Full title:
BioImpedance Spectroscopy To Maintain Renal Output: The BISTRO Trial

Short Title/Acronym: BISTRO

This protocol has regard to the HRA guidance (where applicable).

Protocol version number and date: version 2.0, date 15-Jun-2017.

Research reference numbers:

IRAS number: 206213

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BISTRO is funded by the National Institute for Health Research's Health Research Health Technology Assessment (HTA) Programme.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ..... Date: 21/6/2017

Name (please print): CLARK CRAWFORD

Position: Head of Research Integrity

Chief Investigator:

Signature: ..... Date: 15/6/17

Name: (please print): SIMON DAVID

Statistician:

Signature: ..... Date: 15/6/17

Name: (please print): JULIUS SIM

Position: STATISTICIAN

PROTOCOL VERSION HISTORY LOG

Version	Date Approved	Reason(s) for Change	Implementation Plan
1.0	13-Aug-2016	Not applicable	Original HRA approved protocol version. All sites to be provided with this protocol as part of the local information pack.
2.0	15-Jun-2017	This amendment provides further clarification to sites which will ensure that all procedures are executed by the sites in a standard manner. These clarifications were driven from the sites' feedback at Site Initiation Visits. No research design nor methodology were modified.	Following REC and HRA approval, the protocol will be distributed to all BISTRO participating sites for NHS R&D review and implementation.

KEY TRIAL CONTACTS

Chief Investigator	Professor Simon Davies Kidney Unit Royal Stoke University Hospital University Hospital of North Midlands NHS Trust Newcastle Rd Stoke-on-Trent ST4 6QG Tel: 01782 676346 Email: simonj.davies@uhnm.nhs.uk
Trial Coordinator	Dr Nancy Fernandes da Silva Keele University Clinical Trials Unit Keele University Staffordshire ST5 5BG Tel: 01782 734886 Email: NSTCCG.BISTRO@nhs.net
Sponsor	Clark Crawford Directorate of Engagement and Partnerships IC2 Keele University Science and Innovation Park Keele University Staffordshire ST5 5NH Tel: 01782 733371 E-mail: research.governance@keele.ac.uk
Funder(s)	National Institute of Health Research Health Technology Assessment Programme (HTA) Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road Southampton SO16 7NS Tel: 023 8059 5713 Email: info@netscc.ac.uk

TRIAL SUMMARY

Trial Title	BioImpedance Spectroscopy To Maintain Renal Output	
Internal ref. no. (or short title)	RG-0012-16-IACS; BISTRO	
Clinical Phase	3	
Trial Design	Pragmatic, Multicentre, Open-Label Prospective Randomised Controlled Trial (RCT)	
Trial Participants	NHS patients with a diagnosis of chronic kidney disease and new to centre based haemodialysis (HD) treatment	
Planned Sample Size	516	
Planned Trial Period	24 months	
	Objectives	Outcome Measures
Primary	To recruit 516 patients commencing HD to the trial, sufficient to demonstrate a clinically significant difference in time to anuria in those randomised to the Bioimpedance Spectroscopy (BI) intervention limb versus those randomised to the control limb.	Time to anuria, < 100ml/day or 200ml in the short inter-dialytic period
Secondary	To determine effect of intervention on: -The rate of decline in kidney function -Significant events, including vascular access failure and associated interventions, cardiovascular events, hospital admissions and deaths. - Dialysis efficacy and safety: -Patient reported outcomes, including quality of life dialysis-related	 -Slope of decline of residual renal solute clearance -Significant events: hospitalisations, interventions, deaths, to include long-term legacy effects beyond trial completion using data linkage to routine health care databases such as the UK Renal Registry, Hospital Episode Statistics and the Office for National Statistics (and their equivalent bodies in Wales, Scotland and Northern Ireland via the Renal Registry). -Inter-dialytic fluid gains, intra-dialytic hypotension, urea-reduction ratios -Patient-centred outcomes: Dialysis-related symptoms;

	symptoms, Integrated Palliative Care Outcome Scale- Renal, Patient Activation, Physical function, cognitive function. Cost-effectiveness of the intervention.	Intra-dialytic hypotension; Post-dialysis recovery time; Falls; Inter-dialytic weight gain; Physical function (Duke ASI); Montreal Cognitive Assessment, (MoCA), Patient Activation Measure (PAM); and QOL (QOL: EQ-5D-5L), SF-12, Client Service Receipt Inventory Chronic Kidney Disease (CSRI CKD) as required for the economic evaluation -Use of NHS resources, costs, quality-adjusted life years (QALY) and incremental cost per QALY gained
Intervention	Incorporation of bedside bioimpedance technology to inform the clinical assessment of fluid status (specifically setting of target weight).	
Device Information and accreditation	The Fresenius Body Composition Monitor (Fresenius BCM) will be the device used to measure Bioimpedance. It is currently the best validated device in the renal population both against gold standard methods (i.e. DEXA scanning, deuterium and sodium bromide solution) and in referencing body composition of the dialysis patients to population norms. The BCM – Body Composition Monitor was originally CE-marked to Fresenius Medical Care as a Class IIa medical device in 2003; the CE mark was last updated in June 2011.	

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

- Trial Steering Committee (TSC) and Independent Advisory and Dissemination Board.

  This oversight committee, facilitated by Keele Clinical Trials Unit (CTU), will be independently constituted (>75% externality) and be responsible for the scientific and ethical conduct of the trial. It will receive independent annual reports from the DMC and will provide expertise and oversight for the research dissemination plan.

  The Trial Steering Committee will be chaired by Dr Richard Fluck and include both independent patient/lay and senior statistical representation, providing overall supervision of the study, meeting face to face 3 times and additionally by teleconference over the course of the trial as needed.

- Data Monitoring Committee (DMC)

  The DMC will periodically review (every 4 to 6 months) unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. This DMC will report progress including any safety concerns to the independent Advisory and Dissemination Board.

- Trial Management Group (TMG)

  The Trial Management Group based at Keele University will meet monthly to ensure all practical details of the trial are progressing and working well and everyone within the trial understands them. The Trial Management Group members are the study chief investigator, a senior trial manager, trial manager, data manager and statistician based at Keele University Clinical Trials Unit.

PROTOCOL CONTRIBUTORS

Professor Simon Davies, Consultant Nephrologist and Director of Health Services Research – oversight of integrated delivery of the trial

Dr Fergus Caskey, Medical Director of UK Renal Registry – will ensure outcomes are captured by UK Renal Registry

Mr David Coyle, Patient volunteer – will lead patient and public involvement

Dr Elizabeth Lindley, Specialist Clinical Scientist in Renal Care Leeds Teaching Hospitals NHS Trust – will co-lead on development and delivery of bioimpedance technology training during the trial

Dr Jamie MacDonald, Bangor University – will provide expertise in body composition and co-lead bioimpedance training

Dr Sandip Mitra, Consultant Nephrologist Central Manchester University Hospital, Chair HD Clinical Study Group – will lead assessment of practice patterns in fluid management

Professor Martin Wilkie, Consultant Nephrologist, Sheffield Teaching Hospitals NHS Trust – will provide professional leadership for patient and public involvement

Dr Andrew Davenport, Consultant Nephrologist Royal Free Hospital – will provide clinical expertise in Bioimpedance assessment

Dr Ken Farrington, Consultant East & North Hertfordshire NHS Trust, HD Clinical Studies Group- will provide clinical expertise in haemodialysis and residual renal function measurement

Dr Indranil Dasgupta, Consultant Nephrologist, Birmingham Heartlands NHS Trust, renal speciality lead at West Midlands Local Clinical Research Network – will lead on patient recruitment and safety

Professor Paula Ormandy, Salford University, experienced Researcher and previous senior HD nurse – will lead education and training of nurses in Bioimpedance techniques, feasibility of data collection and patient collaboration techniques using social media

Dr Lazaros Andronis, Lecturer in Health Economics, University of Birmingham- will be responsible for economic evaluation

Professor Julius Sim, Professor of Health Care Research Keele University and chartered statistician- will be responsible for analysis of trial data and statistics

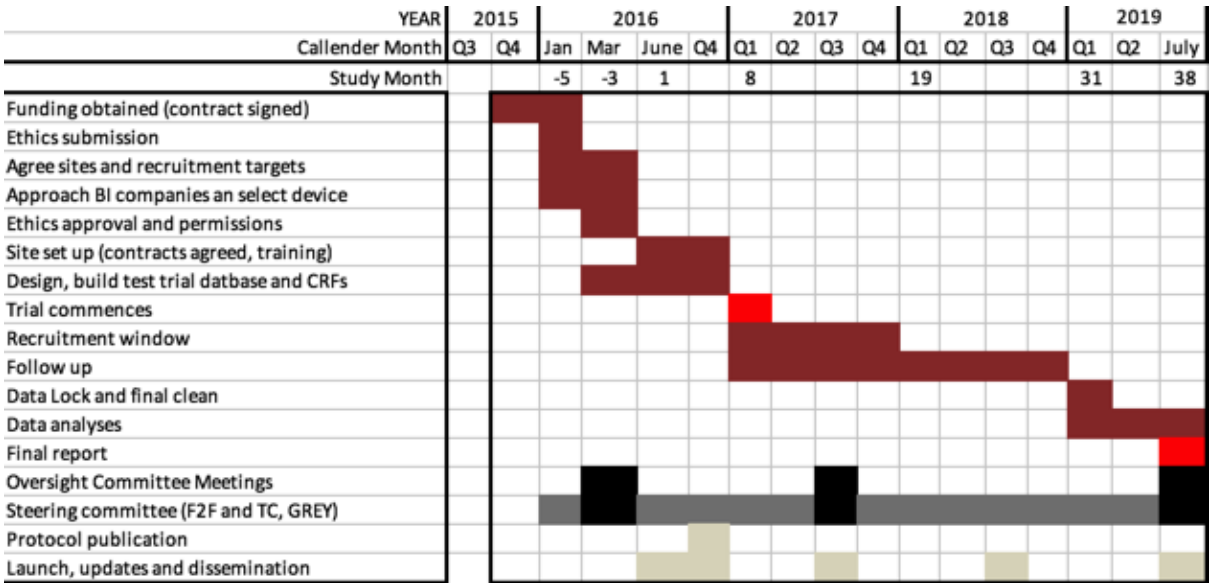
Dr Ivonne Solis-Trapala, Senior Lecturer in Medical Statistics – Oversight of Keele CTU deliverables

LIST OF CONTENTS

LIST OF ABBREVIATIONS

Term/Abbreviation	Definition
AE	Adverse event
BI	Bioimpedance
CI	Chief Investigator
CKD	Chronic kidney disease
CRF	Case report form
CEACS	Cost-effectiveness acceptability curves
DMC	Data monitoring committee
GCP	Good Clinical Practice
HD	Haemodialysis
HES	Hospital Episodes Statistics
HRA	Health Research Authority
ICF	Informed consent form
ISF	Investigator site file
ITT	Intention-to-treat analysis
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant information sheet
QA	Quality assurance
QALY	Quality adjusted life years
QC	Quality control
ONS	Office of National Statistics
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SOP	Standard operating procedure
TMG	Trial management group
TSC	Trial steering committee
UKRR	UK Renal Registry

