A randomized controlled trial to determine whether bioimpedance spectroscopy-guided fluid management maintains residual kidney function in incident haemodialysis patients (BISTRO): statistical analysis plan (ISCCTN Number: 11342007)

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Contents

1 Introduction

1.1 Purpose

This document details the statistical analysis to be carried out on the trial data.

1.2 Background and rationale

Preservation of residual kidney function (RKF) and achieving normal volume status are recognized as two linked and critically important predictors of survival in haemodialysis (HD) patients. However, despite the value of RKF, few clinical trials have focussed on interventions to maintain it as a key benefit to HD patients – the exception being ultrapure water (Schiffl et al, 2002), which is now standard care. A frequently applied fluid management strategy is to reduce the post-dialysis target weight until minimal or no anti-hypertensive drugs are required as evidence of adequate control of volume status. However, this is potentially detrimental to residual kidney function as it causes a continuing vicious cycle of volume depletion, excessive thirst and high inter-dialytic fluid gains.

The introduction of bioimpedance (BI) technology, such as BI spectroscopy, provides clinicians with the opportunity to break this cycle while avoiding the risk of excessive overhydration. BI gives additional information about body composition available at the bedside (Davies & Davenport, 2014). The principle is simple and involves the passing of a low-strength alternating current through the subject's body to measure the resistance and impedance to flow. These two measures are proportional to the amount of fluid and cell membranes, equating to tissue mass, between the electrodes (usually placed on the hand and foot on one side of the body). The measurements are then modelled using information such as the subject's weight and height to estimate the total volume of fluid in the body and the proportion of this that is within tissues or in the extracellular space. In dialysis patients, compared to healthy subjects, the total amount of fluid (intra plus extracellular) can be high or low, but often the latter because of muscle wasting, inflammation or even over-aggressive fluid removal on dialysis. However, if the extracellular fluid is disproportionately high, this is a strong signal for an increased mortality risk (Wizemann et al, 2009; Paniagua et al, 2010). For this reason, until now trials conducted to establish the clinical value of BI in

setting target weights have focussed on clinical endpoints associated with hypervolaemia, such as high blood pressure, left ventricular mass and pulse- wave pressure or worsening extracellular to intracellular fluid distribution. The results of these interventions have been mixed, and more trials are clearly needed, but the price for achieving lower blood pressure through post-dialytic hypovolaemia was accelerated loss of RKF in one such study (Hur et al, 2013). There is also evidence that presence of RKF leads to more stable fluid status without intervention in peritoneal dialysis patients (Tan et al, 2016). Thus, BISTRO will establish the potential for BI to add value to fluid management and address the concern that this technology may be being adopted indiscriminately without clear evidence of benefit and a potential risk of harm.

1.3 Objective

To determine if incorporation of bioimpedance-derived information on body composition into the setting of the post-dialytic target weight reduces loss of residual kidney function in incident centre-based HD patients, with the potential to improve clinical outcomes, dialysis-related symptoms, hospitalization and survival.

1.4 Trial design

A pragmatic, multicentre, open-label prospective two-arm parallel-group randomized controlled trial comparing current best practice in setting the post-dialytic target weight (control group) with the same assessment guided by serial BI measurements (intervention group). BI readings will be taken in both study groups but the results concealed from the clinical teams and trial participants in the control limb. To minimize performance and information bias, the BI measurements will be taken independently from the fluid assessments by trained nurses but within the previous week (i.e. the last 3 dialysis sessions), usually before sessions.

1.5 Study setting

The study will take place in adult, out-patient haemodialysis centres, both main and satellite units, and their associated inpatient renal units during hospital admissions. Patients

admitted for inter-current problems while participating in the trial will remain in the study and be assessed according to randomization. Eligibility criteria are detailed in the trial protocol (Davies et al, 2017).

1.6 Recruitment and allocation

Participants will be recruited over a 29-month period at 33 centre-based haemodialysis centres throughout the UK, including satellite units affiliated with main centres.

