to randomisation as an inclusion criterion to provide a safety margin.

There are a large number of observational studies [5-18] that compare clinical outcomes of patients treated with twice-weekly HD with those on conventional thrice-weekly HD regimens but to date no RCT that compare clinical outcomes of incremental or infrequent HD versus conventional thrice-weekly HD have been published. Though these studies suggest that the rate of decline of RKF is slower using infrequent and incremental HD regimens but prospective, randomised data is not available. Hence it is unclear to what extent the benefits of incremental and infrequent HD are due to patient selection. Similarly, there are no comparative data on Quality of Life measures or on patient experience in conventional versus incremental HD. Mortality risk and survival outcomes have not been reported to be worse in patients treated with twice-weekly dialysis sessions [9, 13, 16] and a large US study found that mortality risk was lower in prevalent patients treated with twice-weekly HD, provided there was adequate RKF [5]. Hence there is a need for a definitive trial of incremental versus conventional dialysis initiation to define the effects on RKF preservation and patient–reported outcome and experience.

The outcome data of this current study will be used to inform the design of such a future definitive study. The proposed feasibility study will test assumptions around the effect size, the eligibility for screening, recruitability, and retainability. Deviations from the assumed values will alter the design of the definitive study eg number of centres required, eligibility criteria, primary outcome measure, sample size, and may indicate that a definitive study is non-viable.

It is likely that the outcomes of a definitive study will be important, not only in defining the potential benefit of incremental HD for patients, but in establishing whether such an approach may allow optimization of resource use. If dialysis intensity can be reduced for patients with sufficient RKF with patient benefit, this will liberate dialysis resources that may permit other patients with high dialysis requirements to dialyse more frequently.

Acknowledgements

The authors are grateful for the British Kidney Patient Association & British Renal Society Joint Grants Programme for funding this study and for the assistance of our patients in the study design.

Competing interests

The authors declare that they have no competing interests. This report is independent research funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme. The views expressed in this publication are those of the authors.

Author's contributions

Design of the study and the development of the protocol: EV, RMKK, KF, SS
Trial set up and running of the study, trial governance, data integrity monitoring: EV, DW
Data analysis: EV, RMKK, KF, DW
Principal Investigators: EV, JB, AD, BA
All authors are involved in the steering group of the study and in the analysis and interpretation of the data.
All authors read and approved the final manuscript.

Abbreviations

AEs: Adverse Events
CFS: Clinical Frailty Score
CI: Chief Investigator
CRFs: Case Report Forms
EQ-5D-5L: EuroQol - 5D-5L
ESRD: End Stage Renal Disease
HD: Haemodialysis
IIRS: Illness Intrusiveness Rating Scale
Kt/V: Urea Clearance normalised to total body water
MACE: Major Adverse Cardiac Events
MoCA: Montreal Cognitive Assessment
PHQ-9: Patient Health Questionnaire 9
PI: Principal Investigator
RCT: Randomised Controlled Trial
RKF: Residual Kidney Function
SAEs: Serious Adverse Events
SUSAR: Suspected Unexpected Serious Adverse Reaction

Legends to Figures

Figure 1. Flow diagram of clinical trial demonstrating data that will be used to calculate eligibility for screening, screen failure rate, recruitability and retainability.

Figure 2. Timing of urine collection and blood tests for dialysis adequacy measurement for patients on twice weekly and thrice weekly HD.

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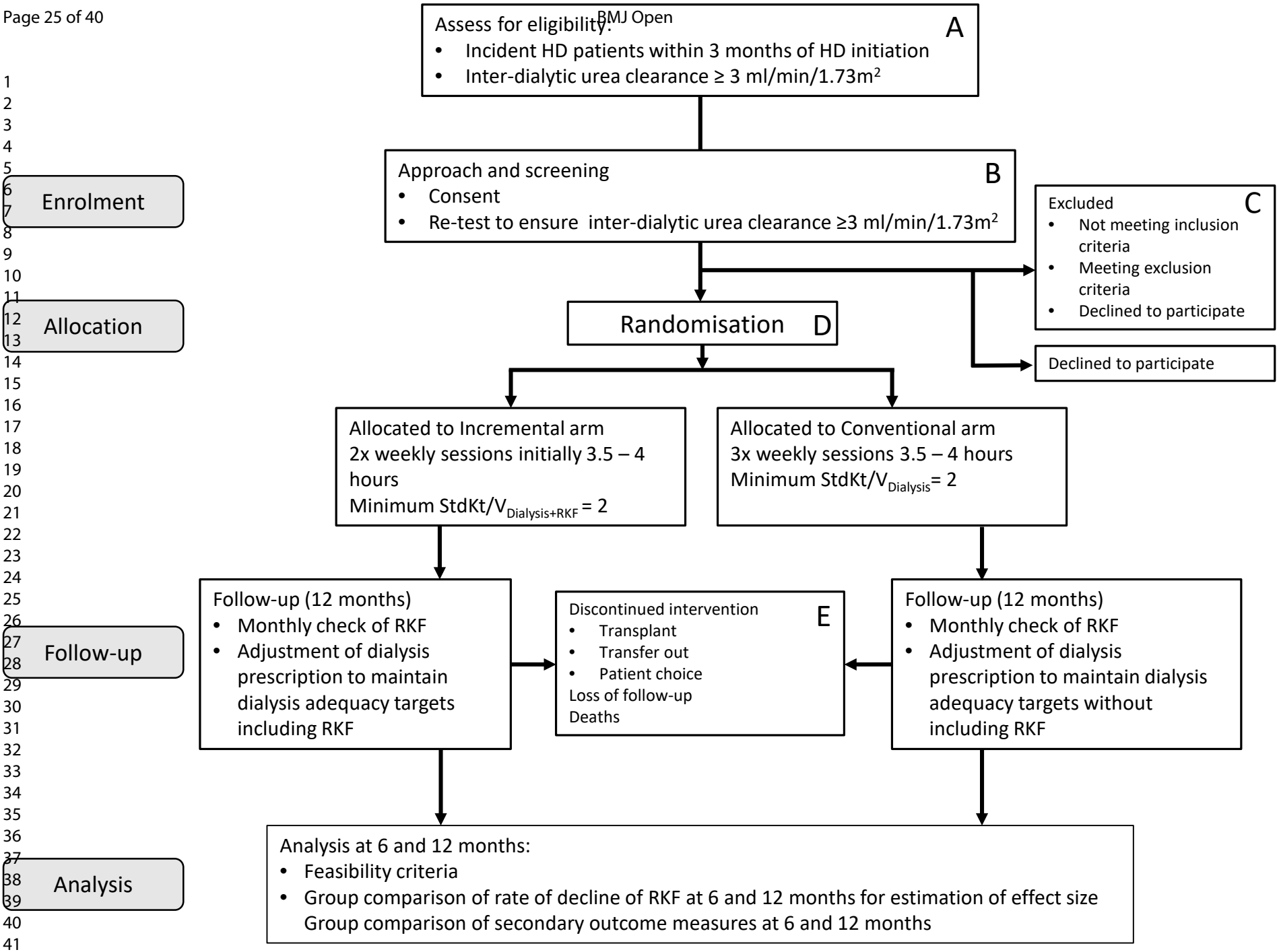
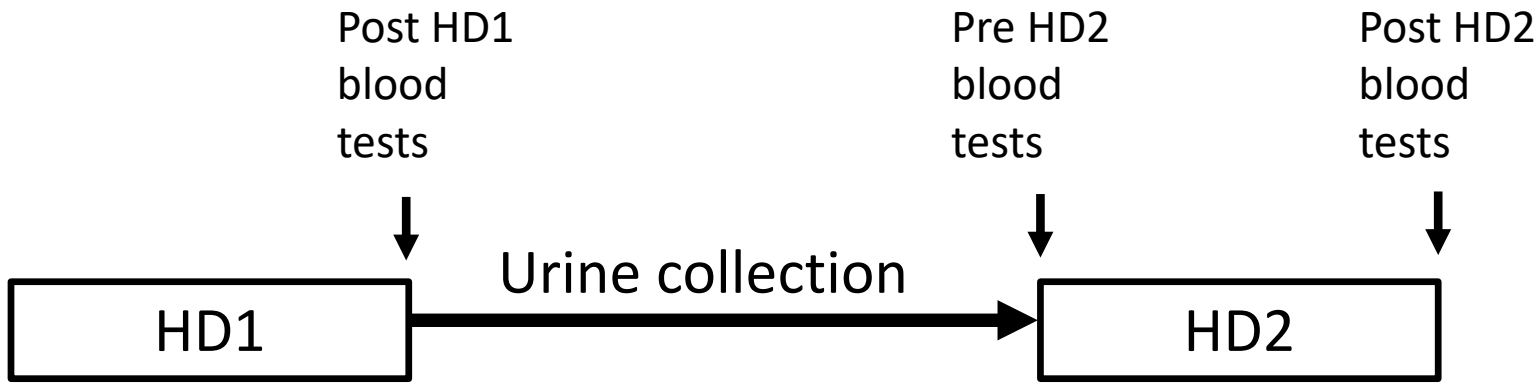


Eligibility: A Recruitability: D/(B-C) Drop-out rate: E



Mon for Mon/Wed/Fri dialysis
Tue for Tue/Thurs/Sat dialysis

Fri for Mon/Fri dialysis
Sat for Tue/Sat dialysis

Wed for Mon/Wed/Fri dialysis
Thurs for Tue/Thurs/Sat dialysis

Mon for Mon/Fri dialysis
Tue for Tue/Sat dialysis

Supplementary material

Method of calculation of dialysis standard KT/V taking into account ultrafiltration weight (Daugirdas methodology)

STEP 1: Calculate spKt/V not taking into account fluid removal

$$spKt/V = \ln\left(\frac{Cpre}{Cpost}\right) \qquad \textit{(EQUATION 1)}$$

Where Cpre s urea concentration pre-dialysis and Cpost is urea concentration post dialysis

STEP 2: Calculate eKt/V not taking into account fluid removal using Tattersall transformation

In this calculation the Tattersall time constant is modified from 35 mins to 30.7mins as per modifications recommended by Daugirdas (Kidney International (2010) 77, 637–644)

eKt/V=spKt/V from step 1* $\frac{\left(\frac{Td}{60}\right)}{(Td\times 60+30.7)}$ ***(EQUATION 2)***

Where Td is dialysis duration expressed in hours

STEP 3: Calculate Adjusted Watson Volume

Watson V needs to be downsized by 10% to account for higher modelled V compared to anthropometric Watson V (Daugirdas Kidney International (2010) 77, 637–644).