TRIAL MANAGEMENT SCHEDULE



FLOW CHART

BISTRO TRIAL

TIMELINE (Months)

0-6: Study set-up → **6-30: enrolment and accrual** → **32: Data-lock; 32-38 Analysis**

SCREENING

RECRUITMENT
(***N=516, from 30 units over 12 months***)

FOLLOW-UP (capture of reasons for loss-to-follow-up, e.g. competing risks)
(***12 -24 months to accrue 185 anuria events plus longitudinal residual clearances, etc.***)

ANALYSIS

Standard Care: Routine electronic data capture, e.g. BP, pre-post weights, biochemistry, via UK Renal Registry

.... Monthly for 3 months..... .... 3 monthly until trial completion or endpoint

Eligible Patients:
Aged > 18 commencing maintenance HD with residual function, planned, unplanned, temporary or permanent access

ALLOCATION:
Home on HD
Check inter-dialytic RRF (if needed)
CONSENT
RANDOMISE 1:1

Capture of fluid assessment using **BISTRO template**

- Target weight review, Reasons for target change and Treatment plan
- **BI data collected independently by research nurses**

STUDY END

.... Monthly for 3 months..... .... 3 monthly until trial completion or endpoint

Standard Care plus BIA measurements: Routine electronic data capture via UKRR as for control group

Screening failures
No RRF
Pacemaker
Amputee
Other

COLLECTION OF END-POINT DATA: *entered into paper CRF by research nurses*
Primary (urine volume) and residual clearances: *monthly for 3 months, then alternate months*

SECONDARY OUTCOMES: *entered into paper CRF by research nurses*
Dialysis related symptoms: e.g. recovery time, headaches, cramps, - *baseline, 3 monthly*
Dialysis related events: e.g. falls, intra-dialytic hypotension episodes, *accrual collected 3 monthly*
QOL measures, PROMS, PAMs, - *3 monthly, to end of study (paper based)*

SIGNIFICANT EVENTS: Hospitalisations, procedures, deaths *captured in real time and obtained from HES data linkage via UK RR until the end of the study*

UNIT BASED PRACTICE PATTERNS (Baseline and annually)

SCHEDULE OF PARTICIPANT VISITS AND PROCEDURES – during the 2 year follow up period

	VISITS (Months) **All undertaken at routine dialysis sessions**						**Urine Collections**	**Trial completion**	**Event based**
PROCEDURE	**Visit -1**	**Baseline Visit 0**	**Visit 1 Mth 1**	**Visit 2 Mth 2**	**Visit 3 Mth3**	**Visits 4-10 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 weeks after primary endpoint is reached***		
Eligibility	**x**								
Consent	**x**								
Residual kidney function tests for normalized GFR (urine volume and urine + routine blood to lab)	**x**		**x**	**x**	**x**		**x**		
Height (cm)	**x**								
Web-based randomisation		**x**							
Date of birth		**x**							
Ethnicity		**x**							
Sex		**x**							
Full medication list		**x**							
Primary Renal Disease Diagnosis		**x**							
Stoke comorbidity score		**x**							
Renal Registry comorbidity fields		**x**							
Planned/unplanned start		**x**							
Access type (fistula/graft/line)		**x**							
HD modality: (HD, HDF)		**x**							
Incremental/full start dialysis		**x**							
Transplant wait listed		**x**							
Dialysis prescription (section 8.5.1)		**x**	**x**	**x**	**x**	**x**			**x if indicated**
Bioimpedance with full dataset using software		**x**	**x**	**x**	**x**	**x**			**x if indicated**
Cljnical fluid assessment using Bioimpedance intervention group / control group CRF		**x**	**x**	**x**	**x**	**x**			**x if indicated**
Participant questionnaire		**x**			**x**	**x**			
Cognitive Assessment (MoCA)		**x**					**x annually**		
Study Termination / completion form								**x**	**x**
Adverse events									**x**

1. BACKGROUND

Historically, 'adequate' dialysis treatment has been equated with targets for small solute clearance, which has led to ever-increasing dialysis dose to achieve this, but with little attention paid to the alternative approach, this being the optimisation of residual kidney function for as long as possible after commencing treatment. Following the HEMO study (1), which did not show that further increasing the dialysis dose had a significant impact on survival, the emphasis has switched to volume management. There is a growing body of evidence that poorly regulated volume status, especially when determined from Bioimpedance (BI) devices showing excess fluid in the extracellular space, often coupled with a loss in muscle mass, is associated with poor survival (2,3,4). Equally, there is evidence that strategies employed to increase fluid removal by increasing the dialysis ultrafiltration rate also increase the risk of intra-dialytic hypotension or cardiac stunning (5), and are also associated with increased mortality (6). Furthermore, volume depletion is an important risk factor for loss of residual renal function (7). This dilemma has led to the concept that BI could be used to set target post-dialysis weights that lead to normalisation of fluid status.

The maintenance of residual kidney function in patients commencing dialysis is associated with considerable advantages, not least improved patient survival. The CANUSA study found that each 250ml of urine per day increased 2-year survival by 36% in peritoneal dialysis (8) and in the NECOSAD study complete anuria in HD patients increased the relative risk of death 17-fold compared to those with some preserved kidney function (9). Other benefits include improved wellbeing, better quality of life (10) and less need to remove high fluid volumes during dialysis sessions with its above mentioned risks of intra-dialytic hypotension (11), cardiac stunning and potentially increased mortality. It is therefore surprising how few clinical trials have focused on interventions to maintain residual kidney function as a key benefit to HD patients – the exception being ultrapure dialysate (12), which is now standard care. Worse than this, 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 that adequate control of volume status has been achieved. Our recent survey of fluid management practice patterns in UK units (13), indicates that this is still being pursued in the majority of units, despite the risk it poses to residual kidney function by setting in place a continuing vicious cycle of volume depletion, excessive thirst and high inter-dialytic fluid gains. The introduction of BI technology provides clinicians with an opportunity to break this cycle while avoiding the risk of excessive over-hydration. The anticipated benefit to patients would be a change in clinical practice in which a more balanced approach to the bidirectional risks of hyper- and hypovolaemia is taken that is associated with improved wellbeing, fewer dialysis-related symptoms, possibly less dialysis in those commencing treatment in an incremental fashion, and potentially better survival.

The concern that this proposed research will address is that BI technology is being adopted indiscriminately in many units around the world without clear evidence of benefit and a potential risk of harm. Specifically, there is a paucity of studies that show how BI might be used to benefit the patient beyond surrogates such as blood pressure and left ventricular mass, and there is evidence from at least one trial that using BI aggressively in this context, i.e. aiming to achieve volume depletion post dialysis, results in a more rapid loss of residual kidney function (14). It is also of note that dialysis regimes employing increased treatment times, such as those investigated by the Frequent HD Trials Network, found that prolonged nocturnal treatments that are more likely to lead to volume depletion resulted in accelerated the loss of residual kidney function (15). The relative preservation of residual kidney function in peritoneal dialysis patients, who unlike HD patients are not rendered hypovolaemic after each dialysis session (16), is likely in part to explain the better early survival observed in patients on this modality (17, 18). If this adjusted survival disadvantage for HD patients – 10-20% during the first 2 years of treatment – could be closed by better preserving residual

kidney function, many lives would be extended. There is therefore a pressing need to undertake studies that focus on surrogates with clear patient benefit, such as residual kidney function, that also ensure that the risks of excessive volume depletion are avoided.

2. RATIONALE

Of 54,000 people in the UK treated with kidney replacement therapies, 24,000 receive centre-based HD at an annual tariff of £24,000 excluding additional costs such as travel, drugs, access procedures and inpatient episodes. In this high-cost setting BI has the potential to enhance the productivity of HD care by helping clinicians make appropriate and safe treatment decisions as defined by principles underpinning the Department of Health's QIPP Policy. BI also has potential to address several of the NHS Outcomes Framework domains, including prevention of premature death, improving outcomes by addressing a number of NICE chronic kidney disease standards such as cardiovascular risk, blood pressure and avoidance of acute illness episodes (19, 20) and enhancing the quality of life for people on dialysis (i.e. long-term condition), and contributing through improved engagement and activation to a more positive patient experience (21, 22).

3. STUDY 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. Measurement of bioimpedance involves the passing of a low-strength alternating current through the subject's body, (using skin electrodes, usually placed on the hand and foot on one side of the body), which is not felt, but sufficient to measure the resistance and reactance to flow. These two measures are proportional to the amount of tissue fluid and cell membranes between the electrodes, equating to tissue mass and hydration. 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. The study intervention is the use of this additional information 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) (23, 24) will be the device used to measure Bioimpedance. It is currently the best validated device in the renal population both against gold standard methods (i.e. DEXA scanning, deuterium and sodium bromide solution) (25, 26, 27) and in referencing body composition of the dialysis patients to population norms (28, 29). The BCM – Body Composition Monitor was originally CE-marked to Fresenius Medical Care as a Class IIa medical device in 2003; the CE mark was last updated in June 2011 (30).

3.1 Training support

Prior to patient enrolment, participating centres will receive on-site training to (a) ensure that research nurses are fully competent in taking good quality BI readings and (b) that clinicians are trained in the use of the BISTRO fluid assessment template and how to incorporate the information from the BI measurements into their clinical decision making. The BISTRO fluid assessment template is designed for shared decision making with participants, and the training will include how this information is best communicated to participants. Throughout the study the research team will provide ongoing support to research nurses and clinicians.

4. OBJECTIVES and OUTCOME MEASURES / ENDPOINTS

Aim

To perform a prospective, multicentre randomised controlled trial to determine if incorporation of bioimpedance into the setting of the post dialytic weight reduces loss of residual kidney function in incident centre-based HD patients, with the potential to improve clinical outcomes, in particular dialysis related symptoms, hospitalisation and survival.

4.1 Primary Objective

To recruit 516 patients commencing centre-based HD to the trial, sufficient to demonstrate a clinically significant lengthening in time to anuria in those randomised to the BI intervention limb versus those randomised to the control limb.

4.2 Secondary Objective

To determine the effect of the intervention on:

- The rate of decline in kidney function
- Significant events, including vascular access failure and associated interventions, cardiovascular events, hospital admissions and death, including the use of routinely collected data and long-term legacy effects beyond trial completion using data linkage to routine health care databases such as the UK Renal Registry, Hospital Episode Statistics and the Office for National Statistics (and their equivalent bodies in Wales, Scotland and Northern Ireland) via the Renal Registry.
- 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 (31); SF12 (32), dialysis-related symptoms (Integrated Palliative Care Outcome Scale- Renal, IPOS) (33), Patient Activation Measure (34), Duke Activity Status index (35), Montreal Cognitive Assessment (MoCA) (36), Client Service Receipt Inventory Chronic Disease (CKD).
- Cost effectiveness of the intervention.