Both planned and unplanned incident HD patients will be randomized after informed consent has been obtained and at the point of commencing haemodialysis as an outpatient. Randomization will be 1:1 to the BI intervention and control groups, with random permuted blocks, stratified by centre (main or satellite, where dialysis will commence).

Randomization will be during office hours using a secure centralized web-based, automated computer-generated randomization system provided by the Keele University Clinical Trials Unit (CTU). The randomization list will employ random permuted blocks and will be constructed at the outset of the study (one of ten randomization lists designed for the study will be selected at random).

1.7 Intervention

The study intervention is the incorporation of bioimpedance technology-derived information about body composition into the clinical assessment of fluid status of dialysis patients. The study intervention is the use of this additional information, specifically the *normally hydrated weight*, in conjunction with usual clinical judgement to set a target dry weight that is as close to normal at the end of a dialysis session, thus avoiding the risks of over- or under-hydration. The Fresenius Body Composition Monitor (Fresenius BCM) is the device to be used in measuring bioimpedance.

1.8 Participant timeline

Trial entry for all participants is at the point of commencing centre-based haemodialysis as an outpatient, see Figure 1. At this point trial eligibility will be confirmed, followed by randomization. All participants will be followed up until study completion or withdrawal

because of death, transplantation, stopping dialysis (e.g. recovery of function) or patient choice, including any period after they reach the primary outcome so that the health economic analysis can be completed. The schedule of trial assessments is shown in Table 1. A flowchart for the trial is shown in Figure 1.

2 Outcomes

2.1 Primary outcome

Time to anuria, defined as urine volume ≤ 100ml/day or ≤ 200ml in the short inter-dialytic period confirmed by a further collection after 2 weeks to exclude temporary illness.

2.2 Secondary outcomes

- The rate of decline in kidney function, defined as the slope in decline of the average residual urea and creatinine clearance.
- Significant events, including vascular access failure and associated interventions, cardiovascular events, hospital admissions and death, including long-term legacy effects beyond trial completion using data linkage.
- Objective measures of dialysis efficacy and safety: e.g. inter-dialytic fluid gains, intra-dialytic hypotension, urea-reduction ratios (routine data)
- Patient-reported outcomes, including quality of life: EQ-5D-5L (Herdman et al, 2011), SF12 (Ware et al, 1996; Brazier & Roberts, 2004), dialysis-related symptoms (Integrated Palliative Care Outcome Scale- Renal, IPOS) www.pos-pal.org, Patient Activation Measure (Greene & Hibbard, 2012), Duke Activity Status Index (Hlatky et al, 1989), Montreal Cognitive Assessment (MoCA) (Tiffin-Richards et al, 2014), Client Service Receipt Inventory Chronic Disease (CKD).
- Cost effectiveness of the intervention.

3 Sample size

3.1 Primary outcome

The primary outcome is time to anuria. The proportion of incident centre-based HD patients anuric by approximately ten months is in the region of 30% (range 25-67%) (Jansen et al, 2002; Fernández-Lucas et al, 2012; Lin et al, 2009; Moist et al, 2000; McKane et al, 2002). The sample size is based on a cumulative 10-month incidence of anuria of 30% in the control group and 20% in the treatment group and 11% competing risks, based on death and transplantation data extrapolated from the 2013 UKRR report (Pruthi et al, 2013). Assuming exponential decline, proportional hazards, 90% power and 5% two-tailed significance, 185 events are required to detect the corresponding hazard ratio, with 12 months accrual and 12 months follow-up. This will require a total of 516 patients to be randomized 1:1, allowing for 5% loss to follow-up (Pintilie, 2002).

3.2 Secondary outcomes

The rate of decline in renal clearance is reported by most studies as a monthly decline of 0.3ml/min/1.73m^2/month (reported range 0.3-0.4) (Jansen et al, 2002; Fernández-Lucas et al, 2012; Lin et al, 2009; Moist et al, 2000; McKane et al, 2002). At the same 5% two-tailed significance level, this sample size would provide just under 95% power to detect a difference in rate of 0.05ml/min/1.73m^2/month, assuming linear change and assessments at 0,1,2,3,5,7,9,11 and 13 months, and a (conservative) autocorrelation of 0.30.