Calculate Watson Volume by standard equation and downgrade by 10%

Adjusted Watson V=Watson V * 0.9 ***(EQUATION 3)***

STEP 4: Calculate Leypoldt standard Kt/V

In this we employ eKt/V from equation 2. This equation for standard Kt/V does not account for UF volume. Leypoldt equation is as below (Leypoldt JK. Hemodial Int 2004; 8: 193–197. and Daugirdas Kidney International (2010) 77, 637–644):

$$\mathrm{stdKt}/V = \frac{10,080\,\frac{1-e^{-\mathrm{eKt}/V}}{t}}{\frac{1-e^{-\mathrm{eKt}/V}}{\mathrm{eKt}/V} + \frac{10,080}{\mathrm{Ft}}} - 1$$

(EQUATION 4)

Where f=frequency, t=dialysis time, eKt/V is results from **Equation 2**

STEP 5: Calculate Standard Kt/V taking into account UF weight using Daugirdas methodology:

$$\mathrm{stK_d t}/V = S/(1 - (0.74/F) \cdot \mathrm{UFw}/V) \qquad \textit{(EQUATION 5)}$$

(equation 2 from Daugirdas et al, Kidney International (2010) 77, 637–644)

where S=StdKt/V from EQUATION 4, F=frequency (sessions/week), UFw=weekly fluid gain between HD sessions, V=adjusted Watson V from **Equation 3**

CALCULATION OF RESIDUAL RENAL FUNCTION STANDARD Kt/V

STEP 1: Calculate Urea clearance

$$\textbf{Urea clearance} = \frac{\boldsymbol{UrineVol \times 1000 \times UreaUrea}}{\frac{\left(\boldsymbol{UrineDuration \times 24 \times 60 - (Td \times 60)}\right)}{\left(\frac{\boldsymbol{(PostUrea + PreUrea)}}{\boldsymbol{2}}\right)}} \qquad \textbf{(EQUATION 6)}$$

Where urea clearance units are ml/min, UrineVol=urine volume (L), UrineUrea=urine urea concentration (mmol/L), UrineDuration=Urine collection duration (whole days between HD session), Td=dialysis duration (hours), PostUrea=Blood urea concentration at end of HD when urine collection starts (mmol/L), PreUrea= Blood urea concentration at start of HD when urine collection ends (mmol/L).

This equation assumes that dialysis is occurring at regular time points and utilises duration of urine collection as days between HD sessions minus dialysis duration.

Step 2: Calculate urea clearance corrected for body surface area (used for screening process of study but not for calculation of Std Kt/V which uses unadjusted urea clearance

BSA=Dubois BSA (m^2)

BSA = 0.007184* Height in $cm^{0.725}$ * Weight in $Kg^{0.425}$ **(EQUATION 7)**

Urea clearance adjusted for BSA=Urea clearance *1.73/BSA **(EQUATION 8)**

Step 3: Calculate Adjustment factor needed to downgrade urea clearance so it can be used to calculate Standard Kt/V

This method applies a multiplier to Urea Clearance to downgrade it so that it is appropriately incorporated into the Standard Kt/V calculation (fKru=approximately 0.7, or 70%)

$$fKrU = \frac{0.974}{(spKt/V+1.62)+0.4}$$ **(EQUATION 9)**

(from Daugirdas Kidney International (2010) 77, 637–644). SpKt/V is that from **Equation 1**

Step 4: Adjust Urea clearance for incorporation into Standard Kt/V

Adjusted KrU=Urea clearance * fKrU **(EQUATION 10)**

Where Urea clearance is from equation 6 and fKrU is from **equation 9**

From equation 4 in Daugirdas, Kidney International (2010) 77, 637–644

Step5: Calculate Residual Renal Function equivalent Standard Kt/V

This is calculated as K*t/V where K=adjusted KrU, t=minutes in 7 days, V=Adjusted Watson Volume

$$\text{Residual Renal Standard Kt/V} = \frac{Adjusted\ KrU \times 10080}{Adjusted\ Watson\ Volume \times 1000}$$

(EQUATION 11)

from equation 5 in Daugirdas Kidney International (2010) 77, 637–644

Where Adjusted KrU is from equation 10 (ml/min) and Adjusted Watson Volume (L) is from **Equation 3** above.

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Tel: 01438 314333

Participant Information Sheet

Does incremental initiation of haemodialysis preserve native kidney function? A multicentre feasibility randomised controlled trial.

You are being invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, your GP or staff on the Renal Unit if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Patients who start haemodialysis usually retain some natural kidney function for months or years after starting dialysis. Even a small amount of this natural kidney function can be helpful in reducing the need for dietary and fluid restriction. There is also good evidence that retaining a small amount of natural kidney function may provide a survival benefit for patients on dialysis.

Most patients who commence haemodialysis start three times per week for 3.5-4 hours per session, irrespective of the amount of natural kidney function they may have. An alternative approach used in some kidney units is to take account of the natural kidney function in prescribing the amount of dialysis. This may allow patients to start treatment needing to spend less time on dialysis or even to start just twice weekly. The amount of dialysis can be adjusted over time as natural kidney function declines. This is called “incremental haemodialysis”. Both of these approaches are considered to be standard care although it is not known which approach is more beneficial to patients.

There are some suggestions that the frequency of dialysis may influence the rate of decline of natural kidney function but this need to be tested in a large randomised study. To inform the design of such a study, a smaller scale feasibility study is required.

We intend to randomise fifty new starters on haemodialysis with adequate natural kidney function into two groups – a group who will have dialysis prescribed in the standard fashion – three times weekly for 3.5-4 hours per session or a group who will have an incremental start beginning with twice weekly treatment. We will investigate how many patients have sufficient natural kidney function to be eligible, whether patients are willing to participate and continue in the study, compare the rate of loss of kidney function between groups, and ascertain whether this individualised dialysis approach is less intrusive to patients. The results will be used to design a larger definitive study.

Why have I been asked to participate?

You have been invited to participate as you are on a haemodialysis programme within the United Kingdom.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep, and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part we will need your permission for the local research nurse and consultant nephrologist to look at your medical records. If you are a female of child bearing age we will need to ensure you are not pregnant with a pregnancy test. You will be randomly allocated to one of two study groups. The amount of dialysis you receive (frequency and time) will depend on which study group you are randomised to.
If you are randomised to standard three times a week dialysis (3.5-4h), then you will be requested to have dialysis using that schedule.

If you are randomised to have incremental dialysis, you will dialyse twice weekly initially and afterwards the amount of dialysis you receive will be then adjusted according to the amount of natural kidney function you have. This may mean increasing the amount of time on dialysis up to 4 hours, or increasing to three times a week dialysis during the study.

We will arrange for a blood sample to be taken for the study at the beginning and end of a dialysis session every month with your routine monthly blood tests. The samples will be securely stored in the laboratory for further analysis of blood markers that indicate level of natural kidney function. We will also measure your weight and blood pressure as part of dialysis care. We will ask you to collect all of your urine in a special container between two consecutive dialysis sessions every month.

You will be asked to complete a series of questionnaires in regards to your health and wellbeing before starting the study, visit 6 and end of the study.

We will also monitor you regularly in regards to fluid status, potassium level, dialysis requirements.
During the study we will see you prior to the study and each month to assess your dialysis quality (total of 13 times). We will see you during a dialysis session for your convenience.

What are the possible benefits of taking part?

It is unknown whether dialysis three times a week or in an individualised way (incremental dialysis) is best to preserve natural kidney function and we hope that this study will give us this information. It may be that you are randomised to a study group which benefits you from this perspective but it is not possible to be certain of this. There are no other direct benefits to you of taking part but it is hoped that information we get from this study may help us in the future to improve treatment for patients on dialysis.

What happens when the research study stops?

At the end of the research, your medical care will continue as usual.

What will happen if I don't want to carry on with the study?