4.3 Outcome measures

4.3.1 Primary outcome

The primary outcome is time to anuria, <100ml/day or 200ml in the short inter-dialytic period confirmed by a further collection after 2 weeks to exclude temporary illness.

4.3.2 Secondary outcomes

- Slope of decline of residual renal solute clearance
- Patient-centred outcomes: Dialysis-related symptoms; Intra-dialytic hypotension; Post-dialysis recovery time; Falls; Inter-dialytic weight gain; Physical function (Duke ASI) (35), Montreal Cognitive Assessment (36)
- Patient Activation Measure; and QOL as required for the economic evaluation

- Significant Events; hospitalisations, interventions, deaths
- Body composition/nutrition (BI-derived)
- Health economics outcomes

5 TRIAL DESIGN

The study will be a pragmatic, multicentre, open-label prospective randomised controlled trial comparing current best practice in setting the post-dialytic target weight with the same assessment guided by serial BI measurements. BI readings will be taken in both study groups but the results concealed from the clinical teams in the controls. To minimise 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. The BISTRO TRIAL flow chart (Appendix 1) illustrates study flow.

6 TRIAL SETTING

The study is within the adult centre-based haemodialysis setting, both main and satellite units, and inpatient renal units during hospital admissions. Patients admitted for inter-current problems during the course of the trial as a result of fluid management problems will remain in the study and be assessed according to randomisation.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

- Adults aged >18 years, within 3 months commencing centre-based maintenance haemodialysis as an outpatient for advanced kidney disease CKD stage 5, planned or unplanned, via arterio-venous fistula, graft or central venous catheter (i.e. with or without permanent vascular access).
- Commencing dialysis on any regimen, including having incremental dialysis initiation. All of the following circumstances are permissible:
    - Failed kidney transplant patients with no planned transplant surgery date booked
    - Permanent transfer from peritoneal dialysis to haemodialysis
    - Patients presenting with acute kidney injury that failed to recover – i.e. 1st session of haemodialysis as outpatients will be day 0
    - Patients on active transplant list with no planned transplant surgery date

- Residual kidney function: For patients who have not yet but are about to start dialysis treatment they should have a daily urine volume > 500ml/day **OR** a measured mean urea and creatinine clearance ≥3ml/min/1.73m^2 determined from a 24 hour collection; for patients already on dialysis they should have a urine volume >500ml during the short inter-dialytic period **OR** a measured mean urea and creatinine clearance ≥3ml/min/1.73m^2, determined from the same timed

inter-dialytic urine collections and an average of the post- and pre-dialysis plasma urea and creatinine concentrations.
- Subjects with limb amputations who fit the above criteria

7.2 Exclusion criteria

- Unable or unwilling to give informed consent
- Unable to comply with trial procedures, e.g. collection of urine output
- Likely survival prognosis or planned modality transfer < 6 months
- Subjects with limb amputations when the foot is not accessible **AND** it is not possible to take hand to hand measurements

8. TRIAL PROCEDURES

8.1 Recruitment

Participants will be recruited over a 12-month period at 30 centre-based haemodialysis centres throughout the UK, including satellite HD centres affiliated with main centres. All adult patients new to centre-based HD treatment will be screened using the trial eligibility criteria. Patients who start dialysis in a planned fashion will be approached in chronic kidney disease clinics at the point of deciding a convenient start date. Patients starting treatment that is unplanned will be approached at the point it is decided they will require long-term dialysis.

8.1.1 Patient Identification

Patients will be identified by members of the clinical team at each centre, delegated this duty by the local site principal investigator. Both planned (defined as patients starting dialysis as planned by the chronic kidney disease team) and unplanned dialysis starts (defined as patients whose first dialysis was precipitated by urgent need for treatment) will be identified at the point when outpatient slots on the dialysis unit are requested. Only members of the patient's existing clinical care team will access patient records without explicit consent in order to identify potential participants, check they meet the inclusion criteria or make the initial approach to patients.

8.1.2 Informed Consent

In the case where the start of haemodialysis is planned, consent will be obtained before the first dialysis session. An unplanned start on dialysis, for example acute-on-chronic deterioration in kidney function, is frequently in the inpatient setting. These patients will be screened and recruited when hospital discharge is planned.

The local Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their centre and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the ethically approved protocol.

The appropriately delegated staff member authorised to perform consent activities on the delegation log, will seek written informed consent from patients whose eligibility is confirmed, and in accordance with local procedures for taking and documenting informed consent for research. Study patient information sheets and consent forms with favourable opinion from a research ethics committee will be used. Consent will be confirmed via completion of a signed

consent form. A copy of the signed consent form will be given to the patient, a copy in in the medical records and the original in the site-file at the centre. In addition, a copy of the signed consent form will be sent in a secured envelope to the Keele Clinical Trials Unit, separately to the study case report forms (CRFs). The consent forms will be kept in a different location in the Keele CTU to the study data.

Consent will also seek permission for linkage of data to routine health care databases such as the UK Renal Registry, Hospital Episode Statistics and the Office for National Statistics (and their equivalent bodies in Wales, Scotland and Northern Ireland).

Patients who do not wish to participate in the trial will resume normal clinical care delivered by their local dialysis unit. The right of the participant to refuse consent without giving reasons will be respected. Further, the participant will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

8.1.3 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide on-going informed consent by virtue of physical or mental capacity, the consent previously given when capable remains legally valid. Participants who lose capacity after informed consent has been obtained and are unable to complete follow-up questionnaires will be excluded from active follow-up but will remain in the trial according to the principle of intention-to-treat.

8.2 Screening

At the point when outpatient dialysis slots are requested, and when informed consent has been obtained from the patient for the study, the patient will have their residual kidney function measured to check eligibility criteria for entry to the trial. Where the residual kidney function is not measured as standard of care, the research team must seek informed consent according to the BISTRO trial protocol, before measuring the patient's residual kidney function.

This will be measured in accordance with the Standard Operating Procedure (SOP) for Measurement and preservation of residual renal function in haemodialysis patients (Appendix 1). This SOP is adapted for the BISTRO study from the SOP in use at The Leeds Teaching Hospitals NHS Trust. Patients will be given instructions as to how to perform this test (Appendix 1). A urine Glomerular Filtration Rate (GFR) calculator will be provided on an excel spreadsheet with the study manual.

A screening log will be retained at each centre in the investigator site file.

8.3 The randomisation scheme

Prior to randomisation, the following must be completed:

- Eligibility assessment
- Informed consent form
- Baseline trial assessments

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

Planned and Unplanned haemodialysis regimes will be confirmed at randomisation stage. (Unplanned start is defined as the need to commence dialysis as an emergency without permanent vascular access, in contradistinction to the deliberate decision to plan to commence dialysis with an intravenous catheter).

8.3.1 Method of implementing the allocation sequence

Randomisation will be during office hours using a secure centralised web-based, automated computer generated randomisation system provided by the Keele University Clinical Trials Unit (CTU). Authorised personnel at the trial site will be allocated personalised log in details by Keele CTU, in order to access the randomisation system.

If, during office hours, the randomisation system is online but the centre network is down, the centre will be instructed to call the Keele CTU and the CTU will perform the randomisation on the centre's behalf. Authorised staff at the CTU will access the randomisation tool to perform randomisation and inform the healthcare professional of the allocation.

8.4 Blinding

To ensure blinding to BI data in control subjects and minimising of performance bias, BI measurements will be taken independently from clinical fluid assessments by the research nurse. BI readings will be taken in both study groups but the results concealed from the clinical teams and participants in the controls. The full BI dataset will be stored for all participants using the proprietary software, but in the BI intervention arm, the key BI metrics used for informing the clinical decision will be transferred to the clinical assessment CRF (Bioimpedance intervention group) prior to their use.

8.5 Trial assessments

8.5.1 Baseline and interval data

(***** indicates clinical data collected at each study time-point to coincide with clinical assessments by research nurse and recorded on CRF)

- Date of data collection*
- Date of birth
- Ethnicity
- Sex
- Full medication list to include diuretic and anti-hypertensive treatment*
- Primary Renal Diagnosis using the EDTA primary renal disease code
- Comorbid conditions using the Renal Registry dataset plus validated comorbidity index (Stoke comorbidity index)
- Planned/unplanned start; if unplanned immediate prior dialysis history plus context (hospitalisation, indications for emergency dialysis)
- eGFR immediately prior to starting dialysis
- Access (fistula, graft, line)*
- HD modality*: Haemodialysis, haemodiafiltration, haemofiltration
- Incremental or full dialysis start (planned number sessions per week)
- Transplant wait listed*
- Dialysis prescription (date of Dialysis Prescription, times per week, time dialysed in minutes, blood flow rate [ml] and sodium in dialysate [mmol/L]) *
- Pre-post dialysis BP, weight, BI full dataset (recorded using proprietary software).*

8.5.2 Clinical fluid status assessments and bioimpedance measurements

- **Clinical fluid status (Baseline, monthly for 3 months, then 3 monthly)**

  All participants will have an assessment of fluid status in setting the target dry weight at the baseline assessment, then monthly for the first 3 months of HD, then every 3 months by either a consultant nephrologist, or an experienced dialysis nurse or nephrology trainee. The data collected during the assessment of the participant's fluid status will be recorded on the both the Bioimpedance Intervention group (Appendix 2) and Bioimpedance control group case report forms. This assessment combines several clinical factors such as inter-dialytic fluid gain, pulmonary oedema and dialysis-related symptoms. The assessment is designed to facilitate a shared decision with the participant and will be used to set a post-dialysis target weight in both the intervention group and the control group, as well as recording the interventions used to achieve this weight (treatment plan).

- **Bioimpedance measurements: (Baseline, monthly for 3 months, then 3 monthly)**

  All participants will have bioimpedance measurements taken and the 'BI normally hydrated weight' recorded by the research nurses on the main CRF for each scheduled visit. Optional tracking sheets (these are not compulsory and not part of CRFs), each for the BI intervention and control groups are available on the BISTRO trial website. These sheets are intended to capture longitudinal BI readings and provide a quality control mechanism for BI measurements. The tracking sheet should be kept in the relevant participant CRF folder. The tracking sheet can be considered by clinicians undertaking fluid assessments in the BI intervention group, but not for the control group.

  Bioimpedance measurements must be performed ± 2 weeks from the planned start date for each BISTRO time point, i.e. start date is randomisation date is day 0. If this timeline is missed, i.e. more than 2 weeks, the site research team will note the missing time point in the CRF and will proceed to the next planned BISTRO time point.