4 Statistical methods

4.1 Descriptive analyses

The following tables will be constructed.

4.1.1 Baseline characteristics

The following will be tabulated by treatment group and by total sample:

- Age (mean, SD)
- Centre (*n*, proportion)
- Sex (*n*, proportion)

- Race (*n*, proportion)
- Primary renal disease diagnosis (*n*, proportion)
- Stoke Comorbidity Score (mean, SD)
- Start; planned versus unplanned (*n*, proportion)
- Haemodyalysis type (*n*, proportion)
- Access type (*n*, proportion)
- Heart failure; yes/no (*n*, proportion)
- Diabetes mellitus; yes/no (*n*, proportion)
- Values of all outcome variables available at baseline (summaries as appropriate to level of measurement)

Denominators per group will be given for all of the above. Median and interquartile range will be used in place of mean and SD if appropriate. Treatment groups will be aliased until analysis is complete to ensure blinding. No hypothesis testing will be performed.

4.1.2 Follow-up timepoints

At each visit (Table 1), values of all outcome variables that have been recorded at that timepoint will be tabulated by treatment group (with summaries appropriate to the level of measurement).

A table detailing, by group, cumulative recruitment, patients randomized, withdrawals (with reasons) and deaths will be generated.

Cumulative totals of adverse events, serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will also be tabulated by treatment group.

Denominators per group will be given for all outcome data. The number of missing values (and reasons for their being missing, where known) will be indicated. Treatment groups will be aliased until analysis is complete to ensure blinding.

4.2 Inferential analyses

4.2.1 General principles

Analysis will be conducted blind to treatment allocation. Statistical significance will be set as $p \leq .05$ (two-tailed). Between-group estimates will be presented with 95% confidence intervals, alongside *p* values (which will be reported to three decimal places). Adjustments to alpha for multiplicity will not be made.

Appropriate checks will be made on the assumptions of all analyses. If any assumptions are not met, appropriate steps will be taken: data transformation, choice of alternative statistical model, or modifications to the current statistical model (e.g. inclusion of a time-varying covariate).

The null and alternative hypotheses for all analyses will be based on superiority:

> H_0: there is no difference in [outcome variable, specifying mean, proportion, hazard etc, as appropriate] between BI and Control
>
> H_1: there is a non-zero difference in [outcome variable, specifying mean, proportion etc, as appropriate] between BI and Control

Analyses will be conducted in Stata and SPSS (versions 14 and 24 or later, respectively).

4.2.2 Primary outcome

Time to anuria will be analysed on an intention-to-treat basis (as the primary analysis) and on an as-treated basis (as the secondary analysis) using competing risks survival analysis (Pintilie, 2006) to estimate the relative risk (as expressed by the sub-hazard ratio) of the outcome (anuria) in patients where BI is used compared to control patients, accounting for the competing risks (death, transplantation). Patients undergoing modality change will be censored at the point of treatment switch. This analysis will implement the Fine and Gray proportional subhazards model for competing risks (Fine and Gray, 1999; Cleves et al, 2016). Key assumptions within this analysis are:

- The proportionality of the sub-distribution hazard ratios
- The functional form of individual predictors in the model is correctly specified
- The link function denoting the exponential form of the sub-distribution hazard function is adequate.

These will be checked using the procedures described by Li et al (2016).

The analysis will control for known baseline covariates affecting residual function (Jansen et al, 2002; Moist et al, 2000), i.e. age, race, sex, comorbidities (separately or using a validated scoring system), antihypertensive drug use (ACE inhibitors/ARBs, calcium antagonists), type of start (planned or unplanned), and diuretic use. The stratification factor (centre) will be included in the model as a fixed effect, provided that this does not induce sparsity.