You may withdraw from the study at any time, without having to explain why, and we will completely respect your decision. If you withdraw from the study, no other samples will be collected from you and we will not contact you again. Information already collected would be retained and used in the study with your consent. The samples which were already collected and the data collected would be used in the study with your consent. If you wish us not to use the information we will respect it. Your clinical care will not be affected by either taking part or by your withdrawal from the study.

Are there any risks to me?

Only patients with an appropriate natural kidney function are recruited into this study to minimise any potential risks such as inadequate dialysis, fluid overload, and high potassium levels. All recruited participants will be closely monitored at least once a month to check for the above risks. Any concerns from participants or haemodialysis staff will be addressed promptly.

As part of the research study, a small blood sample (~20ml, 4 teaspoons) will be required each month in addition to your routine monthly blood tests and this will be taken from you on dialysis. The amount of blood taken is small and will not have any negative impact on your health**.**

Taking part in the study will not affect your current treatment, nor will it affect your ability to obtain insurance for health purposes or receive a kidney transplant if appropriate.

What will happen to my data that we collect?

Baseline information including age, gender, duration of dialysis and other health information will be collected and your data will then be allocated a unique code that will be anonymous. Medical notes may be looked at by responsible individuals from the Sponsor organisation, the NHS Trust, external researchers from the University of Hertfordshire and from regulatory authorities. During follow up the data will be updated to include any changes in your health such as heart attacks and stroke. At the end of the study your data and any health outcomes will be analysed.

Anonymised study data and files will be stored for the duration of the study and up to 5 years. Your personal data collected by the site, will be stored at the site and archived with other study specific documents for at least 5 years after completion or discontinuation of the study.

If I participate will my personal medical information be kept confidential?

All information that is collected about you during the course of the project will be kept strictly confidential. All collected samples will be identified by a code number only. All data collected as part of the study will be de-identified.

If you consent to take part in the research, some parts of your medical records and any of the information collected about you may be inspected by the sponsor (East and North Hertfordshire NHS Trust). Your records may also be looked at by the regulatory authorities or ethics committees to check that the study is being carried out correctly. All those involved with the study will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside of the research team.

What would happen to the results of the research study?

We hope to be able to publish the results of this research and will be happy to provide you with a copy of the publication if you request it. You will not be identifiable in this publication. We will be happy to inform you of the summarised study results by postal letter if you wish to receive it.

Individual data will not be made available to participants unless the results could potentially impact on the individual's clinical care. Results would then be shared with the participant and their dialysis doctor. This decision would be made by the Principal investigator at your hospital.

Will I be paid for taking part in the study?

Participation in this study is voluntary and you will not be paid for taking part.

Will my GP be informed?

Yes, your GP will be informed with your consent that you are involved in this study.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research team will tell you about it and discuss with you whether you want to continue in the study.

Who has reviewed the study?

The study has been reviewed by the East of England – Cambridge South Research Ethics Committee.

Who is organising and funding the research?

This is a multicentre study within the UK funded by The British Renal Society and sponsored by East and North Hertfordshire NHS Trust.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the study doctor/nurse who will do their best to answer your questions.

If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay your own legal costs. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism will be available to you. Formal complaints should be addressed to:
Mr Nick Carver, Chief Executive, Lister Hospital, Corey's Mill Lane, Stevenage, SG1 4AB (Tel: 01438 314333).

Should you require independent advice about making a complaint or seeking compensation, you may wish to contact the Independent Complaints Advocacy Service (ICAS) for Bedfordshire & Hertfordshire at Pohwer ICAS, Hertlands House, Primett Road, Stevenage, Herts, SG1 3EE. Tel: (0845 456 1082).

Independent information and advice is available from the Patient advice and liaison service (PALS).

Please contact: 01438 284678 or call 01438 314333 and ask to speak to the PALS.

Alternatively please email pals.enh-tr@nhs.net

Contact for Further Information

If you have any problems, concerns, complaints or other questions about this study, you should contact:

Principal Investigator: Dr Raja Mohammed Kaja Kamal on 01438 284346
Chief Investigator: Dr Enric Vilar on 01438 286366
Research Nurses: Ewa Kislowska, Jocelyn Berdeprado on 01438 284346

Emergency 24 hour contact number:

If you need to contact someone outside of normal office hours please call the hospital switchboard on **01438 314 333 and ask to speak to the doctor on-call.**

Thank you very much for taking the time to read this information sheet

East and North Hertfordshire NHS
NHS Trust

Lister Hospital, Corey's Mill Lane, Stevenage
Hertfordshire SG1 4AB
Tel: 01438 314333

PARTICIPANT NAME .....

PARTICIPANT IDENTIFICATION NUMBER .....

INFORMED CONSENT FORM

Does incremental initiation of haemodialysis preserve native kidney function? A multicentre feasibility randomised control trial.

INVESTIGATOR: _____

		Please initial
1.	I confirm that I have read and understood the Participant Information Sheet version_____ date _____ for the above study and have had the opportunity to ask questions which have been answered to my satisfaction.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that sections of my medical notes may be looked at by responsible individuals from the Sponsor organisation, the NHS Trust, external researchers from the University of Hertfordshire and from regulatory authorities for regulatory purposes and audit. I give permission for these individuals to have access to my records.	☐
4.	I understand if sections of my medical notes are unclear, the research team may contact my GP for clarification. I give permission for the research team to contact my GP for this purpose.	☐
5.	I give permission for additional blood and urine samples to be collected and used for research purposes. I understand these samples will be stored anonymously for analysis and a portion of the sample will be sent to an external institution for analysis. The stored samples may be used in future research.	☐
6.	I agree to take part in the above study.	☐

Name of patient .....

Date .....

Signature .....

Name of Person Taking Consent .....

Date .....

Signature .....

Three copies required: one for the patient, one for the researcher and one for hospital case notes

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	5
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	13
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, Table 1
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect	8

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6, 7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 2

Notes:

- 13: Table 2, Figure 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 21. November 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035919.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Apr-2020
Complete List of Authors:	KAJA KAMAL, RAJA MOHAMMED; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Farrington, Ken; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Wellsted, David; University of Hertfordshire Sridharan , Sivakumar; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire Alchi, Bassam; Royal Berkshire NHS Foundation Trust, Renal Unit Burton, James; University Hospitals of Leicester NHS Trust, Renal Unit Davenport, Andrew; Royal Free Hospital, Renal Unit Vilar, Enric; East and North Hertfordshire NHS Trust, Renal Unit; University of Hertfordshire
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine
Keywords:	Adult nephrology < NEPHROLOGY, Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY

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TITLE:

Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.

Author:

Kaja Kamal RM[1,2], Farrington K[1,2], Wellsted D[2], Sridharan S[1,2], Alchi B[3], Burton J[4], Davenport A[5] , Vilar E[1,2]

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Word count 3151

ABSTRACT

Introduction

Preserving Residual Kidney Function(RKF) may be beneficial to patients on haemodialysis (HD) and it has been proposed that commencing dialysis incrementally rather than three times a week may preserve RKF. In Incremental HD, target dose includes a contribution from RKF, which is added to HD dose, allowing individualisation of the HD prescription. We will conduct a feasibility randomised controlled trial(RCT) comparing incremental HD and conventional three times weekly treatments in incident HD patients. The study is designed also to provide pilot data to allow determination of effect size to power a definitive study.

Methods and Analysis

After screening to ensure native renal urea clearance >3ml/min/1.73m^2, the study will randomise 54 patients within 3 months of HD initiation to conventional in-centre thrice weekly dialysis or incremental in-centre HD commencing two days a week. Subjects will be followed up for 12 months. The study will be carried out across 4 UK renal centres.

The primary outcome is to evaluate the feasibility of conducting a definitive RCT and to estimate the difference in rate of decline of RKF between the two groups at 6 and 12-month time points. Secondary outcomes will include the impact of dialysis intensity on vascular access events, major adverse cardiac events(MACE) and survival. Impact of dialysis intensity on patient reported outcomes measures, cognition and frailty will be assessed using EQ-5D-5L, PHQ-9, Illness intrusiveness rating score(IIRS), Montreal Cognitive assessment(MoCA), and Clinical Frailty Score(CFS). Safety outcomes include hospitalisation, fluid overload episodes, hyperkalaemia events and vascular access events.

This study will inform the design of a definitive study, adequately powered to determine whether RKF is better preserved after incremental HD initiation compared to conventional initiation.

Ethics and dissemination

Ethics approval has been granted by Cambridge South Research Ethics Committee, United Kingdom(REC17/EE/0311). Results will be disseminated via peer-reviewed publication.

Trial registration number:NCT03418181

Key words: 3 -10 keywords

Residual Kidney Function -End stage renal disease – HD - RCT – Randomised Controlled Trial

Strengths and limitations of this study

- There are no randomised studies comparing incremental HD and conventional three times weekly treatments in incident HD patients. This study will address this gap.
- It will provide data on feasibility of recruitment to a definitive study together with an estimate of the effect size of group differences in rate of loss residual kidney function allowing sample size calculation.
- Impact and intrusiveness of dialysis intensity will also be compared between groups.
- The sample size will not permit definitive determination of differences in the rate of decline of RKF between groups.