  The Fresenius Fluid Management Tool version 3.3 will be used to store BCM raw data which is recorded on individual Patient Cards. When creating a Patient Card, the participant's height, gender, weight and date of birth are entered. The date of birth is entered to the card as the first day of the date of birth month and year for each patient (i.e. pseudonymised, 01/mm/yyyy). This allows the Cole-Cole Plot to be created by the BCM software. The raw data will be downloaded and saved in a csv file in anonymised format on local NHS secure network servers. The pseudonymised date of birth will be removed. The file will be transferred via NHS mail accounts to Keele University and retained for monitoring purposes.

  In addition, the research nurse will record the 'BI normally hydrated weight' obtained on the **CRF for the BI intervention group only**. This is to be passed to the clinician setting the post-dialysis target weight, with the explicit intention of avoiding unnecessary post-dialysis volume depletion, whilst taking the full clinical picture into account.

  Fluid status assessment between scheduled study visits
  It is recognised that clinicians will need to do additional fluid assessments between study visits, e.g. on hospital admission or following clinical events/need. These will be recorded on the **CRF for the BI intervention group and control group.**

8.5.3 Residual kidney function: (Baseline, monthly for 3 months and alternate months)

Residual kidney function will be measured at baseline, monthly for 3 months and alternate months until trial completion. This is determined from a urine collection and routinely collected blood samples for urea and creatinine.

Urine collection SHOULD be planned to occur at the same monthly time point as the routine blood samples are taken.

Urine collection can be performed at other times, however this will mean extra blood samples will need to be obtained.

The research nurse will enter these data (from the blood and urine samples) to a GFR calculator to calculate residual kidney function. The whole procedure will be carried out in accordance with a study specific standard operating procedure for measurement of residual renal function in haemodialysis patients by The Leeds Teaching Hospitals NHS Trust (Appendix1) and adapted for the BISTRO trial.

8.5.4 Participant questionnaire booklet (Baseline and 3 monthly).

The participant questionnaire should be completed either before dialysis starts, within 30 minutes of starting dialysis, or at home. Questionnaires should not be completed immediately post dialysis as the participant may feel unwell. Participant questionnaire can be performed ± 2 weeks from the planned start date for each BISTRO time point.

The participant questionnaire includes the self-reported assessments listed below:

- Physical function (Duke Activity Status Index)
- Patient Activation Measure (PAM)- Self management
- EQ-5D-5l to assess quality of life
- Integrated Palliative Outcomes Scale, IPOS- renal -to assess dialysis related symptoms
- Intra and post dialytic haemodialysis symptoms questionnaire
- Short Form-12
- Client Service Receipt Inventory Chronic Kidney Disease

8.5.5 Cognitive assessment

The Montreal Cognitive Assessment (MoCA) will be administered at baseline and annually, by research nurses who have received training. The MoCA can be performed ± 2 weeks from the planned start date for each BISTRO time point. Full instructions can be found at the MoCA website address (http://www.mocatest.org/). The MoCA is available in different languages listed on the MoCA website.

8.6 Unit level survey (annually)

A unit level survey will be completed annually for the project duration by the Lead Consultant of each dialysis unit level survey. The survey is will be completed within 3 months of unit opening for recruitment, at 12 months (end of recruitment period) and 24 months (end of follow-up).

8.7 Data variables extracted from the UK Renal Registry (RR)

Routine clinical data collected by units for the Renal Registry returns will be transferred to the CTU for incorporation into the trial database annually (2017, 2018 and final download at study end) in the form of an electronic download (following appropriate testing procedures to ensure data integrity). This includes data collected for individual dialysis sessions (e.g. pre and post weights, blood pressure dialysis prescription), haematology and biochemistry results, and treatment modality timelines, using the Renal Registry Dataset bV4.2 (UKRR website). If sites are not providing this information as part of their routine submission to the UKRR then they will be required to send a separate file with the fields by an appropriate secure mechanism to the UKRR at least once at the end of the trial. By the time this study goes live it is anticipated that the routine Renal Registry data collection will include Hospital Episodes and Statistics summary data via direct linkage. Admission and discharge dates, diagnostic and procedural codes will be obtained from HES (or its equivalent body) by the UK Renal Registry.

9 Study Completion

The study follow-up period is a minimum of 12 months and a maximum of 24 months. All study participants, including those who switch dialysis modality, will be followed up for the duration of the study for clinical events, patient reported outcomes and data for health cost analysis or until study withdrawal for the following reasons: death, kidney transplantation, recovery of renal function (resulting in the stopping of dialysis), loss to follow up (e.g. moving dialysis units) or participant choice. Reasons for leaving the study will be recorded on a study completion CRF. Fluid management assessments will discontinue once the primary endpoint is reached. However, Patient Reported Outcome Measures and the MoCA should continue to be completed until the trial completion.

9.1 Discontinuation of trial

If the participant discontinues the trial for any reason, a trial termination CRF must be completed by the research nurse.

9.2 End of Trial

The trial end is at the point at which the trial database is locked. All original CRFs will have been received by the data management team at Keele CTU and any data queries will have been resolved. Copies of CRFs will remain at each participating site. The Chief Investigator will notify the REC of the end of the Trial within 90 days of trial completion.

10. SAFETY REPORTING

Collaborating centres should record events or concerns about the safety of subjects that arise as a result of the study, even if these events or concerns do not meet the definition of a serious adverse event requiring notification to the regulatory authorities. All SAEs occurring from the point when participants are registered on the trial must be notified to the study Sponsor:

- via telephone +44 (0)1782 734886 within 24 hours of the research staff at the site becoming aware of the event

AND
- via email research.governance@keele.ac.uk (for Sponsor oversight only) AND NSTCCG.BISTRO@nhs.net.

The Study Team (Keele University) will then provide the appropriate case report form, which must be completed and returned (via fax or secure e-mail) within 24 hours of receipt.

Any follow-up information should be sent to the Sponsor via the Study Team as it is available. Events will be followed up until the event has been resolved or a final outcome has been reached.

All SAEs either confirmed or suspected to be related to the trial intervention will be reviewed by the Data Monitoring Committee and reported to the Trial Oversight Committee (Independent Advisory and Dissemination Board).

Clinicians will be asked to assess whether they considered the event was due to fluid-related complications. Serious Adverse Events are defined as:

Any event that:

(a) results in death;

(b) is life threatening (i.e., the subject was at immediate risk of death from the event as it occurred);

(c) is a persistent or significant disability/incapacity;

(d) requires unscheduled inpatient hospitalisation;

(e) prolongs hospitalisation;

(f) is a congenital anomaly/birth defect; or

(g) is an important medical event that jeopardizes the subject and requires medical/surgical intervention to prevent one of the outcomes listed in this definition which relate directly to being in the BISTRO study. E.g. including additional unscheduled haemodialysis sessions as outpatients, falls leading to admission or surgery

10.1 Safety reporting exceptions

- The SAE form should **not** be used to report expected common symptoms and/or complications of chronic kidney disease and haemodialysis; e.g., anaemia, lethargy, headaches, muscle cramps, fluid imbalance, weight loss, malnutrition, dialysis access problems (unless it is believed that they resulted from being in the BISTRO study).

10.2 Responsibilities for safety reporting

10.2.1 Principal Investigator (PI) at centre

- Using medical judgement in assigning seriousness, causality.
- Ensuring that all SAEs are reported to the Sponsor immediately or within 24 hours on becoming aware
- Ensuring that SAEs are recorded and reported to the Sponsor in line with requirements of the protocol.

10.2.2 Chief Investigator (CI) delegate or independent reviewer

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness and causality where it has not been possible to obtain local medical assessment.
- Review of all SAEs as detailed in the trial monitoring plan.

10.2.3 Sponsor

- Central data collection and verification of SAEs.
- Ensuring SAEs are reported to the trial oversight committee and DMC.
- Ensuring that SAEs are reported in REC annual reports.

10.3 Death notification form

All deaths must be recorded on the death detail case report form.

11. STATISTICS AND DATA ANALYSIS

11.1. Sample size calculation

11.1.1 Primary outcome (time to anuria)

It can be determined from cohort studies and data collection from a large dialysis unit of 615 patients that the proportion of incident centre-based HD patients anuric by one year is in the region of 30% (range 25-67%) (7, 37, 38, 39, 40). Given a cumulative incidence of anuria of 30% in the control group and 20% in the treatment group and accounting for 11% competing risks (based on death and transplantation data extrapolated from the 2013 UKRR report (41) – assuming exponential decline, proportional hazards, 90% power and 5% two-tailed significance – 185 events are required to detect the corresponding hazard ratio. This will require a total of 516 patients to be randomised 1:1, allowing for a 5% loss to follow up.

11.1.2 Secondary outcome

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). At the same 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 assessments at 0, 1, 2, 3, 5, 7, 9, 11 and 13 months, and a (conservative) autocorrelation of 0.30.

11.2 Planned recruitment rate

Centre-based haemodialysis patients will be recruited from a mixture of 30 main and satellite dialysis centres. This will require a recruitment rate of 1.4 patients per month per centre, or 15-20 patients over the 12-month recruitment period. Screen failures will be captured in the paper CRF.

11.3 Statistical analysis plan

Statistical significance will be set at $p \leq 0.05$ (two-tailed) for all analyses, and estimates will be presented with 95% confidence intervals. Analyses will be in accordance with a pre-determined statistical analysis plan.

11.3.1 Summary of baseline data

Baseline data will be presented, for each treatment group and for the total sample, as count (percentage), mean (standard deviation), or median (interquartile range), as appropriate.

11.3.2 Primary outcome analysis

Time to anuria will be analysed on an intention-to-treat basis (as the primary analysis) and an as treated basis (as the secondary analysis) using competing risks survival analysis (42), to estimate the relative risk (as expressed by the sub-hazard ratio) of the outcome (anuria) in participants where BI is used compared to control participants, accounting for the competing risks (death, transplantation). Participants undergoing modality change or recovery will be censored at the point of treatment switch. The analysis will control for known baseline covariates affecting residual function (7, 39), i.e. age, race, sex, comorbidities (separately or using a validated scoring system), antihypertensive drug use (ACE inhibitors/ARBs, calcium antagonists) and diuretic use.

11.3.3 Secondary outcomes analysis

Difference in rate of decline in renal clearance will be analysed using a random slopes linear mixed model, with adjustment for baseline characteristics, as for the primary endpoint. We will determine the effect of randomisation on the 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. intra-dialytic weight gain, which following adjustment for comorbidity is a surrogate measure of patient survival.

Other secondary outcomes will be analysed by appropriate methods.