The intention-to-treat dataset will comprise all randomized patients, analysed according to randomized groups, and including those deviating from protocol, switching treatment, withdrawn or lost to follow-up. The as-treated dataset will include all randomized patients, analysed according to the intervention that they received, irrespective of randomized allocation.

Patients who recover renal function, and thus cease dialysis, will not be followed up within the trial, but their status will be determined at the end of the study by means of Registry data. Any censoring or identification of a competing risk would then be performed retrospectively in accordance with the timeline provided by the Registry data, thereby allowing these participants to be included in the assessment of the primary outcome measure.

4.2.3 Secondary outcomes

Difference in rate of decline in renal clearance will be analysed using a random slopes linear mixed-effects model, with adjustment for the same baseline characteristics as for the primary outcome and with the stratification factor in the model.

We will analyse the effect of randomization on fluid status and body composition as determined by BI (to ascertain the effect of the intervention on the fluid assessment decision) and undertake corresponding appropriate analyses of the other secondary outcomes such as (i) *dialysis-related symptoms and treatment efficacy* (e.g. inter-dialytic fluid gain, falls, post-dialysis recovery time), (ii) *critical events* such as cardiovascular events and interventions, access-related interventions/failures and death, and (iii) *patient-reported measures* (e.g. EQ-5D-5L, SF-12, PAM, POS-S renal, CSRI CKD). In analysing the effect of the intervention on patient activation measures we will look to see if this is associated with

objective measures of fluid management, e.g. inter-dialytic fluid gain which, following adjustment for comorbidity, is a surrogate measure of patient survival.

For analyses at a single timepoint, numerical secondary outcome data will be analysed through analysis of covariance. Nominal outcome data will be analysed through logistic regression. Count data will be analysed through Poisson regression or negative binomial regression, depending on the distribution of the data. For longitudinal analyses, linear mixed-effects models or generalized estimating equations will be used as appropriate, with observations clustered within patients.

4.2.4 Missing data

If necessary, missing baseline values will be imputed using methods described by White and Thompson (2004). For outcome data analysed using a likelihood-based method, and where a missing-at-random assumption is plausible having examined the pattern of missing data, imputation of missing data is not normally necessary.

4.2.5 Subgroup analyses

In separate models, pre-specified subgroup analyses will be undertaken, for the primary outcome only, and will be limited to planned versus unplanned start and comorbid conditions that affect management of fluid status – specifically, heart failure and diabetic status; these will be assessed through an interaction term in the model (Brookes et al, 2001). The study has not been powered for these analyses and they will therefore be exploratory; forest plots with 95% confidence intervals will be presented for the stratum-specific estimates, but no formal hypothesis testing will be undertaken.

4.2.6 Sensitivity analyses

In addition to the adjusted intention-to-treat analysis, an unadjusted intention-to-treat analysis (including only the treatment factor and the stratifying factor) will be performed as a sensitivity analysis, for the primary outcome.

A sensitivity analysis will also be performed by means of a comparison of data collected prior to the COVID-19 pandemic in March 2020 with data collected subsequently, to gauge the extent to which the impact of the pandemic on the National Health Service may have influenced the delivery of the interventions in one or both of the study arms and thereby affected the treatment effect calculated for time to anuria and for the GFR outcome data.

Accordingly, for time to anuria, we will consider adding a binary variable representing the pre- and post-COVID-19 samples (collected before and after March 20th, 2020) as a time-varying indicator and an interaction term with the treatment factor into the Fine and Gray model. From the resulting model, subdistribution hazard ratios reflecting the effect of treatment on the subdistribution hazard function in both phases can be generated. It is also proposed to undertake a multi-state analysis if the model assumptions for the Fine and Gray model are not met. A corresponding sensitivity analysis for the longitudinal analysis of the GFR data can be accommodated using a random-effects segmented regression technique in order to compare level and slope changes before and after lockdown.