Background

Most end stage renal failure (ESRF) patients have a degree of native kidney function (Residual Kidney Function, RKF) remaining when they initiate HD. There has been recent interest in incremental HD, a method of individualising HD according to the level of RKF to permit dialysis to be commenced at a lower intensity than conventional approaches allow. Most patients commence dialysis using conventional three times weekly dialysis with RKF usually not accounted for in prescribing dialysis dose. In Incremental HD, RKF is combined with dialysis clearance to provide an overall measure of solute removal allowing the dose provided by dialysis to be individualised. Various algorithms are available to assist with this such as Standard Kt/V (Std Kt/V) which includes contributions from both Std Kt/V_{RKF} and Std $Kt/V_{dialysis}$ [1-3]. In this approach, reduction of dialysis dose may be considered provided that the combined urea clearance targets are met and other markers of dialysis adequacy such as blood pressure, inter-dialytic weight gains, anaemia, potassium, phosphate control, nutrition and general well-being are not compromised. The technique requires that the proportion of target dose provided by dialysis is increased as the RKF declines or if there are any other indicators for inadequate dialysis. The dialysis team and patients need to be aware of the importance of regular measurement of RKF 1 to 3 monthly [4]. This incremental approach may not be suitable for patients who are unable or unwilling to collect urine samples.

Traditionally RKF has been incorporated into peritoneal dialysis dosing but it has not been included in calculating HD dose due to limited practical experiences and outcome data from clinical studies. There are no RCTs that compare clinical outcomes of incremental HD and those of conventional thrice-weekly HD. A number of observational studies have compared clinical outcomes of twice-weekly HD and conventional thrice-weekly HD regimens [5-19]. These studies suggest that the mortality risks and survival outcomes are not inferior in those on the twice weekly dialysis regimen compared and those treated conventionally, provided there is adequate RKF. Importantly, several non-randomised studies have suggested that RKF is better preserved in those dialysed twice weekly commencing soon after dialysis initiation [6,10, 11, 17, 18]. Preservation of RKF may provide clinical benefits to HD patients including

better fluid control, significant solute and fluid removal. It is also associated with improved quality of life and survival.

These findings indicate the need for a prospective RCT comparing RKF preservation following incremental and conventional initiation of dialysis. We are undertaking a study to determine the feasibility of conducting such a study. Our study will also provide pilot data to estimate differences in the rate of decline of RKF in the first year after commencing dialysis using either conventional or incremental approaches. The primary outcome of our study is to evaluate the feasibility of conducting a RCT in patients who have recently started HD. Patients will be randomised either to an incremental arm initiating with twice weekly dialysis or to a conventional three times weekly dialysis. Our study will explore key methodological, design, and safety issues, and also estimate an effect size. These findings will facilitate the design of a subsequent definitive study.

Methods/Design

Funding and governance

The study is funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme, grant number 16-020. The trial is sponsored by East and North Hertfordshire NHS Trust. The University of Hertfordshire Clinical Trial Support Network (CTSN) will provide independent support for randomisation and monitoring of the study. The conduct of the trial will be overseen by a Steering group which will meet regularly and will include an independent Chair and co-applicants. The CTSN will monitor compliance with the study protocol at 3 months following study initiation and then as required by sponsor scrutiny of data returns.

Ethics and dissemination

The study received ethical approval from East of England – Cambridge South (REC reference 17/EE/0311; IRAS project ID 219032). Study endpoints, whether negative or positive, will be published with the intention of reaching a wide audience in nephrology both in peer-reviewed publication and also submitted for presentation at international and UK meetings

including the British Renal Society Conference. Following publication of final data an anonymised data set will be made available on request.

Patient and public involvement

A summary of the initial protocol was shared with ten patients who were asked to comment on the study design, the potential willingness of patients to participate in the study, and the burden of study procedures and interventions. Their comments were taken account of in preparing the final version of the protocol. Patients will be involved in interpreting study finding and in design of definitive study. We will report a summary of results to patients in a personal communication by mail. We will also summarise results to local patient association newsletters.

Setting

The study will take place in four NHS Trust renal units – East and North Hertfordshire, Royal Free Hospitals, Royal Berkshire Hospitals and University Hospitals of Leicester. The total number of participants from all centres will be 54. Recruitment commenced in January 2018 and completion of follow up will be in May 2020.

Study Objectives and End Points:

The study's primary objective is to determine the feasibility of conducting a definitive RCT of incremental HD initiation, compared with conventional thrice weekly in-centre HD initiation. There are a number of aspects to this primary objective which are summarised in Table 1. We will determine, at each study site, the proportion of incident HD patients it is practical to approach, who pre-screen as suitable for formal study screening (eligibility for screening). We will determine the proportion of those patients who consent undergo formal screening, pass the screening test and are randomised (recruitability). We will also determine the study retention rate (retainability) as well as fidelity to the protocol (protocol adherence) of patients in the study. Numerators and denominators for these parameters are shown in Figure 1. The study will establish evidence for the safety of the incremental approach. It will also generate data allowing estimation of the effect size of the difference in rate of decline of RKF in the 6 months following randomisation between incremental and conventional HD arms.

Secondary objectives of the study are to determine whether there is a signal of benefit for incremental HD initiation for improving Quality of Life, mood, cognitive function, illness

intrusiveness, functional status, frailty, risk of vascular access failure or interventions, major adverse cardiac events and survival. Specific tools used and methods to measure secondary outcomes related to these secondary objectives are detailed in Table 1. Illness intrusiveness will be measured with the Illness Intrusiveness Rating Scale, a validated tool to measure impact of the dialysis treatment and disease on physiologically meaningful activity and its psychosocial impact[20]. Quality of Life will be measured using EQ-5D-5L, a validated tool which will capture different dimensions of quality of life including anxiety/depression and pain/discomfort and can be used in health-economic evaluation[21]. Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA) which is a tool for assessment of cognitive function that has been validated in dialysis patients against detailed neurophysiological testing covering different domains of cognitive function and provides good sensitivity and specificity for identifying cognitive impairment in this population [22, 23]. Clinical frailty will be measured using the Clinical Frailty Score[24, 25].

Table 1 Study objectives

Primary Objective	Primary Outcome
The proportion of eligible subjects agreeing to participate in the study – **Recruitability**	* Proportion incident HD patients it is practical to approach, who pre-screen as suitable for screening (eligibility for screening) *Proportion of screened patients who fulfil all eligibility criteria for participation in the study *Proportion of these patients who agree to participate in the study
The proportion of randomised subjects who remain in the study – **Retainability**	Proportion of patients randomised who remain in the study excluding study withdrawals, and reasons for withdrawals
The proportion of subjects who adhere to protocol-driven changes in dialysis frequency - **Protocol adherence**	Proportion of patients who adhere to protocol dialysis frequency
The number of adverse and serious adverse events - **Safety of the study**	Frequency of hospital admission due to hyperkalemia and fluid overload, and lower respiratory tract infection (LRTI)
An estimate of the effectiveness of the intervention - **Effect size**	*Dialysis dose and residual kidney function as measured by Std Kt/V *Rate of change (mean) of RKF in the first 6 and 12 months after randomisation.
Secondary Objectives	**Secondary Outcome**
Retention of RKF	Proportion of patients with interdialytic urea clearance ≥2 and ≥3 ml/min/1.73m^2 at 6 months.
Quality of life (QOL)	QOL is assessed using EQ-5D-5L questionnaire
Mood – Depression	Depression assessed using PHQ-9 questionnaire.
Cognitive function	Change in cognitive function as assessed by MOCA tool
Illness intrusiveness	Illness intrusiveness is assessed using Illness intrusiveness rating scale
Functional status /Frailty	Functional status assessed by Clinical Frailty Score (CFS)
Vascular access failures or problems	Frequency of vascular access failures and interventions
Major Adverse Cardiac Events (MACE)	MACE is assessed by recording of the frequency of the events.
Survival	Survival is measured by all-cause mortality

Participants

All adult patients who have commenced HD in the previous 3 months will be considered for the study. Those who potentially meet the eligibility criteria after pre-screening by review of medical records including the requirement for a standard of care inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will eligible for study screening. Those consenting for the study will undergo formal screening to include confirmation of their meeting the eligibility criteria including having an inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA on retesting.

Consent

Consent will be required prior to screening procedures and will include agreement to screening which includes confirmation of urea clearance ≥3ml/min/1.73m^2 BSA and an explicit consent to a protocol-driven dialysis regimen and to randomisation to incremental HD or standard thrice weekly HD arms.

Inclusion Criteria:

- Age ≥ 18 years.
- Advanced kidney failure - established as a new starter on HD within the previous 3 months.
- RKF likely to permit twice weekly dialysis as defined by inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA measured routinely as part of standard care or as pre-screening.
- Sufficient understanding of the study procedures and requirements including capacity for explicit agreement to be randomised to standard or incremental HD regimens.

Exclusion Criteria:

- Planned organ transplantation within 3 months from study screening.
- Anticipated requirement for high-volume ultrafiltration on dialysis (e.g. subjects with daily enteral or parenteral nutrition)
- Blood-borne virus positivity.
- Subjects unable to comply with requirement for monthly inter-dialytic urine collection.

- Pregnancy.
- Prognosis <12 months as judged by the Principal Investigator.