11.4 Subgroup analyses

Pre-specified subgroup analyses will be limited to comorbid conditions that affect management of fluid status – specifically heart failure and diabetic status – and will be assessed through an interaction term in the model (43). They will also explore, in a separate analysis, the effects of unit-level practice patterns as defined by our pre-study survey of 66 dialysis units, e.g. routine use of blood volume monitors, BI, dialysate sodium concentration, including stated approaches to fluid management (e.g. intention to reduce weight in order to avoid the use of antihypertensive drugs). Where appropriate, an instrumental variable approach will be employed for this purpose, as developed by the Dialysis Outcomes and Practice Patterns Study (44).

11.5 Missing data and sensitivity analyses

For the ITT analyses, missing data will be accounted for by using appropriate techniques, such as multiple imputation, depending on the extent and type of missing items and patterns of missingness (45). A sensitivity analysis will be performed using only complete data (46), so as to examine the effect of the assumptions underlying multiple imputation of missing values.

Additionally, one or more per protocol sensitivity analyses will be carried out (where not already specified), such as an 'as treated' analysis, where participants are analysed according to the intervention actually received, rather than that to which they were randomized, and an 'adherers only' analysis, where the analysis is restricted to those participants who received the interventions to the extent specified in the trial protocol.

11.6 Interim analysis and criteria

If the study intervention really provides substantial benefit or harm, this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that the study intervention is definitely effective, ineffective, or adverse. To protect against this, during the period of recruitment to the study, the DMC will review interim analyses along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will advise the chair of the Trial Steering Committee (TSC) and the oversight committee (IADB) if, in their view, the accruing evidence from the trial has provided "proof beyond reasonable doubt" that for all, or for some, types of patient the study intervention is definitely indicated or definitely contraindicated in terms of a difference in the major outcomes. Determining appropriate criteria of proof beyond reasonable doubt will be the prerogative of the DMC, but it is anticipated that one of the commonly used approaches to interim analysis will be used as a stopping rule (e.g. Haybittle-Peto approach, O'Brien-Fleming approach). The number of interim analyses will be determined by the DMC and, as the primary outcome is survival, their timing will relate to the number of events that have accrued rather than the number of participants that have been recruited (47). As repeated analyses of a dataset lead to Type 1 error inflation, an alpha spending function will be identified to ensure that the nominal alpha is maintained, by allocating the nominal alpha across the analyses in relation to an information fraction – the amount of information accumulated on the outcome concerned at the time of the interim analysis, as a fraction of the total information for the study (48). Some such functions require the number of interim analyses to be pre-specified (e.g. O'Brien-Fleming), whereas others (e.g. Haybittle-Peto) do not. Accordingly, the alpha spending function to be used, and other aspects of the interim analyses, will be discussed and agreed with the DMC before the trial starts in relation to their intended strategy regarding interim analyses. This will include consideration of the specific distribution of the alpha spend; e.g. a conservative approach to monitoring specifies wide boundaries for the test statistic early in the process and thereby spends a small amount of alpha, in order to retain a substantial amount for the final analysis (49).

11.7 Economic evaluation

An economic evaluation will be undertaken to explore the relative cost-effectiveness of *BI-informed post dialytic fluid management* against *current management without BI*.

In line with recommendations, the base-case analysis will adopt a health care system (payer's) perspective by considering costs incurred by the NHS and personal social services (50). Results of the analysis will be presented in terms of cost per additional quality-adjusted life year (QALY) gained. Additional analyses will be undertaken from a wider societal perspective, by considering private (patient-incurred) costs and productivity loss, using

added questions from a modified Client Services Receipt Inventory developed for patients with chronic kidney disease. Costs and benefits accruing in the future will be discounted to reflect positive time preference. A trial-based analysis will be carried out alongside the BISTRO study to determining the cost-effectiveness of the compared strategies on the basis of patient-level data obtained within the study period. Conditionally on the availability of appropriate data, a 'model-based' analysis will be carried out to assess costs and effects likely to accrue beyond the study follow-up period.

11.7.1 Resource use and costs

Data on use of health care resources will be collected alongside the BISTRO trial, through case report forms and participant questionnaires. Relevant resource use will include: (i) expenditures for purchasing BI devices; (ii) costs of training professionals to operate BI devices; (iii) cost of measuring the primary endpoint; (iv) costs due to use of secondary care, including outpatient appointments, hospital stay and cardiovascular interventions, (v) costs related to use of primary care services, including GP appointments, (vi) patient personal costs (out-of-pocket payments) and (vii) costs associated with productivity loss.

Use of health care resources will be weighted by unit cost values taken from up-to-date national sources and tariffs, including the Unit Cost of Health and Social Care report (51), the British National Formulary (52) and the NHS Reference Cost Schedules (53).

11.7.2 Outcomes

The main outcome in the economic evaluation will be the QALY, a measure that combines expected survival and quality of life (QoL). QoL will be obtained through participants' responses to the EuroQol EQ-5D-5L (21) and SF-12 (54) instrument at baseline and 3-monthly thereafter. Each participant's health status descriptions obtained from these instruments will be translated into a single, preference-based (utility) index score using a UK specific value set for the EQ-5D-5L (55) and the SF-6D scoring algorithm for SF-12 (31). QALYs will be calculated as the area under the curve connecting utility scores reported at different time points. Deceased participants will be assigned a utility of zero from the date of death.

11.7.3 Analysis

This will be conducted on an intention-to-treat basis. Missing data will be accounted for by using appropriate techniques, as noted above. As the distribution of cost is usually skewed by the existence of patients with very high costs, the calculated mean per-patient cost will be given alongside confidence intervals obtained through non-parametric bootstrap methods (56). Incremental analysis will be undertaken to calculate the difference in costs and the difference in outcomes (QALYs) associated with the compared fluid management options. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the extra cost for an additional unit of outcome. To account for the inherent uncertainty due to sampling variation, the joint distribution of differences in cost and outcomes (QALYs) will be derived by carrying out a large number of non-parametric bootstrap simulations.(57) The simulated cost and outcome pairs will be depicted on a cost-effectiveness plane and will be plotted as cost-effectiveness acceptability curves (CEACs) (58). CEACs will show the probability of the BI-guided and standard fluid management options being cost-effective across a range of possible values of willingness to pay for an additional QALY.

11.7.4 Model-based analysis

In addition to the trial-based evaluation, a model-based analysis will be conducted to consider costs and benefits likely to accrue over a lifetime time horizon. A decision analytic model, possibly in the form of a Markov model, will be built to serve as a framework for quantifying long-term costs and outcomes. It is envisaged that the model will be populated with data from various sources, including patient-level data obtained from the trial and information from a review of the literature. Both deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and plausible variations in key assumptions and employed analytical methods (59). If appropriate, value of information analysis (expected value of perfect information and expected value of partial perfect information) will be conducted to infer the benefits from obtaining further information for all or a subset of the parameters affecting the choice of fluid management strategies (60).

12. DATA HANDLING

A dedicated trial database will be developed and maintained on a secure password protected network environment at Keele University Clinical Trials Unit (registered with UK Clinical Research Collaboration) and managed by a Senior Data Manager and will be the final repository for the data collection.

12.1 Source data

Source data is defined as ‘All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)’ (61).

12.1.1 Case report forms

A case report form (CRF) is a form on which individual participant data required by the trial protocol are recorded. The BISTRO trial will use a paper-based case report form, developed by Keele University CTU, primarily because it will more easily enable capture of fluid status assessments, which are usually conducted at the bedside rather than at a computer station. Data collected via these forms will be kept to a minimum as it will be supported by enriched datasets collected via the Renal Registry and BI device proprietary software.

12.1.2 User requirements

Research nurses at the sites will be trained in the completion of CRFs, administration to participants of self-reported outcome forms and the completion of data entry into the algorithm that will calculate residual kidney function (GFR) and the completion of the Montreal Cognitive Screening Assessment (MoCA) assessment.

The GFR will be calculated using a GFR calculator, provided in spreadsheet format, which stores the raw data and will be stored electronically on a secure network drive in individual participant files at the local site. The GFR spreadsheet file will be emailed to Keele CTU for storage at the same time as the paper CRF is sent to Keele CTU.

CRFs will be supported by a user manual and requests for clarification will be supported through a dedicated email account overseen by the trial manager.

12.2 Participant questionnaire data

The research nurse will enter the centre ID number, the participant's study ID and the visit in months to each participant self-report questionnaire. The questionnaires will be given to participants and returned when they routinely attend for dialysis treatment. Participants will be asked to forward their completed questionnaires in a sealed envelope to the research nurse at the dialysis unit. These Questionnaires with the Montreal Cognitive Screening Assessment (MoCA) will be posted from each dialysis unit in batches, on a monthly basis, to the Keele CTU. Question data entry will be captured using electronic data capture (Teleform).

12.3 Data handling and record keeping

Completed CRFs will be sent, at a minimum monthly, to the Keele CTU data management team in pre-paid envelopes provided to each centre. The CTU data administrator will enter CRF data to the trial database around the time that they are received. All protocol deviations are expected to be reported to Keele CTU as soon as the Investigator has become aware of the event. These will be reported accordingly to Keele University's SOPs (refer to section 14.1.3).

A Data Manager based at the Keele University CTU will oversee all responsibilities delegated to the CTU for data management and data entered to the trial database.

All dialysis event data that are routinely collected via the UKRR will be transferred to an electronic encrypted password protected file and sent via to a secure e-mail address to the data management team at the Keele University CTU at an agreed annual time point.

12.4 Access to data

Direct access to trial-specific data only will be given to authorised representatives of the Sponsor to permit trial monitoring and audit.

12.5 Archiving

At the end of trial, archiving of essential study documents at participating sites will be authorised by the sponsor following submission of end of study reports which will be for five years after the end of the trial. Destruction of essential documents requires authorisation from the Sponsor.

13. MONITORING

The Keele CTU data management team will perform data quality checks of CRF data. Data queries will be entered to a log which will be sent to the trial manager, who will work with each site to resolve data queries in a timely fashion and provide further training as required. This, along with safety reports, will inform a risk-based approach towards assessing a need for any onsite monitoring visits. Trial monitoring reports will be reviewed by the Trial Management Group, Data Management Committee and Trial Steering Committee – as specified in the "*Roles and Responsibilities*" sub-section of "*General Information*" section of this protocol.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) review & report requirements:

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and patient self-report questionnaires
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed by NHS R&D departments before they can be implemented in practice at sites)
- All correspondence with the REC will be retained in the Sponsor Trial Master File/ local Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

14.1.2 NHS Permission

NHS permission will be sought via the Health Research Authority Approval (HRA) process and letter of HRA approval. Agreements will need to be fully executed between the Sponsor and local centres before patients can be approached for recruitment.

14.1.3 Protocol Deviations and Violations

Protocol Deviation: Accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff. A deviation may be due to the research subject's non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher.

Examples of a deviation include but are not limited to:

- A rescheduled study visit
- Failure to collect an ancillary self-report questionnaire
- Subject's refusal to complete scheduled research activities

Protocol Violation: Accidental or unintentional change to, or non-compliance with the REC approved protocol without prior sponsor and REC approval. Violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data.