4.3 Practice patterns

A separate analysis will explore the effects of unit-level practice patterns as defined by our pre-study survey of 66 dialysis units (Dasgupta et al, 2016; Pisoni et al, 2009; Table 2).

5 Economic evaluation

Economic analysis will be carried out to explore the relative cost-effectiveness of the intervention compared to standard management. This analysis is detailed separately.

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Table 1: Schedule of visits and outcome measurement

	VISITS (months) **All undertaken at routine dialysis sessions**						**Urine Collections**
PROCEDURE	**Visit –1**	**Visit 0 baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visits 4-11 at 6,9,12,15, 18,21,24 months**	**At 5,7,9,11,13 15,17,19,21, 23,24 months.** ***includes extra 2/52 after primary endpoint***
Residual kidney function tests for normalized GFR	**x**		**x**	**x**	**x**		**x**
Stoke comorbidity score		**x**					
Renal Registry comorbidity fields		**x**					
Incremental/full start dialysis		**x**					
Transplant wait listed		**x**					
Dialysis prescription		**x**					
Bioimpedence with full dataset using software		**x**	**x**	**x**	**x**	**x**	
Duke Activity Status Index (ASI)		**x**			**x**	**x**	
Patient Activation Measure (PAM)		**x**			**x**	**x**	
EQ-5D-5L		**x**			**x**	**x**	
IPOS-Renal patient version		**x**			**x**	**x**	
Haemodialysis symptoms questionnaire		**x**			**x**	**x**	
Short Form (SF-12) Health Survey		**x**			**x**	**x**	
CSRI CKD		**x**			**x**	**x**	
Cognitive Assessment (MoCA)		**x**					**x annually**
Adverse events			**x**	**x**	**x**	**x**	

Table 2. Unit level practice patterns, measured annually: first completion just before the first patient is enrolled.

Dialysate sodium concentration

- Is there a standard sodium concentration in your unit?
- What is the concentration of sodium used most frequently?
- What proportion of patients have an individualised sodium concentration?
- If individual sodium used
    - If low, what reason? If high, what reason?
    - Is your practice to match the plasma sodium?

Nutrition and sodium intake

- Does your HD unit have a dedicated dietitian? If so, how much time per patient do they have?
- Do you have a policy on sodium restriction? If so what is the advised intake?
- Do you have a policy on fluid restriction? If so what is the advised intake?
- What information/training is given to nurses on the HD unit about fluid/salt restrictions?
- Are patients given written advice about dietary intake and restrictions?

Diuretics

- Are the majority patients with residual kidney function routinely prescribed loop diuretics?
- What is the typical dose (e.g. Furosemide, Bumetanide)?
- Do you routinely use other diuretics (metolazone, thiazides, aldosterone inhibitors)?

Incremental dialysis

- Is it routine practice in your unit to commence HD incrementally?
- If so, is this to preserve residual kidney function?
- What proportion of patients on your unit do (a) 1 or (b) 2 sessions per week in the context of incremental start?

Measurement of residual Kidney Function

- Do you routinely measure residual kidney function on your unit? If so how frequently?
- If so, do you use this to reduce the (a) frequency, (b) length of dialysis sessions?

Assessment and prescription

- Do you have a standardised protocol for assessing fluid status in new HD patients?
- Protocol or not, in addition to clinical assessment do you routinely use (a) bioimpedance – of so state device, (b) Chest Xray,(c) Echocardiogram (d) central vein diameter, (e) blood volume monitoring?
- Who assesses fluid status on your unit (a) consultants (b) HD dedicated staff grades (c) HD nurses (d) training grade doctors.

Fluid management strategies

- Who prescribes fluid management on your unit (a) consultants (b) HD dedicated staff grades (c) HD nurses (d) training grade doctors.
- Do you have a policy to maximise UF rates in your unit? If so, what is the maximum rate permitted?
- If you are changing the target weight, typically what is the maximum change per session you would prescribe? (Exclude urgent situations and tell us if there is no specific policy on this).

Figure 1: Flowchart for the BISTRO Trial