Screening phase

At screening inclusion and exclusion criteria will be confirmed. Confirmation of inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will be performed. Pregnancy test will be performed in females of child-bearing age to reduce chance of unexpected pregnancy occurring during the study which would require study withdrawal. Patients who, at screening, are eligible for study participation according to eligibility criteria, and who are confirmed to have a screening inter-dialytic urea clearance ≥3ml/min/1.73m^2 BSA will eligible for randomisation. Subjects who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of dialysis initiation. At re-screening, a urea clearance ≥3ml/min/1.73m^2 BSA will be required for randomisation into the study.

Randomisation

Web-based randomisation will be carried out by each centre using Qualtrics, supported by the Clinical Trials Support Network, University of Hertfordshire. Subjects will be randomised on a 1:1 basis to each study arm and each subject allocated a unique study ID.

Study phase

Following randomisation, study subjects will be dialysed according to the protocol of their randomisation arm as per the schematic in Figure 1. Monthly quality assessment of dialysis in both arms will include a measure of dialysis clearance (Std Kt/$V_{Dialysis}$). RKF will be measured monthly by urea clearance in both arms and converted to Std Kt/V_{RKF}.

In the standard dialysis arm, dialysis adequacy will be assessed only using the Std Kt/$V_{Dialysis}$. In the incremental dialysis arm, the adequacy will be assessed using a composite of dialysis clearance (Std Kt/$V_{Dialysis}$) and RKF (Std Kt/V_{RKF}) as detailed below. This composite is termed Std Kt/$V_{Dialysis+RKF}$. HD modes will remain standard throughout the study. Haemodiafiltration may be used where blood flow>250 ml/min, otherwise high-flux HD will be used.

Assessment of residual kidney function

There are two main methods of including residual kidney function in HD prescription. The first converts residual urea clearance to an equivalent dialysis sessional clearance[7]. The second converts sessional Kt/V to a weekly equivalent clearance. Both these allow the addition of dialysis and renal clearances. There are two variants of the second method: standard Kt/V[26] and the Casino-Lopez Equivalent renal urea clearance (EKR)[27]. Both these are urea clearance based. The ERBP guidelines recommend use of GFR (mean of urea and creatinine clearance) in the EKR equation rather than urea clearance which was intrinsic to originally derived equation. We have used standard Kt/V which takes a more conservative view of RKF since urea clearance is around 30% lower than GFR. Further details of the methodology for assessment of residual kidney function can be found in Supplementary Material 1.

Groups

Control Group: Standard HD arm

Subjects in the standard HD arm will be dialysed to target minimum Std $Kt/V_{Dialysis}$ of 2 per week. Subjects will be dialysed after randomisation initially for 3.5-4 hours thrice weekly. Dialysis dose will be adjusted using standard measures including maximising blood flow, dialysis time, membrane surface area and improving vascular access. Reduction in dialysis frequency will not be permitted.

Interventional Group: Incremental HD arm

Subjects randomised to the incremental HD arm will be dialysed to a target minimum Std Kt/V_{Total} (Std $Kt/V_{dialysis}$ + Std Kt/V_{RKF}) of 2 per week. Following randomisation dialysis will be initiated twice weekly, with a session duration of 3.5-4 hours. If Std Kt/V_{Total} exceeds the minimum target, clinicians will be permitted to reduce dialysis duration provided the target level is still achieved. If Std Kt/V_{Total} does not meet the target, clinicians will be permitted to increase dialysis dose by optimising dialysis clearance (membrane selection, blood flow, vascular access, increasing dialysis time or frequency). Clinicians will also be permitted to increase the dialysis frequency to thrice-weekly or greater if required. The main trigger for

this will be failure to meet minimum adequacy targets but clinicians will have the freedom to make this transition on other clinical grounds including hyperkalaemia and fluid overload. The reasons for switching from twice to thrice weekly will be recorded. Hyperkalaemia and fluid overload are also captured as Serious Adverse Events.

Deviations to study protocol

If subjects are admitted to hospital, efforts will be made to maintain adherence to the dialysis protocol. However, during admissions, modifications to the dialysis prescription, which include increasing dialysis frequency, are permitted in the interests of patient safety. These will be recorded as protocol deviations.

In the event of subjects in the incremental HD arm not providing inter-dialytic urine samples for calculation of Standard Kt/V_{Renal} for two consecutive months, the subject will be advised to dialyse thrice weekly and will remain in the study with target Standard $Kt/V_{Dialysis}$ >2 (i.e. assuming RRF is zero), until an inter-dialytic urine collection is provided. Additional study visits may be performed if necessary following hospital admission, holiday or non-adherence to treatment schedule.

Procedures to avoid loss from follow up or study withdrawal

The patient information sheet (Supplementary Material 2) and consent form (Supplementary Material 3)will draw attention to the requirement for patients to agree that their dialysis regimen and frequency will be adjusted according to the study protocol.

For patients wishing to withdraw consent, the investigator will explore with the patient the reasons for wishing to withdraw. In patients who wish to withdraw because they are unable to tolerate the intensity, frequency or duration of dialysis, the investigator will be permitted to offer to the patient to remain in the study with reduced dialysis intensity according to clinical judgement and record this as a protocol deviation (intention-to-treat approach). Patients who withdraw will be encouraged to remain in the study for the purpose of outcome data collection including measurement of RKF.

Data Collection

Data will be collected by the research team members at baseline and then monthly thereafter for 12 months. Table 2 summarises study assessments during the study and study time points.

Table 2 Schedule of events.

*Patients who fail screening will be eligible for re-screening one month later provided their screening urea clearance is >2ml/min/1.73m^2 BSA and the rescreening time point remains within 3 months of HD initiation.

** Dialysis adequacy can be calculated using either PostHD1 Urea, PreHD2 Urea, PostHD2 Urea or optionally using PreHD1 Urea, PostHD1 Urea, PreHD2 Urea.

	Study Period		
	Pre-screening	**Baseline/Screening**	**Visit 1-12**
Months	**-12 to 0**	**0**	**1-12**
Study Procedures/Assessments			
Consent		**X**	
Inclusion/Exclusion Criteria	**X**	**X**	
Demographics, Medical History, Physical examination, Height		**X**	
Randomisation		**X**	
Rescreening*		**X**	
Concomitant medications -Diuretics, Erythropoietin Stimulating Agents, Antihypertensive, Phosphate Binders		**X**	**X**
Monthly dialysis blood tests		**X**	**X**
Monthly dialysis Adequacy assessments		**X**	**X**
Pre HD1 Urea, Post HD1 Urea, Pre HD2 Urea, Post HD2 Urea**	**X**	**X**	**X**
Inter-dialytic urine collection for Urea & Creatinine Clearance measurement		**X**	**X**
Frozen samples for β-2 Microglobulin & β Trace Protein		**X**	**X**
Bioimpedence measurement		**X**	**X**
Safety Assessments			
Adverse Events, Serious Adverse Events, MACE, End points			**X**
Questionnaires			
EQ-5D-5L, IIRS, PHQ9, MoCA, CFS		**Months 0, 6, 12**	

Measurement of dialysis adequacy

Details of the method of measuring dialysis adequacy are provided in Supplementary Material 1. The dialysis dosing adjustment will be carried out monthly using Std Kt/V calculated by this method. For patients dialysing thrice weekly (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday) the Monday/Tuesday session is considered to be session 1 of the week (HD1) and the Wednesday/Thursday session is considered session 2 of the week (HD2). For patients dialysing twice weekly (Monday/Friday or Tuesday/Saturday) the Friday/Saturday is considered HD1 and the Monday/Tuesday HD2. Blood and urine samples to be taken are shown in Table 2 (Schedule of Events) and in Figure 2. The urine collection and measurement of RKF is performed from HD1 to HD2 and will be calculated from post-HD1 and pre-HD2 serum urea/creatinine, urine volume and urine urea/creatinine concentration as per the equations in the Supplementary Material 1. The measurement of dialysis dose is calculated from dialysis session data (pre- and post-weight HD2 weight, Watson Volume, pre- and post HD2 urea and dialysis session duration (Td) (see Supplementary Material 1 for calculation procedure).

Urine collection will consequently be over approximately three days for twice weekly patients and two days for thrice weekly patients. Although there is a small risk of bias due to longer duration urine collections for twice weekly HD patients, this is likely to be balanced by the incentive for these patients to provide complete urine collections to ensure their dialysis intensity is not increased.

Sample size

Retrospective studies suggest that decline of RKF may be attenuated in patients who receive twice weekly dialysis compared to thrice weekly, and that this effect occurs early such that a difference in RKF at 6 months is likely to be an optimal time point for the basis of a power analysis. Our initial power analysis, based on our own retrospective data[28] indicated an effect size (Cohen's d) of 0.37 calculated from mean and standard deviations of urea clearance slopes in the first 6 months after HD initiation between two groups of patients, one initiating

HD twice weekly and the other thrice weekly. Based on this, the sample size for the proposed definitive RCT would be 180 (90 each arm). If the definitive study were to be carried out using the same 4 centres, the available incident HD population would be around 600 annually or 1200 over a proposed 2 year recruitment period. We anticipate that 40% of these patients will meet the eligibility criteria ie 480 patients. To achieve 180 analysable patients at 6 months following randomisation we will need to recruit 50% of eligible patients assuming a retention rate of 75% over 6 months.