Examples of protocol violations include but are not limited to:

- Failure to obtain valid informed consent (e.g. obtained informed consent on a non-date stamped form)

- Loss of laptop computer that contained identifiable, private information about subjects
- Not following inclusion/exclusion criteria

Incident reporting

Each investigator is reminded to report any Incident to the Trust as per their local Trust Incident reporting policy under the Research Governance Framework 2005.

Non-serious incident: Participating sites are expected to comply with local Trust policies for reporting.

Serious Breaches of the Protocol and/or GCP: Participating sites are expected to report these breaches to Keele CTU as soon as the Investigator has become aware of the event. These will be reported accordingly to Keele University's SOPs.

14.2 Peer Review

The study has been funded via a National Institute for Health Research Health Technology Assessment Programme and hence has undergone external peer review by appropriate patient and healthcare professional representatives.

14.3 Public and Patient Involvement

- Grant Application and Study Set Up: David Coyle, the Steering Group Patient representative, has helped on the grant application preparation and in the development of patient related documents for the study set up.

- Management of the Research: David Coyle, the Steering Group Patient representative, and Professor Martin Wilkie will co-chair a Patient Advisory Group who are funded to meet regularly and provide advice, support and oversight of patients' involvement throughout the study. This group will report regularly to the steering group (TSC) and Oversight Committee (IADB).

- Undertaking/analysing the research: David Coyle is a member of the steering group and will participate fully in the decision of the group and interpretation of results.

- Dissemination of the Results: David Coyle is experienced in producing materials to aid implementation of the findings to patients, and with support of the key stakeholders represented by the enhanced oversight committee will ensure that there is PPI input into this aspect of dissemination.

14.4 Data protection and patient confidentiality

A unique centre number will be allocated to each centre. A study number will be used to identify each participant's research data. This will be stored securely in the local centre and in the Keele University Clinical Trials Unit. The study number and participant identifiers (NHS identifier, name, date of birth) will also need to be shared with the UK Renal Registry (UKRR) to enable linkage of the main BISTRO trial database with the UK Renal Registry/HES/ONS linked database, as outlined in the patient information sheet and consent form. UKRR/HES/ONS linked data will be transferred to the Keele University Clinical Trials Unit in an electronic encrypted password protected file via a secure internet server.

Copies of each patient signed consent form will be sent to the Keele University CTU separately to the CRF data, where they will also be stored separately.

14.5 Indemnity

The trial is sponsored by Keele University and therefore Keele University will be liable for negligent harm caused by the design of the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a trial, and the NHS organisation remains liable for clinical negligence and other negligent harm to patients under this duty of care.

Agreements between the sponsor and participating NHS organisations detailing trial conduct and the responsibilities to be honoured by each party will be fully executed before the trial can start at the local NHS Trust.

14.6 Amendments

If the sponsor wishes to make a substantial amendment to the documents that supported the original application for REC and HRA approvals, the sponsor must submit a valid notice of amendment to the REC for consideration. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to Health Research Authority and NHS R&D departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D. Centres should ensure amendment history for most recent trial documents are recorded and tracked in accordance with local SOP.

15. DISSEMINATION POLICY

The following outputs are planned:

- Publication of the trial protocol (in an open access journal to coincide with the start of the trial).
- Efficacy of the intervention, to include primary and selected secondary endpoints, especially dialysis related efficacy, safety and significant events.
- Economic evaluation of the intervention and analysis of the benefits of residual kidney function.
- In-depth analysis of effect of the intervention on the patient activation and engagement with fluid management
- The impact of dialysis unit practice patterns on primary and secondary endpoints.
- Publication of the clinically validated fluid assessment tool and associated educational material, with the potential to develop this into an application suitable for hand-held devices

The dissemination plan will be developed in close collaboration with the study oversight committee (*Advisory and Dissemination Board* facilitated by Kidney Research UK on behalf

of the UK Kidney Research Consortium) and the steering group. Routes of dissemination will be as follows:

National Meetings (to include study updates and findings):

Renal Association and British Renal Society (e.g. annual Kidney Week, usually multidisciplinary meeting covering all aspects of nephrology and dialysis treatment).

International Meetings (via submitted abstracts):

American Society of Nephrology, European Dialysis and Transplantation Association/European Renal Association, European Dialysis and Transplantation Nurses Association, International Society of Nephrology.

16. REFERENCES

1. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med [Internet]. 2002 Dec 19 [cited 2015 May 17];347(25):2010–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12490682

2. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant [Internet]. 2009 May [cited 2014 Jun 28];24(5):1574–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2668965&tool=pmcentrez&rendertype=abstract

3. Pillon L, Piccoli A, Lowrie EG, Lazarus JM, Chertow GM. Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. Kidney Int [Internet]. 2004 Sep;66(3):1266–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15327426

4. Paniagua R, Ventura M-J, Avila-Díaz M, Hinojosa-Heredia H, Méndez-Durán A, Cueto-Manzano A, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. Nephrol Dial Transplant [Internet]. 2010 Feb [cited 2014 Jun 27];25(2):551–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19679559

5. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol [Internet]. 2009 Dec [cited 2015 May 8];4(12):1925–31. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2798881&tool=pmcentrez&rendertype=abstract

6. Movilli E, Gaggia P, Zubani R, Camerini C, Vizzardi V, Parrinello G, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant [Internet]. 2007 Dec [cited 2014 Jun 28];22(12):3547–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17890254

7. Jansen MAM, Hart AAM, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int [Internet]. 2002 Oct [cited 2014 Dec 31];62(3):1046–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12164889

8. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol [Internet]. 2001 Oct;12(10):2158–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11562415

9. Termorshuizen F. Relative Contribution of Residual Renal Function and Different Measures of Adequacy to Survival in Hemodialysis Patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol [Internet]. 2004 Apr 1 [cited 2014 Jun 6];15(4):1061–70. Available from: http://www.jasn.org/cgi/doi/10.1097/01.ASN.0000117976.29592.93

10. Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. The Necosad Study Group. Am J Kidney Dis [Internet]. 1997 May [cited 2014 Dec 31];29(4):584–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9100049

11. Dasgupta I, Farrington K, Davies SJ, Davenport A. UK national survey of practice patterns of fluid volume management in haemodialysis patients: a need for evidence. 2016 Apr; 41: 324-331.

12. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation [Internet]. 2009 Mar 10 [cited 2014 May 30];119(5):671–9. Available from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2773290&tool=pmcentrez&rendertype=abstract

13 Schiffl H, Lang SM, Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. Nephrol Dial Transplant. 2002;17(10):1814–8.

14 Hur E, Usta M, Toz H, Asci G, Wabel P, Kahvecioglu S, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis [Internet]. 2013 Jun [cited 2014 Jun 7];61(6):957–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23415416

15. Daugirdas JT, Greene T, Rocco M V, Kaysen GA, Depner TA, Levin NW, et al. Effect of frequent hemodialysis on residual kidney function. Kidney Int [Internet]. 2013 May [cited 2014 Dec 31];83(5):949–58. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3855839&tool=pmcentrez&rendertype=abstract

16. Van Biesen W, Claes K, Covic A, Fan S, Lichodziejewska-Niemierko M, Schoder V, et al. A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. Nephrol Dial Transplant [Internet]. 2013 Oct [cited 2014 Jun 27];28(10):2620–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078645

17. Lukowsky LR, Mehrotra R, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis. Clin J Am Soc Nephrol [Internet]. 2013 Apr [cited 2015 May 17];8(4):619–28. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3613949&tool=pmcentrez&rendertype=abstract

18. Yeates K, Zhu N, Vonesh E, Trpeski L, Blake P, Fenton S. Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. Nephrol Dial Transplant [Internet]. 2012 Sep [cited 2014 May 30];27(9):3568–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22391139

19. NICE quality standard 5. Chronic kidney disease. guidance.nice.org.uk/qs5. 2014;(November).

20. NICE quality standard 72. Renal replacement therapy services. guidance.nice.org.uk/qs72. 2014;(November).

21. Greene J, Hibbard JH. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. J Gen Intern Med [Internet]. 2012 May [cited 2014 Nov 6];27(5):520–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3326094&tool=pmcentrez&rendertype=abstract

22. Hibbard J, Gilburt H. Supporting people to manage their health An introduction to patient activation. King's Fund. 2014;(May).

23. Gudivaka R, Schoeller DA, Kushner RF, Bolt MJG, Thijssen S, Zhu F, et al. Single- and multifrequency models for bioelectrical impedance analysis of body water compartments disease disease Single- and multifrequency models for bioelectrical impedance analysis of body water compartments. 2012;1087–96.

24. Macdonald JH, Phanish MK, Marcora SM, Jibani M, Bloodworth LLO, Holly JMP, et al. Muscle insulin-like growth factor status, body composition, and functional capacity in hemodialysis patients. J Ren Nutr [Internet]. 2004 Oct [cited 2015 May 17];14(4):248–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15483786

25. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body composition spectroscopy in health and disease. Physiol Meas

[Internet]. 2006 Sep [cited 2015 Apr 21];27(9):921–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16868355 18.

26. Bedogni G, Malavolti M, Severi S, Poli M, Mussi C, Fantuzzi a L, et al. Accuracy of an eightpoint tactile-electrode impedance method in the assessment of total body water. Eur J Clin Nutr [Internet]. 2002 Nov;56(11):1143–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12428182 19.

27. Chertow GM, Lowrie EG, Wilmore DW, Gonzalez J, Lew NL, Ling J, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. J Am Soc Nephrol. 1995;6(1):75–81.

28. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant [Internet]. 2009 May [cited 2014 Jun 28];24(5):1574–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2668965&tool=pmcentrez&rendertype=abstract

29. Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V. Importance of normohydration for the long-term survival of haemodialysis patients. Nephrol Dial Transplant [Internet]. 2012 Jun [cited 2014 Aug 15];27(6):2404–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22253067

30. NICE Medtech Innovation Briefing MIB41. The BCM – Body Composition Monitor for managing fluid in people having dialysis. nice.org.uk/guidance/mib4113. 2015; (October)

31. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res [Internet]. 2011 Dec [cited 2014 Nov 3];20(10):1727–36. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3220807&tool=pmcentrez&rendertype=abstract

32. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care [Internet]. 2004 Sep [cited 2015 May 17];42(9):851–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15319610

33. www.pos-pal.org, © 2012 Cicely Saunders Institute, accessed 12th Jul 2016

34. Greene J, Hibbard JH. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. J Gen Intern Med [Internet]. 2012 May [cited 2014 Nov 6];27(5):520–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3326094&tool=pmcentrez&rendertype=abstract

35. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989;64(10):651-4.

36. Tiffin-Richards FE, Costa AS, Holschbach B, Frank RD, Vassiliadou A, Krüger T, Kuckuck K, Gross T, Eitner F, Floege J, Schulz JB, Reetz K. The Montreal Cognitive Assessment (MoCA) - a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. PLoS One. 2014 Oct27;9(10):e106700

37. Fernández-Lucas M, Teruel-Briones JL, Gomis-Couto A, Villacorta-Pérez J, Quereda-Rodríguez-Navarro C. Maintaining residual renal function in patients on haemodialysis: 5-year experience using a progressively increasing dialysis regimen. Nefrologia [Internet]. 2012 Jan [cited 2014 Dec 31];32(6):767–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23169359

38. Lin Y-F, Huang J-W, Wu M-S, Chu T-S, Lin S-L, Chen Y-M, et al. Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. Nephrology (Carlton) [Internet]. 2009 Feb [cited 2014 Dec 17];14(1):59–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19019171

39. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol [Internet]. 2000 Mar [cited 2014 Dec 31];11(3):556–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10703680

40. McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. Kidney Int. 2002;61(1):256–65.

41. Pruthi R, Steenkamp R, Feest T. UK Renal Registry 16th annual report: chapter 8 survival and cause of death of UK adult patients on renal replacement therapy in 2012: national and centre-specific analyses. Nephron Clin Pract [Internet]. 2013 Jan [cited 2014 Dec 31];125(1-4):139–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24662172

42. Pintilie M. Dealing with competing risks: testing covariates and calculating sample size. Stat Med [Internet]. 2002 Nov 30 [cited 2015 May 5];21(22):3317–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12407674

43. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technol Assess [Internet]. 2001 Jan [cited 2015 May 12];5(33):1–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11701102

44. Pisoni RL, Arrington CJ, Albert JM, Ethier J, Kimata N, Krishnan M, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. Am J Kidney Dis [Internet]. 2009 Mar [cited 2015 May 11];53(3):475–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19150158

45. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess [Internet]. 1999 Jan [cited 2015 May 17];3(2):1–134. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10448202

46. Wright CC, Sim J. Intention-to-treat approach to data from randomized controlled trials: a sensitivity analysis. J Clin Epidemiol [Internet]. 2003 Sep [cited 2015 May 17];56(9):833–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14505767

47. Polcock SJ. Clinical Trials: a Practical Approach. John Wiley, Chichester

48. De Mets DL, Lang G. The alpha spending function approach to interim data analyses. In Thall PF (ed) Recent advances in clinical trial design and analysis. Kluwer, Boston

49. Whitehaed J. The design and analysis of sequential clinical trials. 2nd ed. John Wiley, Chichester

50. NICE. Guide to the methods of technology appraisal 2013. London: National Institute for Health and Excellence. 2013.

51. L C. Unit Cost of Health and Social Care. Available from:http://www.pssru.ac.uk/pdf/uc/uc2014/uc2014.pdf [Internet]. Available from: http://www.pssru.ac.uk/pdf/uc/uc2014/uc2014.pdf

52. Association BM. British National Formulary. London BNA RPS. 2005;

53. Health D of. National Schedule of Reference Costs 2013-2014. Available from https//www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 [Internet]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014

54. Ware J, Kosinski S, Keller M. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 43(3): 220-233

55. Van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health [Internet]. Jan [cited 2015 Apr 10];15(5):708–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22867780

56. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med [Internet]. 2000 Dec 15 [cited 2015 May 17];19(23):3219–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11113956

57. Glick HA, Jalpa DA, Sonnad SS PD. Economic evaluation in clinical trials. Oxford University Press; 2007.

58. Barton G, Briggs A, Fenwick E. Optimal Cost-Effectiveness Decisions: The Role of the Cost-Effectiveness Acceptability Curve (CEAC), the Cost-Effectiveness Acceptability Frontier (CEAF), and the Expected Value of Perfection Information (EVPI). Value in Heath. 2008;11(5):886–97.

59. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making. Health Technol Assess [Internet]. 2009 Jun [cited 2015 May 17];13(29):iii, ix – xi, 1–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19500484

60. Claxton K, Palmer S, Longworth L, Bojke L, Griffin S, McKenna C, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. Health Technol Assess [Internet]. 2012 Jan [cited 2015 May 17];16(46):1–323. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23177626

61. ICH Harmonised Tripartite Guideline : Guideline for Good Clinical Practice. 1996 Jun E6 (R1) V4

APPENDICES

APPENDIX 1

STANDARD OPERATING PROCEDURE

BISTRO Trial: Primary Outcome. Measurement of residual kidney function in haemodialysis patients

This procedure has been adapted from a standard operating procedure produced by The Leeds Teaching Hospitals NHS Trust by permission of the author Dr Elizabeth Lindley, also a member of the BISTRO Trial Steering Committee

SCOPE

This procedure describes the techniques for measuring residual renal function (RRF) in patients to be recruited to the BISTRO TRIAL. This includes:

- patients with CKD who have not yet but are about the start haemodialysis.

-patients having thrice weekly, twice weekly and once weekly haemodialysis.

TRAINING REQUIREMENTS

Staff organising urine collections must be familiar with this procedure to ensure that the appropriate blood samples are taken, the participant receives the correct instructions and the labs perform the right tests. All data should be recorded on the BISTRO trial case report form.

Staff analysing urine collections need to be able to locate lab results, use the 'Urine Collection GFR Calculator' (included separately in excel format) and enter data into the trial case report form.

WARNINGS AND SPECIAL PRECAUTION

The standard precautions for handling bodily fluids as per local policy should be followed.

When obtaining urine U&E data, ensure that the results are concentrations (mmol/L) not 24 hour excretion (mmol/day).

EQUIPMENT REQUIRED

One or two urine collection canisters for collections (and disposable jugs for female participants)

'Urine collection GFR calculator' (in spreadsheet format and provided by the BISTRO Trial Manager

Patient instructions

Local hospital biochemistry form. To be completed and labelled in accordance with routine practice.

HEALTHCARE PROFESSIONAL INSTRUCTIONS

Note that urine collections always start and end with an empty bladder. So the start time is the last time the patient emptied their bladder before they started to collect urine in the canister NOT the first time they use the canister.

Carrying out a 24 hour urine collection

This is the test used to measure residual kidney function in patients that have not started dialysis but are expected to start soon. Although it is called a 24-hour collection, it is better for patients to finish the collection when they need to pass urine naturally at about the same time of day as they started. It is important for the patient to note the time they start (after a pee in the loo) and the time of the last pee that went into the canister so that you can calculate the collection time. The collection should be done the day before they are due to have blood samples taken in clinic or in the community. The instructions assume that the patient will start the collection after the first pee in the morning but an alternative period of approximately 24 hours could be arranged if preferred.

The 'last-day' collection spreadsheet in the GFR calculator that is used when patients are having dialysis less than twice a week can be used to calculate GFR for patients who are not yet on dialysis. Enter the urea and creatinine concentrations from the blood sample and the clinic weight in the red section of the GFR calculator spreadsheet.

Instructions for data collection

1. Plan the collection for the day before the patient is due to have routine blood tests for urea and creatinine concentrations.

2. Check that the patient's height has been recorded in centimetres. If not, measure and record it.

3. Record the patient's weight in kg.

4. Give the patient the instruction sheet '**PATIENTS' INSTRUCTIONS FOR DOING A URINE COLLECTION FOR 24 HOURS'**

5. Give the patient a canister (and a jug if required) and make sure that they know they need to collect all the urine they pass for approximately 24 hours.

6. The urine collection should be started in the morning when the patient wakes up, after they have emptied their bladder in the loo for the first time.

7. Ask the patient to write the time they pee in the loo on the label attached to the canister. This is the start time.

8. Once the collection has started, the patient must add all urine to the canister until the following morning.

9. The first pee the following morning needs to go into the canister so that the patient ends the collection with an empty bladder.

10. Ask the patient to write the time they last used the canister on the label.

11. Either send the complete collection to the lab for measurement of volume and urine urea and creatinine concentration **or**

    Use an empty canister to tare the scales and record the weight of the collection in grams or the volume in mL then transfer a sample of urine into a universal tube (or whatever you normally use for random urine tests) and send the sample to the lab for measurement of volume and urine urea and creatinine concentration.

12. Send the blood sample to the lab for serum urea and creatinine concentrations.

13. When the lab results come back follow the instructions provided with the **Urine collection GFR calculator** to calculate GFR, using the '**Last day collection'** option.

Carrying out an interdialytic urine collection

This is the test used to measure residual kidney function in patients who are dialysing 3 times a week. As the patient will have to collect all the urine they pass between the end of one session and the start of the next, it is usually done over one of the short breaks.

The ideal time is just after the monthly bloods because samples are needed for both sessions to calculate the average serum urea and creatinine concentration during the collection.

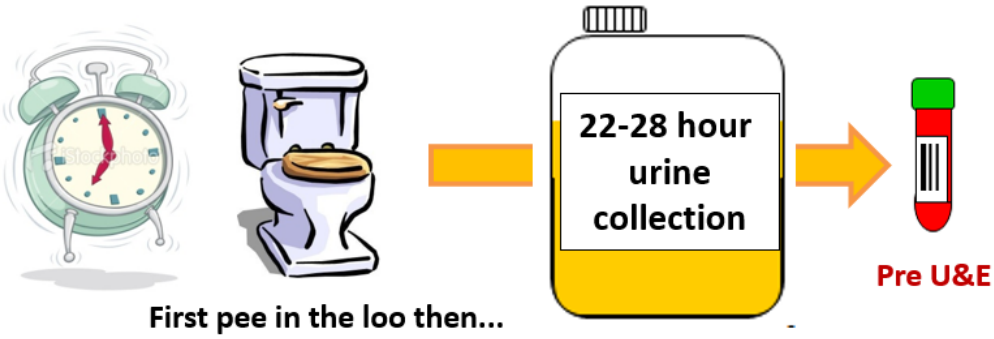
A collection can be made over the long break if the patient prefers this option (sometimes working patients prefer to collect over the weekend). The calculator supports 48 and 72 hour collections.

Instructions for data collection

1. If you don't have a height for the patient, measure or estimate it.
2. Ask the patient to empty their bladder (in the loo) before the first HD session.
3. Take pre- and post-dialysis blood samples and send them to the lab for urea and creatinine concentrations (serum U&Es).
4. Make sure the patient's post-dialysis weight is recorded.
5. Give the patient a canister (and, a jug if required) and make sure that they know they need to collect **all** the urine they pass until they next come for dialysis.
6. Make sure that the patient empties their bladder (into the canister) before the second HD session.
7. Take a pre-dialysis blood sample.
8. Either send the complete collection to the lab for measurement of volume and urine urea and creatinine concentration **or**

   Use an empty canister to tare the scales and record the weight the collection in grams or the volume in mL then transfer a sample of urine into a universal tube (or whatever you normally use for random urine tests) and send the sample to the lab for measurement of volume and urine urea and creatinine concentration.
9. Send the pre-dialysis blood sample to the lab for serum urea and creatinine concentrations.
10. When the lab results come back follow the instructions provided with the **Urine collection GFR calculator** to calculate GFR.

Carrying out a 'last day' urine collection



This is the test used to measure residual kidney function in patients who are dialysing once or twice a week. The patient needs to start with an empty bladder about 24 hours before they are due for dialysis, then collect all the urine they pass until the start of the session.

For twice weekly dialysis, the collection should be done at the end of the longer break when the serum levels are closest to steady state so that the pre-dialysis sample is approximately the average urea and creatinine concentrations during the collection.

Instructions for data collection

1. If you don't have a height for the patient, measure or estimate it.
2. Decide on the day that the patient will start the collection and write it on the canister followed by 'Time = ' (e.g. 'Thursday 2nd Time = ').
3. If the patient has dialysis on a day-time shift, ask them to empty their bladder **in the loo** when they get up in the morning and write the time on the canister.
4. If the patient has dialysis on a twilight or night shift, ask them to empty their bladder **in the loo** at about tea-time and write the time on the canister.
5. Give the patient the canister (and a jug if required) and make sure that they know they need to collect **all** the urine they pass from the time they write on the canister until they empty their bladder just before the dialysis session.
6. Take a pre-dialysis blood sample and record the patient's post-dialysis weight. Calculate and record the time from the start time on the canister to the HD session.
7. Either send the complete collection to the lab for measurement of volume and urine urea and creatinine concentration **or**

   Use an empty canister to tare the scales and record the weight of the collection in grams or the volume in mL then transfer a sample of urine into a universal tube (or whatever you normally use for random urine tests) and send the sample to the lab for measurement of volume and urine urea and creatinine concentration.
8. Send the pre-dialysis blood sample to the lab for urea and creatinine concentrations.
9. When the lab results come back follow the instructions provided with the **Urine collection GFR calculator** to calculate GFR.

Insert local hospital header

BioImpedance Spectroscopy To Maintain Renal Output

BISTRO Trial

PATIENTS' INSTRUCTIONS FOR DOING A URINE COLLECTION FOR 24 HOURS

Your kidney doctor or nurse has asked you to do a urine collection for approximately 24 hours. The collection doesn't have to be exactly 24 hours but you need to record how long it was. The results will be used in the BISTRO study. You will already have received an information sheet telling you about the study and signed a consent form. Please follow the instructions below. Please ask your nurse if you are unsure about anything.

1. Empty your bladder in the loo when you get up in the morning and write the time on the canister.
2. Please collect all of the urine you pass for approximately 24 hours.
3. You may find it easier to collect urine in a jug and then pour it into the container. Please ask the staff for a jug, if one has not been provided.
4. Keep the container properly closed (in a cool place if possible) when you are not using it.
5. If you need to pass faeces (open your bowels) as well as urine, please try to collect the urine first. It is important that the urine collection is not contaminated with faeces.
6. Finish by collecting the first urine passed the next morning and adding it to the canister.
7. Please note the time of the final collection on the canister label, even if it is not the same time as when collection began the day before.
8. Return the collection bottle to the clinic as instructed by the hospital staff.

Insert local hospital header

BioImpedance Spectroscopy To Maintain Renal Output

BISTRO Trial

PATIENTS' INSTRUCTIONS FOR DOING A URINE COLLECTION INBETWEEN HAEMODIALYSIS SESSIONS

Your kidney doctor or nurse has asked you to do a urine collection in between 2 dialysis sessions. The results will be used in the BISTRO study. You will already have received an information sheet telling you about the study and signed a consent form. Please follow the instructions below. Please ask your dialysis nurse if you are unsure about anything.

1. For a dialysis-to-dialysis collection, please empty your bladder before the start of your dialysis session, collect ALL the urine that you pass until the next dialysis.
2. You may find it easier to collect urine in a jug and then pour it into the container. Please ask the staff for a jug, if one has not been provided.
3. Keep the container properly closed (in a cool place if possible) when you are not using it.
4. If you need to pass faeces (open your bowels) as well as urine, please try to collect the urine first. It is important that the urine collection is not contaminated with faeces.
5. When you next come for dialysis, try to empty your bladder just before the session to complete your urine collection.
6. Hand the container to your nurse before dialysis. It is a reminder to the staff that you need a pre-dialysis blood sample to go with the collection.

Insert local hospital header

BioImpedance Spectroscopy To Maintain Renal Output

BISTRO Trial

PATIENTS' INSTRUCTIONS FOR DOING A URINE COLLECTION THE DAY BEFORE A HAEMODIALYSIS SESSION

Your kidney doctor or nurse has asked you to do a urine collection starting the day before a dialysis session. The results will be used in the BISTRO study. You will already have received an information sheet telling you about the study and signed a consent form. Please follow the instructions below. Please ask your dialysis nurse if you are unsure about anything.

1. If you have dialysis in the morning or the afternoon, empty your bladder in the loo when you get up in the morning and write the time on the canister.
   OR
   If you have dialysis on a twilight or night shift, empty your bladder into the loo at about tea-time and write the time on the canister.

2. Please collect ALL the urine that you pass until you come for dialysis the next day.

3. You may find it easier to collect urine in a jug and then pour it into the container. Please ask the staff for a jug, if one has not been provided.

4. Keep the container properly closed (in a cool place if possible) when you are not using it.

5. If you need to pass faeces (open your bowels) as well as urine, please try to collect the urine first. It is important that the urine collection is not contaminated with faeces.

6. When you next come for dialysis, try to empty your bladder just before the session to complete your urine collection.

7. Hand the container to your nurse before dialysis. It is a reminder to the staff that you need a pre-dialysis blood sample to go with the collection.

APPENDIX 2: BISTRO STUDY INTERVENTION RECORD

(to be used as a shared decision record between clinician and patient)

BISTRO Trial
v.1.0, 07-Mar-2017

Form 19
BioImpedance Intervention Group

Centre ID: ☐☐☐☐☐

Study ID: ☐☐☐☐

BioImpedance Intervention Group Record

Name of staff member ☐

Visit Date (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

Current target weight: ☐☐☐.☐ kg

Actual pre-dialysis weight: ☐☐☐.☐ kg

Actual post-dialysis weight: ☐☐☐.☐ kg

Pre-dialysis BP (Systolic/Diastolic):
☐☐☐/☐☐☐ mmHg

Post-dialysis BP (Systolic/Diastolic):
☐☐☐/☐☐☐ mmHg

BI measurement date (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐

BI normally hydrated weight ☐☐☐.☐ kg

Target weight adjustment:

☐ Increase to ☐☐☐.☐ kg

☐ No change

☐ Decrease to ☐☐☐.☐ kg

Implementation:
☐ Immediate
☐ Gradual

Other instructions:
☐

Dietary advice and BP medication:
☐ Salt and fluid advice required
☐ Enhanced nutrition required
☐ Weight reduction advice required
☐ Blood pressure medication increased
☐ Blood pressure medication decreased

Next target weight review:
☐ One week
☐ Two weeks
☐ One month
☐ On indication

Did you use any of the following to aid your clinical decision?
☐ Chest X -Ray
☐ ECHO cardiogram
☐ Other- please specify:
☐

Please tick the correct visit box:
☐ Baseline (M0) ☐ Visit 1 (M1) ☐ Visit 2 (M2) ☐ Visit 3 (M3)
☐ Visit 4 (M6) ☐ Visit 5 (M9) ☐ Visit 6 (M12) ☐ Visit 7 (M15)
☐ Visit 8 (M18) ☐ Visit 9 (M21) ☐ Visit 10 (M24) ☐ Other

Contributing factors

Physical indication:
☐ Physical signs of fluid overload (e.g. oedema, full neck veins)
☐ Lack of physical signs of fluid overload or depletion
☐ Physical signs of fluid depletion (e.g. flat neck veins)

Flesh weight changes:
☐ Likely recent weight gain (e.g. better appetite, nutritional support)
☐ Absence of reason(s) for loss or gain of flesh weight
☐ Likely recent weight loss (e.g. poor diet, D&V, hospitalisation)

Fluid gains:
☐ High inter-dialytic fluid gain
☐ Moderate inter-dialytic fluid gain
☐ Low or no inter-dialytic fluid gain

Blood pressure and symptoms during dialysis:
☐ High pre-dialysis blood pressure
☐ Low pre-dialysis blood pressure
☐ Asymptomatic intra-dialytic hypotension
☐ IDH with symptoms (e.g. dizziness, nausea, vomiting)
☐ Cramps

Other clinical issues:
☐ Post-dialysis fatigue
☐ Breathlessness
☐ Clinical indications for keeping as dry as possible (e.g. heart failure)
☐ Clinical indications for not getting too dry (e.g. postural hypotension)

Patient's issues:
☐ Feels better with higher target weight and would like an increase
☐ Feels okay with current target weight does not want to change
☐ Feels better with lower target weight and would like a decrease

Level of confidence in the assessment of fluid status:
☐ Very High
☐ High
☐ Moderate
☐ Low

BioImpedance Control Group Record

Name of staff member

Visit Date (dd/mm/yyyy)

Current target weight: ___.___ kg

Actual pre-dialysis weight: ___.___ kg

Actual post-dialysis weight: ___.___ kg

Pre-dialysis BP (Systolic/Diastolic):
___/___ mmHg

Post-dialysis BP (Systolic/Diastolic):
___/___ mmHg

Target weight adjustment:

- ☐ Increase to ___.___ kg
- ☐ No change
- ☐ Decrease to ___.___ kg

Implementation:

- ☐ Immediate
- ☐ Gradual

Other instructions:

Dietary advice and BP medication:

- ☐ Salt and fluid advice required
- ☐ Enhanced nutrition required
- ☐ Weight reduction advice required
- ☐ Blood pressure medication increased
- ☐ Blood pressure medication decreased

Next target weight review:

- ☐ One week
- ☐ Two weeks
- ☐ One month
- ☐ On indication

Did you use any of the following to aid your clinical decision?

- ☐ Chest X -Ray
- ☐ ECHO cardiogram
- ☐ Other- please specify:

Please tick the correct visit box:

- ☐ Baseline (M0) ☐ Visit 1 (M1) ☐ Visit 2 (M2) ☐ Visit 3 (M3)
- ☐ Visit 4 (M6) ☐ Visit 5 (M9) ☐ Visit 6 (M12) ☐ Visit 7 (M15)
- ☐ Visit 8 (M18) ☐ Visit 9 (M21) ☐ Visit 10 (M24) ☐ Other

Contributing factors

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- ☐ Feels better with lower target weight and would like a decrease

Level of confidence in the assessment of fluid status:

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- ☐ High
- ☐ Moderate
- ☐ Low