This feasibility study will test these assumptions on effect size, the proportion of incident patients who can be pre-screened who are eligible to be approached for study consent, the proportion of patients approached for screening who consent, pass formal screening and undergo randomisation (recruitability), and the retention rate during the 6 months after randomisation (retainability). Sample sizes between 24 and 50 have been recommended for feasibility studies [29, 30]. Initially we chose a sample size of 50 but, because of a higher than anticipated recovery of renal function in the first few weeks of recruitment, increased this to 54. A sample of this size will enable us to estimate eligibility, recruitability, screen-failure rate and retainabililty rate to within a 95% confidence interval of +/- 11-14%.

Adverse events (AE) and Serious Adverse Events (SAE)

All AE will be recorded in an AE log. SAEs will be reported to the CI and sponsors within 24 h of the research team becoming aware of the event. For the purpose of this study, SAE which result in death, hospitalisation, MACE, infections requiring antibiotic use, episodes of fluid overload needing resetting of dry weight, episodes of hyperkalemia (potassium level > 6.5 mmol/L), vascular access events (tunnelled line failures, tunnelled line infections, fistula thrombosis, fistula stenosis, false aneurysm) will be captured.

Data Analysis

The primary outcome is to evaluate the feasibility of conducting an RCT comparing the effect, on RKF decline, of incremental and conventional approaches to HD initiation. The study will be analysed as intention-to-treat. In order to estimate the study power for a future large scale RCT, estimates of change in RKF in the first 6 and 12 months after dialysis initiation will be determined.

Change in RKF will be determined using several methods. We will calculate, using linear regression analysis for individual subjects, rate of decline in GFR (mean of urea and creatinine clearance) for individual subjects and compare means of these rates between incremental and conventional HD groups with a t test if normally distributed. This effect size will be important in powering future definitive trials. Using a previously described method we will employ a mixed effects model to compare rate of decline in GFR between randomisation groups[28]. As an indicator of RKF, we will compare urine volume data between groups using similar statistical techniques to the above. We will also compare proportions of patients in the two groups who have a residual interdialytic urea clearance ≥ 2 and ≥ 3 ml/min/1.73m^2 at 6months. In addition, we will estimate RKF (GFR) from monthly measured pre-dialysis middle molecule concentrations of β trace protein and β2-microglobulin converted to an equivalent GFR using the algorithm reported by Wong et al[31]. We will calculate rate of decline in GFR for individual patients from these middle molecule concentrations and using regression analysis for individual patient data to determine GFR slope and will compare mean slope between incremental HD and standard care groups..

Data from the EQ-5D-5L, PHQ-9, MoCA, IIRS and CFS will be compared between study arms with repeated measures parametric or non-parametric tests as appropriate (repeated measures ANOVA or Friedman tests). Comparison of MACE, vascular access events (access failure, access intervention, access related infections, fistula stenosis and fistula thrombosis), hyperkalaemic episodes, fluid overload episodes and lower respiratory tract infection episodes will be compared between groups using time-to-event analysis by the Nelson-Aalen approach.

Discussion

Clinical practise guidelines for HD adequacy, update 2006 [32] suggests that reduction of treatment frequency to less than thrice-weekly should only be considered in patients with inter-dialytic urea clearance >2ml/min/1.73m^2 since urea kinetic modelling simulations have shown that when residual urea clearance is less than this, it is not possible to achieve a weekly standard Kt/V of 2.0 with twice-weekly dialysis regimens. Hence in this study we have opted

for a required inter-dialytic urea clearance (RKF) of ≥3ml/min/1.73m^2 BSA prior to randomisation as an inclusion criterion to provide a safety margin.

There are a large number of observational studies [5-18] that compare clinical outcomes of patients treated with twice-weekly HD with those on conventional thrice-weekly HD regimens but to date no RCT that compare clinical outcomes of incremental or infrequent HD versus conventional thrice-weekly HD have been published. Though these studies suggest that the rate of decline of RKF is slower using infrequent and incremental HD regimens but prospective, randomised data is not available. Hence it is unclear to what extent the benefits of incremental and infrequent HD are due to patient selection. Similarly, there are no comparative data on Quality of Life measures or on patient experience in conventional versus incremental HD. Mortality risk and survival outcomes have not been reported to be worse in patients treated with twice-weekly dialysis sessions [9, 13, 16] and a large US study found that mortality risk was lower in prevalent patients treated with twice-weekly HD, provided there was adequate RKF [5]. Hence there is a need for a definitive trial of incremental versus conventional dialysis initiation to define the effects on RKF preservation and patient–reported outcome and experience.

The outcome data of this current study will be used to inform the design of such a future definitive study. The proposed feasibility study will test assumptions around the effect size, the eligibility for screening, recruitability, and retainability. Deviations from the assumed values will alter the design of the definitive study eg number of centres required, eligibility criteria, primary outcome measure, sample size, and may indicate that a definitive study is non-viable.

It is likely that the outcomes of a definitive study will be important, not only in defining the potential benefit of incremental HD for patients, but in establishing whether such an approach may allow optimization of resource use. If dialysis intensity can be reduced for patients with sufficient RKF with patient benefit, this will liberate dialysis resources that may permit other patients with high dialysis requirements to dialyse more frequently.

Abbreviations

AEs: Adverse Events
CFS: Clinical Frailty Score
CI: Chief Investigator
CRFs: Case Report Forms
EQ-5D-5L: EuroQol - 5D-5L
ESRD: End Stage Renal Disease
HD: Haemodialysis
IIRS: Illness Intrusiveness Rating Scale
Kt/V: Urea Clearance normalised to total body water
MACE: Major Adverse Cardiac Events
MoCA: Montreal Cognitive Assessment
PHQ-9: Patient Health Questionnaire 9
PI: Principal Investigator
RCT: Randomised Controlled Trial
RKF: Residual Kidney Function
SAEs: Serious Adverse Events
SUSAR: Suspected Unexpected Serious Adverse Reaction

Legends to Figures

Figure 1. Flow diagram of clinical trial demonstrating data that will be used to calculate eligibility for screening, screen failure rate, recruitability and retainability.

Figure 2. Timing of urine collection and blood tests for dialysis adequacy measurement for patients on twice weekly and thrice weekly HD.

Contributorship statement

Design of the study and the development of the protocol: EV, RMKK, KF, SS
Trial set up and running of the study, trial governance, data integrity monitoring: EV, DW
Data analysis: EV, RMKK, KF, DW
Principal Investigators: EV, JB, AD, BA
All authors are involved in the steering group of the study and in the analysis and interpretation of the data.
All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests. This report is independent research funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme. The views expressed in this publication are those of the authors.

Funding

This study is funded by the British Kidney Patient Association & British Renal Society Joint Grants Programme (Grant 16-020).

Acknowledgements

The authors are grateful for the British Kidney Patient Association & British Renal Society Joint Grants Programme for funding this study and for the assistance of our patients in the study design.

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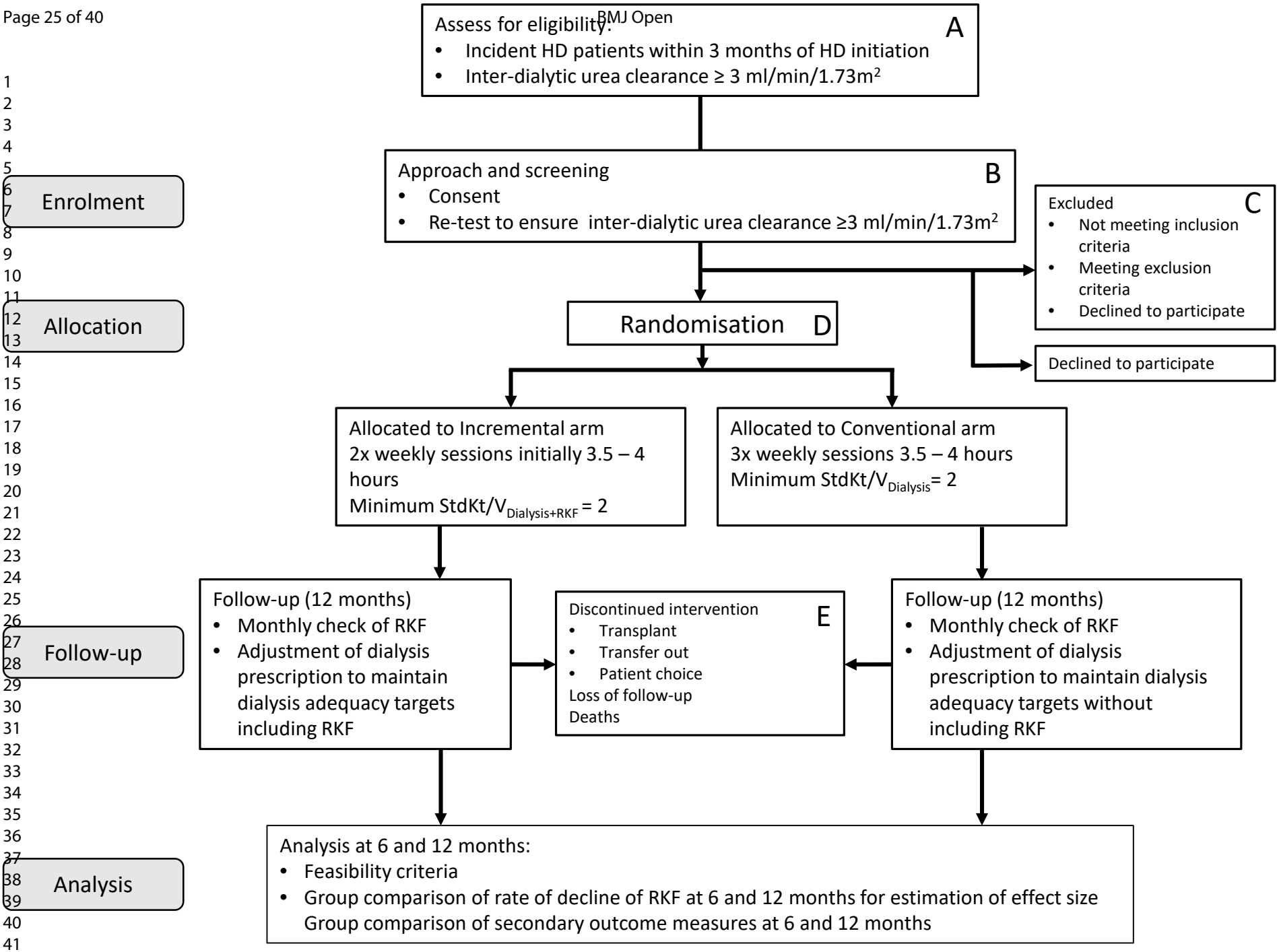
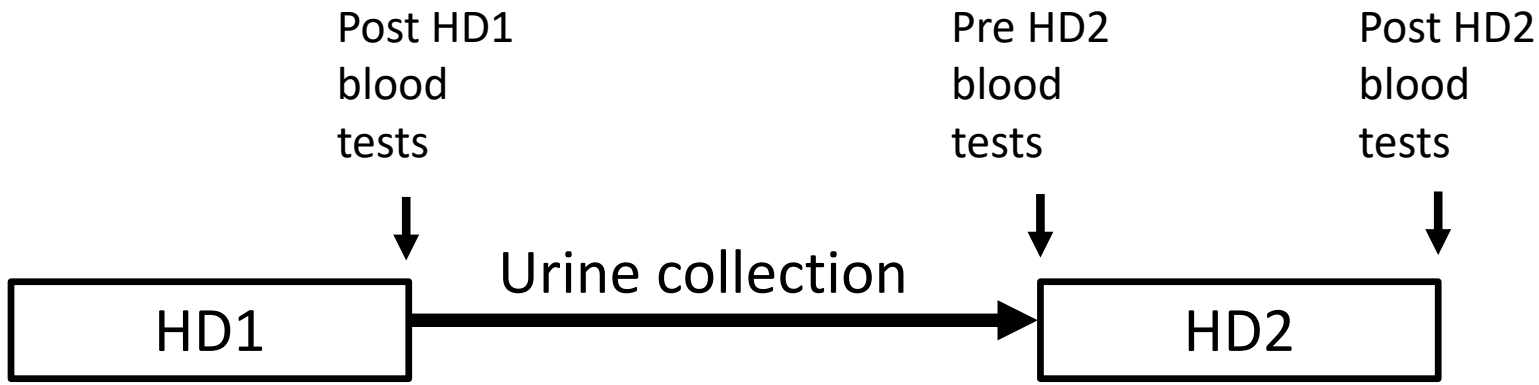


Eligibility: A Recruitability: D/(B-C) Drop-out rate: E



Mon for Mon/Wed/Fri dialysis
Tue for Tue/Thurs/Sat dialysis

Fri for Mon/Fri dialysis
Sat for Tue/Sat dialysis

Wed for Mon/Wed/Fri dialysis
Thurs for Tue/Thurs/Sat dialysis

Mon for Mon/Fri dialysis
Tue for Tue/Sat dialysis

Supplementary material

Method of calculation of dialysis standard KT/V taking into account ultrafiltration weight (Daugirdas methodology)

STEP 1: Calculate spKt/V not taking into account fluid removal

$$spKt/V = \ln\left(\frac{Cpre}{Cpost}\right) \qquad \textit{(EQUATION 1)}$$

Where Cpre s urea concentration pre-dialysis and Cpost is urea concentration post dialysis

STEP 2: Calculate eKt/V not taking into account fluid removal using Tattersall transformation

In this calculation the Tattersall time constant is modified from 35 mins to 30.7mins as per modifications recommended by Daugirdas (Kidney International (2010) 77, 637–644)

eKt/V=spKt/V from step 1* $\frac{\left(\frac{Td}{60}\right)}{(Td\times 60+30.7)}$ ***(EQUATION 2)***

Where Td is dialysis duration expressed in hours

STEP 3: Calculate Adjusted Watson Volume

Watson V needs to be downsized by 10% to account for higher modelled V compared to anthropometric Watson V (Daugirdas Kidney International (2010) 77, 637–644).

Calculate Watson Volume by standard equation and downgrade by 10%

Adjusted Watson V=Watson V * 0.9 ***(EQUATION 3)***

STEP 4: Calculate Leypoldt standard Kt/V

In this we employ eKt/V from equation 2. This equation for standard Kt/V does not account for UF volume. Leypoldt equation is as below (Leypoldt JK. Hemodial Int 2004; 8: 193–197. and Daugirdas Kidney International (2010) 77, 637–644):

$$\mathrm{stdKt}/V = \frac{10,080\,\frac{1-e^{-\mathrm{eKt}/V}}{t}}{\frac{1-e^{-\mathrm{eKt}/V}}{\mathrm{eKt}/V} + \frac{10,080}{\mathrm{Ft}}} - 1$$

(EQUATION 4)

Where f=frequency, t=dialysis time, eKt/V is results from **Equation 2**

STEP 5: Calculate Standard Kt/V taking into account UF weight using Daugirdas methodology:

$$\mathrm{stK_d t}/V = S/(1 - (0.74/F) \cdot \mathrm{UFw}/V) \qquad \textit{(EQUATION 5)}$$

(equation 2 from Daugirdas et al, Kidney International (2010) 77, 637–644)

where S=StdKt/V from EQUATION 4, F=frequency (sessions/week), UFw=weekly fluid gain between HD sessions, V=adjusted Watson V from **Equation 3**

CALCULATION OF RESIDUAL RENAL FUNCTION STANDARD Kt/V

STEP 1: Calculate Urea clearance

$$\textbf{Urea clearance} = \frac{\boldsymbol{UrineVol \times 1000 \times UreaUrea}}{\frac{\left(\boldsymbol{UrineDuration \times 24 \times 60 - (Td \times 60)}\right)}{\left(\frac{\boldsymbol{(PostUrea + PreUrea)}}{\boldsymbol{2}}\right)}} \qquad \textbf{(EQUATION 6)}$$

Where urea clearance units are ml/min, UrineVol=urine volume (L), UrineUrea=urine urea concentration (mmol/L), UrineDuration=Urine collection duration (whole days between HD session), Td=dialysis duration (hours), PostUrea=Blood urea concentration at end of HD when urine collection starts (mmol/L), PreUrea= Blood urea concentration at start of HD when urine collection ends (mmol/L).

This equation assumes that dialysis is occurring at regular time points and utilises duration of urine collection as days between HD sessions minus dialysis duration.

Step 2: Calculate urea clearance corrected for body surface area (used for screening process of study but not for calculation of Std Kt/V which uses unadjusted urea clearance

BSA=Dubois BSA (m^2)

BSA = 0.007184* Height in $cm^{0.725}$ * Weight in $Kg^{0.425}$ **(EQUATION 7)**

Urea clearance adjusted for BSA=Urea clearance *1.73/BSA **(EQUATION 8)**

Step 3: Calculate Adjustment factor needed to downgrade urea clearance so it can be used to calculate Standard Kt/V

This method applies a multiplier to Urea Clearance to downgrade it so that it is appropriately incorporated into the Standard Kt/V calculation (fKru=approximately 0.7, or 70%)

$$fKrU = \frac{0.974}{(spKt/V+1.62)+0.4}$$ **(EQUATION 9)**

(from Daugirdas Kidney International (2010) 77, 637–644). SpKt/V is that from **Equation 1**

Step 4: Adjust Urea clearance for incorporation into Standard Kt/V

Adjusted KrU=Urea clearance * fKrU **(EQUATION 10)**

Where Urea clearance is from equation 6 and fKrU is from **equation 9**

From equation 4 in Daugirdas, Kidney International (2010) 77, 637–644

Step5: Calculate Residual Renal Function equivalent Standard Kt/V

This is calculated as K*t/V where K=adjusted KrU, t=minutes in 7 days, V=Adjusted Watson Volume

$$\text{Residual Renal Standard Kt/V} = \frac{Adjusted\ KrU \times 10080}{Adjusted\ Watson\ Volume \times 1000}$$

(EQUATION 11)

from equation 5 in Daugirdas Kidney International (2010) 77, 637–644

Where Adjusted KrU is from equation 10 (ml/min) and Adjusted Watson Volume (L) is from **Equation 3** above.

East and North Hertfordshire NHS
NHS Trust

Lister Hospital
Coreys Mill Lane
Stevenage
Hertfordshire
SG1 4AB

Tel: 01438 314333

Participant Information Sheet

Does incremental initiation of haemodialysis preserve native kidney function? A multicentre feasibility randomised controlled trial.

You are being invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, your GP or staff on the Renal Unit if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Patients who start haemodialysis usually retain some natural kidney function for months or years after starting dialysis. Even a small amount of this natural kidney function can be helpful in reducing the need for dietary and fluid restriction. There is also good evidence that retaining a small amount of natural kidney function may provide a survival benefit for patients on dialysis.

Most patients who commence haemodialysis start three times per week for 3.5-4 hours per session, irrespective of the amount of natural kidney function they may have. An alternative approach used in some kidney units is to take account of the natural kidney function in prescribing the amount of dialysis. This may allow patients to start treatment needing to spend less time on dialysis or even to start just twice weekly. The amount of dialysis can be adjusted over time as natural kidney function declines. This is called “incremental haemodialysis”. Both of these approaches are considered to be standard care although it is not known which approach is more beneficial to patients.

There are some suggestions that the frequency of dialysis may influence the rate of decline of natural kidney function but this need to be tested in a large randomised study. To inform the design of such a study, a smaller scale feasibility study is required.

We intend to randomise fifty new starters on haemodialysis with adequate natural kidney function into two groups – a group who will have dialysis prescribed in the standard fashion – three times weekly for 3.5-4 hours per session or a group who will have an incremental start beginning with twice weekly treatment. We will investigate how many patients have sufficient natural kidney function to be eligible, whether patients are willing to participate and continue in the study, compare the rate of loss of kidney function between groups, and ascertain whether this individualised dialysis approach is less intrusive to patients. The results will be used to design a larger definitive study.

Why have I been asked to participate?

You have been invited to participate as you are on a haemodialysis programme within the United Kingdom.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep, and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part we will need your permission for the local research nurse and consultant nephrologist to look at your medical records. If you are a female of child bearing age we will need to ensure you are not pregnant with a pregnancy test. You will be randomly allocated to one of two study groups. The amount of dialysis you receive (frequency and time) will depend on which study group you are randomised to.
If you are randomised to standard three times a week dialysis (3.5-4h), then you will be requested to have dialysis using that schedule.

If you are randomised to have incremental dialysis, you will dialyse twice weekly initially and afterwards the amount of dialysis you receive will be then adjusted according to the amount of natural kidney function you have. This may mean increasing the amount of time on dialysis up to 4 hours, or increasing to three times a week dialysis during the study.

We will arrange for a blood sample to be taken for the study at the beginning and end of a dialysis session every month with your routine monthly blood tests. The samples will be securely stored in the laboratory for further analysis of blood markers that indicate level of natural kidney function. We will also measure your weight and blood pressure as part of dialysis care. We will ask you to collect all of your urine in a special container between two consecutive dialysis sessions every month.

You will be asked to complete a series of questionnaires in regards to your health and wellbeing before starting the study, visit 6 and end of the study.

We will also monitor you regularly in regards to fluid status, potassium level, dialysis requirements.
During the study we will see you prior to the study and each month to assess your dialysis quality (total of 13 times). We will see you during a dialysis session for your convenience.

What are the possible benefits of taking part?

It is unknown whether dialysis three times a week or in an individualised way (incremental dialysis) is best to preserve natural kidney function and we hope that this study will give us this information. It may be that you are randomised to a study group which benefits you from this perspective but it is not possible to be certain of this. There are no other direct benefits to you of taking part but it is hoped that information we get from this study may help us in the future to improve treatment for patients on dialysis.

What happens when the research study stops?

At the end of the research, your medical care will continue as usual.

What will happen if I don't want to carry on with the study?

You may withdraw from the study at any time, without having to explain why, and we will completely respect your decision. If you withdraw from the study, no other samples will be collected from you and we will not contact you again. Information already collected would be retained and used in the study with your consent. The samples which were already collected and the data collected would be used in the study with your consent. If you wish us not to use the information we will respect it. Your clinical care will not be affected by either taking part or by your withdrawal from the study.

Are there any risks to me?

Only patients with an appropriate natural kidney function are recruited into this study to minimise any potential risks such as inadequate dialysis, fluid overload, and high potassium levels. All recruited participants will be closely monitored at least once a month to check for the above risks. Any concerns from participants or haemodialysis staff will be addressed promptly.

As part of the research study, a small blood sample (~20ml, 4 teaspoons) will be required each month in addition to your routine monthly blood tests and this will be taken from you on dialysis. The amount of blood taken is small and will not have any negative impact on your health**.**

Taking part in the study will not affect your current treatment, nor will it affect your ability to obtain insurance for health purposes or receive a kidney transplant if appropriate.

What will happen to my data that we collect?

Baseline information including age, gender, duration of dialysis and other health information will be collected and your data will then be allocated a unique code that will be anonymous. Medical notes may be looked at by responsible individuals from the Sponsor organisation, the NHS Trust, external researchers from the University of Hertfordshire and from regulatory authorities. During follow up the data will be updated to include any changes in your health such as heart attacks and stroke. At the end of the study your data and any health outcomes will be analysed.

Anonymised study data and files will be stored for the duration of the study and up to 5 years. Your personal data collected by the site, will be stored at the site and archived with other study specific documents for at least 5 years after completion or discontinuation of the study.

If I participate will my personal medical information be kept confidential?

All information that is collected about you during the course of the project will be kept strictly confidential. All collected samples will be identified by a code number only. All data collected as part of the study will be de-identified.

If you consent to take part in the research, some parts of your medical records and any of the information collected about you may be inspected by the sponsor (East and North Hertfordshire NHS Trust). Your records may also be looked at by the regulatory authorities or ethics committees to check that the study is being carried out correctly. All those involved with the study will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside of the research team.

What would happen to the results of the research study?

We hope to be able to publish the results of this research and will be happy to provide you with a copy of the publication if you request it. You will not be identifiable in this publication. We will be happy to inform you of the summarised study results by postal letter if you wish to receive it.

Individual data will not be made available to participants unless the results could potentially impact on the individual's clinical care. Results would then be shared with the participant and their dialysis doctor. This decision would be made by the Principal investigator at your hospital.

Will I be paid for taking part in the study?

Participation in this study is voluntary and you will not be paid for taking part.

Will my GP be informed?

Yes, your GP will be informed with your consent that you are involved in this study.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research team will tell you about it and discuss with you whether you want to continue in the study.

Who has reviewed the study?

The study has been reviewed by the East of England – Cambridge South Research Ethics Committee.

Who is organising and funding the research?

This is a multicentre study within the UK funded by The British Renal Society and sponsored by East and North Hertfordshire NHS Trust.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the study doctor/nurse who will do their best to answer your questions.

If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay your own legal costs. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism will be available to you. Formal complaints should be addressed to:
Mr Nick Carver, Chief Executive, Lister Hospital, Corey's Mill Lane, Stevenage, SG1 4AB (Tel: 01438 314333).

Should you require independent advice about making a complaint or seeking compensation, you may wish to contact the Independent Complaints Advocacy Service (ICAS) for Bedfordshire & Hertfordshire at Pohwer ICAS, Hertlands House, Primett Road, Stevenage, Herts, SG1 3EE. Tel: (0845 456 1082).

Independent information and advice is available from the Patient advice and liaison service (PALS).

Please contact: 01438 284678 or call 01438 314333 and ask to speak to the PALS.

Alternatively please email pals.enh-tr@nhs.net

Contact for Further Information

If you have any problems, concerns, complaints or other questions about this study, you should contact:

Principal Investigator: Dr Raja Mohammed Kaja Kamal on 01438 284346
Chief Investigator: Dr Enric Vilar on 01438 286366
Research Nurses: Ewa Kislowska, Jocelyn Berdeprado on 01438 284346

Emergency 24 hour contact number:

If you need to contact someone outside of normal office hours please call the hospital switchboard on **01438 314 333 and ask to speak to the doctor on-call.**

Thank you very much for taking the time to read this information sheet

East and North Hertfordshire NHS
NHS Trust

Lister Hospital, Corey's Mill Lane, Stevenage
Hertfordshire SG1 4AB
Tel: 01438 314333

PARTICIPANT NAME .....

PARTICIPANT IDENTIFICATION NUMBER .....

INFORMED CONSENT FORM

Does incremental initiation of haemodialysis preserve native kidney function? A multicentre feasibility randomised control trial.

INVESTIGATOR: _____

		Please initial
1.	I confirm that I have read and understood the Participant Information Sheet version_____ date _____ for the above study and have had the opportunity to ask questions which have been answered to my satisfaction.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that sections of my medical notes may be looked at by responsible individuals from the Sponsor organisation, the NHS Trust, external researchers from the University of Hertfordshire and from regulatory authorities for regulatory purposes and audit. I give permission for these individuals to have access to my records.	☐
4.	I understand if sections of my medical notes are unclear, the research team may contact my GP for clarification. I give permission for the research team to contact my GP for this purpose.	☐
5.	I give permission for additional blood and urine samples to be collected and used for research purposes. I understand these samples will be stored anonymously for analysis and a portion of the sample will be sent to an external institution for analysis. The stored samples may be used in future research.	☐
6.	I agree to take part in the above study.	☐

Name of patient .....

Date .....

Signature .....

Name of Person Taking Consent .....

Date .....

Signature .....

Three copies required: one for the patient, one for the researcher and one for hospital case notes

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	5
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	13
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, Table 1
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect	8

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6, 7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 2

Notes:

- 13: Table 2, Figure 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 21. November 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai