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Synopsis

BioImpedance Spectroscopy to maintain Renal Output: the BISTRO randomised controlled trial

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Abstract

Background: Fluid removal is a key component of dialysis treatment but, if excessive, can result in a faster decline in residual kidney function. Prescribing the optimal removal of fluid on dialysis to avoid this is therefore important. Bioimpedance spectroscopy, a bedside device that estimates tissue hydration, might improve this prescription, so reducing the rate of decline in kidney function and improving patient outcomes. We wished to establish the efficacy and cost-effectiveness of bioimpedance in pursuing this treatment strategy.

Methods: We undertook a multicentre, open-label, parallel, individually randomised controlled trial in incident haemodialysis patients, with clinicians and patients blinded to bioimpedance readings in the control group. Eligible patients had a urine output of > 500 ml/day or a glomerular filtration rate > 3 ml/minute/1.73 m^2. Randomisation was 1 : 1 using a concealed automated computer-generated allocation system stratified by centre. Clinical assessments were made monthly for 3 months and then every 3 months for up to 24 months using a standardised proforma in both groups, supplemented in the intervention group by the bioimpedance estimate of the normally hydrated weight. The primary outcome was time to anuria; secondary outcomes were rate in decline of residual kidney function, blood pressure, dialysis-related symptoms (Integrated Palliative Care Outcome Scale-Renal), quality of life (EuroQol) and incremental cost per additional quality-adjusted life-year gained.

Results: Four hundred and thirty-nine patients were recruited and analysed from 34 United Kingdom centres. There were no between-group differences in cause-specific hazard rates of anuria, 0.751 (95% confidence interval 0.459 to 1.229) or subdistribution hazard rates 0.742 (95% confidence interval 0.453 to 1.215). Kidney function decline was slower than anticipated, pooled linear rates in year 1: −0.178 (95% confidence interval −0.196 to −0.159) ml/minute/1.73 m^2/month; year 2: −0.061 (95% confidence interval −0.086 to −0.036) ml/minute/1.73 m^2/month.

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Longitudinal blood pressure, symptoms and patient-reported outcomes did not differ by group. The intervention was associated with £382 (95% confidence interval −£3319 to £2556) lower average cost per patient (price year 2020) and 0.043 (95% confidence interval −0.019 to −0.105) more quality-adjusted life-years and no harm compared to control. A post hoc 5-year analysis found better survival with more residual kidney function at enrolment and at any time over the next 2 years.

Conclusion: The use of a standardised clinical protocol for fluid assessment to avoid excessive fluid removal is associated with excellent preservation of residual kidney function and better medium-term survival in this cohort. Bioimpedance measurements are not necessary to achieve this. Probability of the intervention being cost-effective was 76% and 83% at the willingness-to-pay thresholds of £20,000 and £30,000 per quality-adjusted life-year gained, respectively.

Limitations: The trial did not recruit to target (85%), and the number of primary outcomes was fewer than predicted. The trial was interrupted by coronavirus disease discovered in 2019, during which 193 (6.7%) fluid assessments and 276 (8.1%) kidney function measures but no primary outcomes were missed.

Future work: Associations between age, ethnicity and the decline in residual kidney function require further investigation. BioImpedance Spectroscopy to maintain Renal Output identified centre-level variation in practices related to fluid management in haemodialysis that require evaluation.

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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/RHON2378.

Synopsis

This report describes the research undertaken to establish whether the prescribing of an optimum weight at which a patient should be at the end of a haemodialysis session, usually referred to as the postdialysis target weight (TW_{POST}), when guided by the use of bioimpedance spectroscopy (BI), can reduce the rate in decline of residual kidney function (RKF) and potentially improve patient outcomes. The research was designed and conducted in response to a call by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (14/216)[1] and includes the results of a multicentre randomised clinical trial,[2] validation of the method to measure RKF,[3] a health economic evaluation of the intervention,[4] a survey of dialysis-centre practices related to fluid management and an exploration of their association with fluid status in the trial participants[5] and finally an analysis of the association between the RKF (both the initial amount and its rate of decline) observed in this cohort and subsequent survival.[6]

Clinical uncertainty

Haemodialysis is used to treat 25,000 people with kidney failure in the UK.[7] In the majority, dialysis is started when kidney function is between 3% and 10% of normal, and this can persist for several months, even years. Maintaining this RKF has several advantages. It is associated with better quality of life (QoL), potentially longer survival and may mean that less dialysis is needed.[8–10] Despite these advantages, there is little research investigating interventions that might preserve RKF for a longer time after the initiation of dialysis. One possible intervention would be avoiding excessive fluid removal during the haemodialysis treatment, as this might mitigate any reduction in perfusion of the kidneys which, in turn, will accelerate their decline in function.[11] This is not without risk, as insufficient fluid removal may lead to serious complications. Determining the weight that reflects optimal fluid status for a patient on dialysis is a complex decision that needs to take several things into account, including comorbidities, blood pressure (BP), symptoms and patient preferences. However, it might be helped if an objective bedside measure of the body fluid content were available. Bioimpedance is such a bedside device that measures body composition, including the amount of fluid in the body.[12] It is useful in predicting survival on dialysis,[13–15] but it is uncertain whether it can be used as a guide to clinical fluid management, by avoiding excessive fluid removal and thus helping to preserve RKF. The value of bioimpedance in guiding clinical management of fluid status on dialysis was reviewed by National Institute for Health and Care Excellence (NICE) in 2017, and it was concluded that there was insufficient evidence to support its use.[16,17] There were also, at that time, no health economic data to support its use. This uncertainty led the NIHR Health Technology Assessment programme to commission research that would establish the clinical value of using bioimpedance to guide fluid management in the preservation of RKF in people new to haemodialysis treatment.[1]

Protocol

The BioImpedance Spectroscopy to maintain Renal Output (BISTRO) trial protocol was published in full prior to initiation of recruitment to the trial.[18] The statistical analysis plan (see *Report Supplementary Material 1*) and the health economics evaluation plan (see *Report Supplementary Material 2*) were signed off by the Trial Steering Committee

prior to undertaking any analyses. The post hoc analyses of practice patterns and the effects of preservation of kidney function on 5-year survival were developed later and are described in full in the associated publications.[5,6] The trial was registered prior to recruitment of participants (ISRCTN11342007). Recruitment to the trial was slower than anticipated, and this did result in a funded extension of the trial in an attempt to meet the recruitment target of 516. This led to a protocol change such that all patients could be followed up for 2 years (rather than between 1 and 2 years), which would allow the capture of more anuria events, as it became clear that the rate of these occurring was slower than originally anticipated. These changes were approved by the ethics committee.

The intervention

Prior to designing the BISTRO trial, we undertook a survey of practices associated with the fluid management of haemodialysis patients.[19] This survey found that a structured approach to assessing fluid status was not usual practice, with a high proportion of units (53%) reporting that they usually reduced the TW_{POST} as low as it could be tolerated with the aim of reducing the need for antihypertensive drugs, whereas 38% reported a policy of reaching a compromise between reducing the weight (i.e. with the intention of reducing body fluid content) to improve BP while attempting to maintain kidney function. It was clear that in designing a trial to test whether there was added value from BI in making this decision, a structured approach to setting the TW_{POST} would be needed in both the control and the intervention groups. This led to the development of a fluid assessment proforma (*Figure 1*), which would, at the same time, capture information influencing the decision-making process by acting as a case report form (CRF) for the trial. This proforma, which was developed in consultation with the Patient Advisory Group (PAG), sought to prompt clinicians to think systematically about the decision by providing key information (actual weight, BP), physical signs of fluid status, recent clinical history that might indicate changes in flesh weight, interdialytic fluid gains, BP symptoms, postdialysis fatigue and patient preferences. Use of this proforma was supported by educational materials (also required for training in how to undertake BI measurements and undertake urine collections for the measurement of RKF), and these were used at the site initiation visit to ensure that sites were properly trained. These training materials were published as supplementary files (slide decks) with the main trial findings.[2]

It was recognised that these proforma and training were in themselves a complex intervention[20] and, as such, were not conventional clinical practice, especially as they explicitly discouraged the strategy of removing fluid with the aim of controlling and reducing antihypertensive medication.

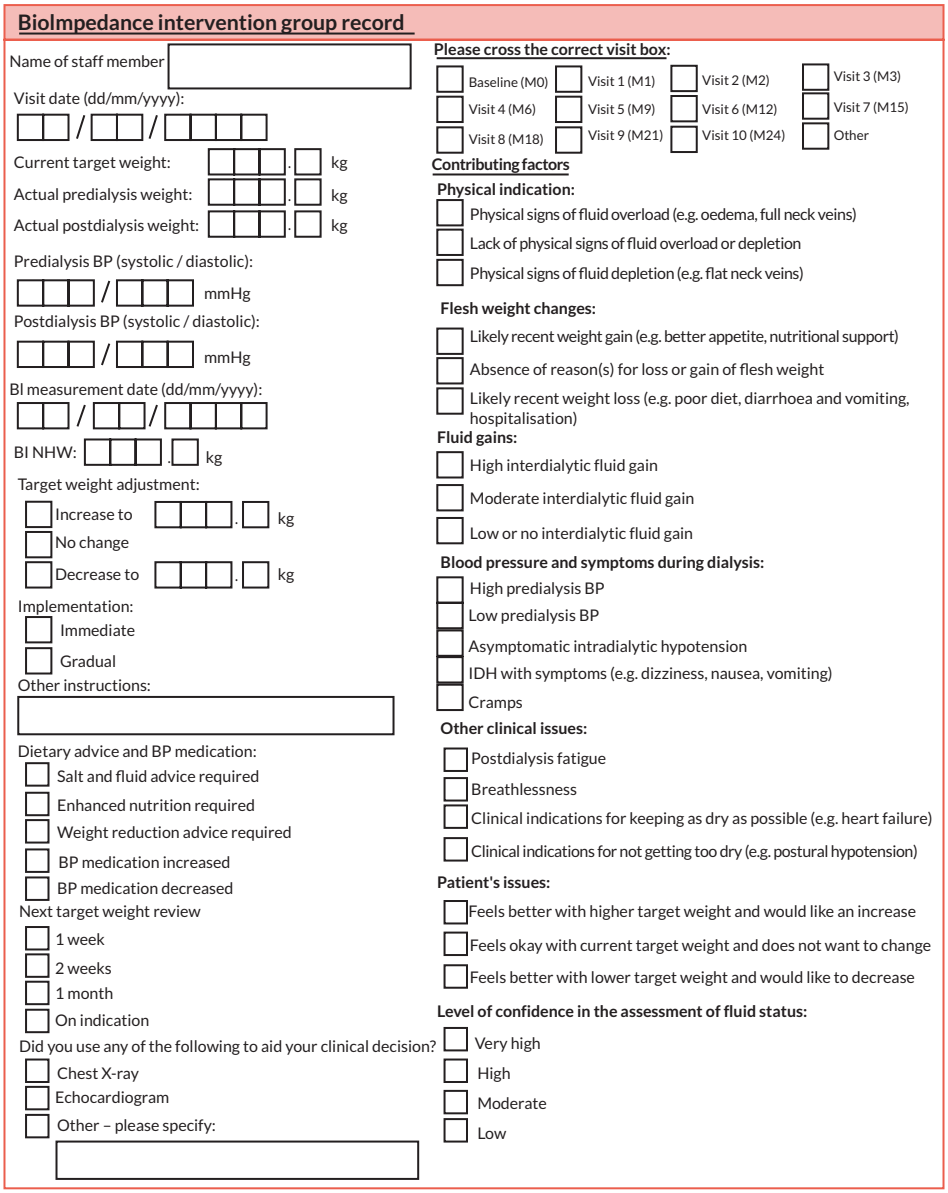
Selection of the bioimpedance device

The funder specified that the bioimpedance device to be used in the trial was chosen by an open, fair and objective process. This was overseen by Kidney Research UK with input from the NIHR Devices for Dignity MedTech Co-operative to ensure independent scrutiny, and the panel included input from dialysis and bioimpedance experts as well as the patient perspective. A set of criteria were developed that included technical specifications, current and projected use, supporting evidence base, patient interface and value for money. Six manufacturers of BI devices were approached, of which four submitted the required information for the above criteria to be assessed. In each of the domains, the *Fresenius Body Composition Monitor* (www.freseniusmedicalcare.com/en/body-composition-monitor) was judged as the optimal device to support the trial. Most importantly, the evidence base supporting use in the kidney failure population far exceeded the others for the selected device (> 100 vs. 0–2 publications), and at that time, it was the only device reporting the normally hydrated weight (NHW), which was essential for our trial design.

Main clinical findings of the BISTRO trial

The results of the BISTRO trial were published in the leading global kidney disease journal, *Kidney International*, in 2023.[2] This was a multicentre, open-label, randomised controlled trial (RCT) conducted in 34 dialysis units throughout the UK. Clinicians, including both doctors and nurses responsible for deciding the TW_{POST}, which in turn determines the amount of fluid that will be removed during a dialysis session, used the clinical proforma to structure this decision. This was made monthly for 3 months and then 3-monthly for up to 2 years in all trial participants while in the study or until they stopped passing any urine. There was scope to make additional fluid assessments if clinically indicated. In the intervention group, an estimate of the NHW from bioimpedance was made available to support this decision. Clinicians and patients were blinded to this information in the control group.

A total of 439 patients with RKF, defined as > 500 ml urine/day or a residual glomerular filtration rate (GFR) exceeding 3 ml/minute/1.73 m^2, were randomised in a 1 : 1 ratio within 3 months of initiating dialysis treatment. The primary outcome was time taken for a complete loss of urine output to occur, that is, anuria, and cause-specific hazard rates and subdistribution hazard rates were estimated considering death and transplantation



BioImpedance intervention group record

Name of staff member

Visit date (dd/mm/yyyy): / /

Current target weight: . kg

Actual predialysis weight: . kg

Actual postdialysis weight: . kg

Predialysis BP (systolic / diastolic): / mmHg

Postdialysis BP (systolic / diastolic): / mmHg

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

BI NHW: . 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
- BP medication increased
- BP medication decreased

Next target weight review
- 1 week
- 2 weeks
- 1 month
- On indication

Did you use any of the following to aid your clinical decision?
- Chest X-ray
- Echocardiogram
- Other – please specify:

Please cross 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, diarrhoea and vomiting, hospitalisation)

Fluid gains:
- High interdialytic fluid gain
- Moderate interdialytic fluid gain
- Low or no interdialytic fluid gain

Blood pressure and symptoms during dialysis:
- High predialysis BP
- Low predialysis BP
- Asymptomatic intradialytic hypotension
- IDH with symptoms (e.g. dizziness, nausea, vomiting)
- Cramps

Other clinical issues:
- Postdialysis 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 and does not want to change
- Feels better with lower target weight and would like to decrease

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

IDH, isolated diastolic hypertension; M, month.

FIGURE 1 The proforma used during fluid assessments in the BISTRO trial. It acts as both a source of information and a prompt when setting the TW_{POST}, as well as the CRF, to collect data for the trial.

as competing events. This was complemented by a secondary outcome, the rate of decline in RKF over 2 years. Additional secondary outcomes included BP, measured pre and post dialysis at each fluid assessment and a number of patient-reported outcomes, collected every 3 months. These included a measurement of QoL, of which the generic health-related question 'how good is your health today', rated on a visual analogue scale using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), was reported with the main trial findings, and dialysis-related symptoms using the Integrated Palliative Care Outcome Scale-Renal.

The randomisation procedure – which was concealed using a secure, centralised web-based system and stratified by the centre – successfully randomised 437 individuals and resulted in well-balanced trial groups. There were no group differences in cause-specific hazard rates of time to anuria, 0.751 [95% confidence interval (CI) 0.459 to 1.229] or subdistribution hazard rates, 0.742 (95% CI 0.453 to 1.215). The rate of decline in kidney function (GFR), measured every 2 months in the trial, was considerably slower than anticipated from the literature, with pooled linear rates being in year 1 −0.178 (95% CI −0.196 to −0.159) ml/minute/1.73 m^2/month and in year 2 −0.061 (95% CI −0.086 to −0.036) ml/minute/1.73 m^2/month. It did not differ between the trial groups: bioimpedance group: year 1: −0.182 (95% CI −0.206 to −0.157), year 2: −0.083 (95% CI −0.117 to −0.049); control group: year 1: −0.173 (95% CI −0.199 to −0.147), year 2: −0.034 (95%

CI −0.069 to −0.001). There were no differences between the trial groups in longitudinal pre- or postdialysis BP measurements, nor in patient-reported outcomes that might reflect fluid status, such as dialysis recovery time or symptoms experienced while on dialysis, such as cramps, dizziness, palpitations, hypotension or shortness of breath. Examples of the secondary outcomes that were measured (BP and patient-reported outcomes) are shown for BP, dialysis recovery cramp time and symptoms of low BP in the *Figures 2–5*. For more detail, please see Table 4 of the primary publication.[2]

The single measure of overall health rating was not different by group; however, more detail on QoL outcomes is reported in the health economic evaluation. In general, the reporting of these symptoms in this cohort with RKF was relatively low compared to the published literature.

We wished to establish the integrity of adherence to the intervention and compare this between the trial groups. To do this, we calculated the difference between the TW_{POST} set by clinicians and the estimate of the NHW obtained from the BI device. On average, the difference in the intervention group was negligible −0.038 kg [standard deviation (SD): 2.7], suggesting that clinicians were, where possible, avoiding volume depletion during dialysis, and this was very similar in the control group −0.25 kg (SD: 2.62). On multivariable analysis, this between-group difference was not significant, 0.108 kg (95% CI −0.282 to 0.498). It was also the case that the TW_{POST} set by clinicians was well adhered to in both groups for the duration of the trial, with an average difference between target and actual weight < 0.5 kg.[2] When clinicians made the decision to increase, decrease or keep the postdialysis weight the same, these decisions were in line with the bioimpedance measurements in both trial groups. Finally, there was strong evidence of alignment between target weight setting decisions and patient preferences, recorded in two-thirds of the 2675 fluid assessments. This is especially pleasing as an indicator of shared decision-making, not always experienced by people with kidney disease. https://ukkidney.org/sites/renal.org/files/Kidney%20PREM%20Report%202023%20Final.pdf

BISTRO has some limitations, most notably that it did not recruit to target and that the accumulation of primary outcomes was slower and thus fewer than we anticipated. The trial recruitment period was extended in an attempt to rectify this, including extending the follow-up period

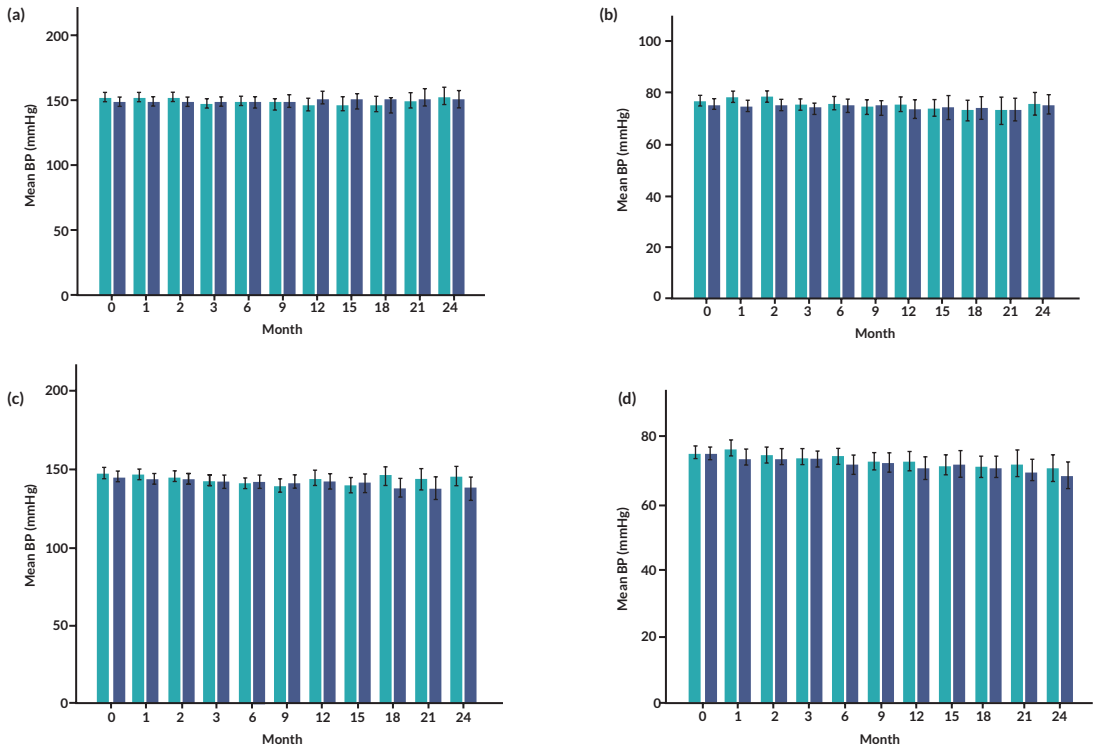


FIGURE 2 Blood pressure readings (±1.9 SE) taken at the time of fluid assessments (bioimpedance group shown in light blue, control group in dark green). (a) Predialysis systolic BP; (b) predialysis diastolic BP; (c) postdialysis systolic BP; and (d) postdialysis diastolic BP.

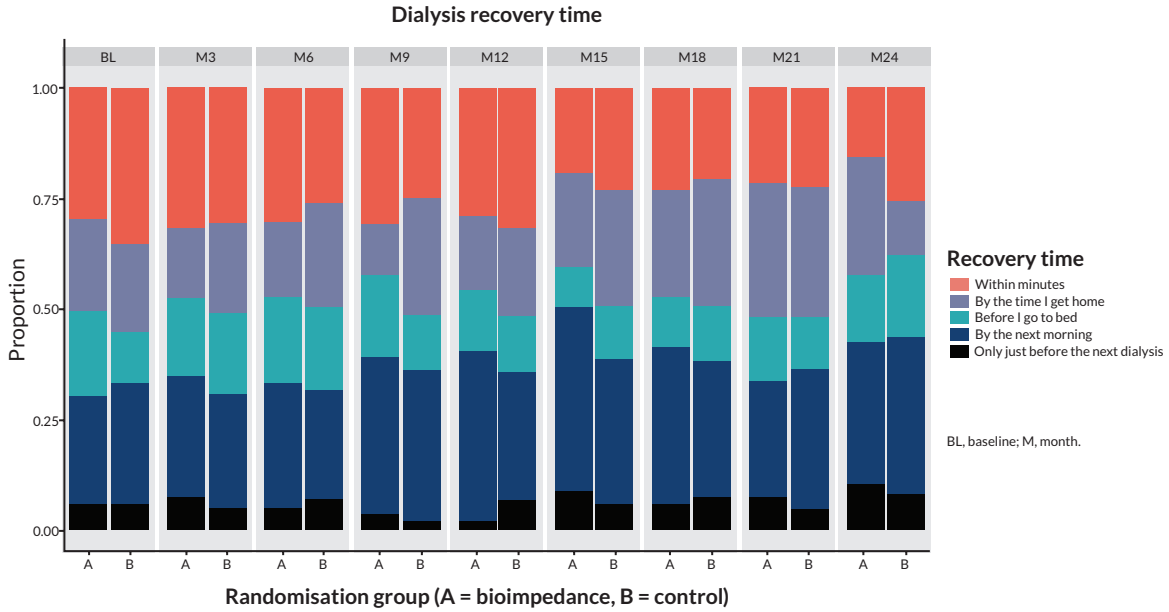


FIGURE 3 Between-group comparison of how long it took patients to recover from their dialysis session. There were no between-group differences but a tendency for the recovery time to worsen over the 2 years of trial participation.

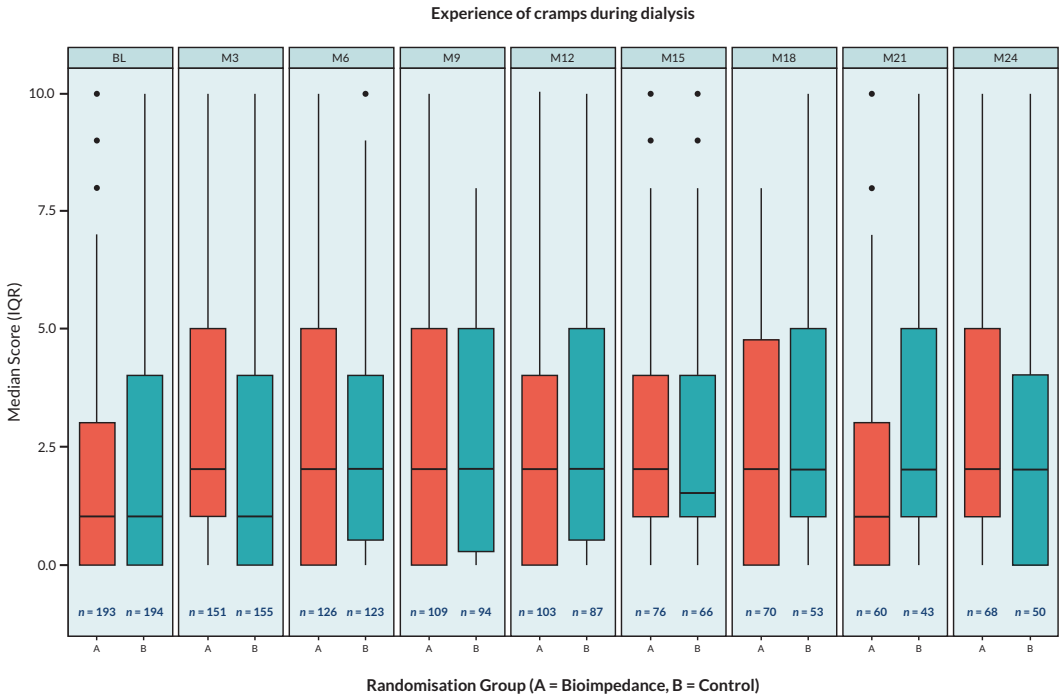


FIGURE 4 Between-group comparison of the median score (IQR) between 0 and 10 of patients experiencing cramp during dialysis sessions. BL, baseline; M, month.

of all the patients to 2 years so that clinically important differences could be detected. Extending it even further was discussed with the funders, but this was not an option. If we had been able to do this, then any effect size might have changed, and there would have been less likelihood of a type 2 error. However, the precision of the parameter estimates at the end of the study was acceptable, supporting our conclusion of no significant interventional effect. Furthermore, the interpretation of the primary outcome should be considered alongside two other important study findings. Our other measure of the main outcome of interest, the rate of decline in RKF, which is of equal importance to the primary outcome to patients and clinicians, was also not different between the trial groups. In fact, we strongly considered making this the primary outcome when planning the trial, and

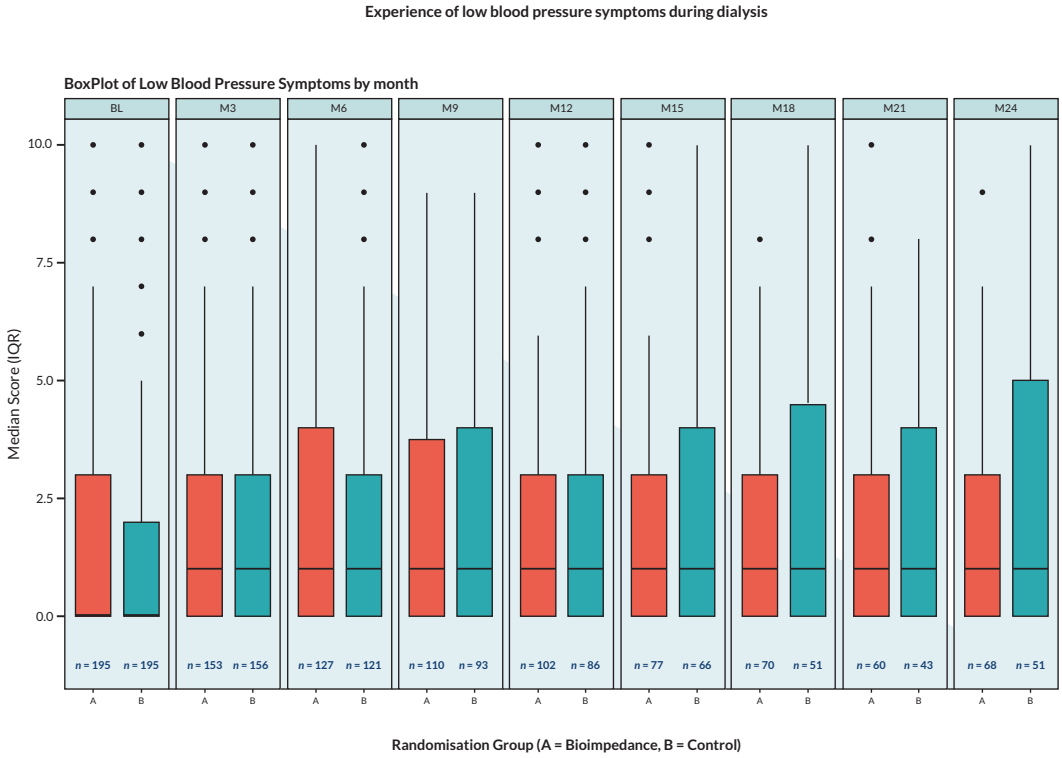


FIGURE 5 Between-group comparison of the median score (IQR) between 0 and 10 of patients experiencing symptoms attributable to a low BP during dialysis. BL, baseline; M, month.

of note, it is this measure which conferred benefit in the post hoc joint survival analysis (see later). Also, when we came to measure the effect of the intervention on setting the target weight after the trial was completed, we found, somewhat unexpectedly, that the difference between the target weight and the NHW was not different by trial group, arguing strongly in favour of a null result. BISTRO was also interrupted by the COVID-19 pandemic, which did lead to a modest loss in data, although we did not miss any of the primary outcome events.

It is concluded from the trial that there is no evidence that the addition of bioimpedance measurement to clinical fluid assessment can lead to better preservation of RKF in incident dialysis patients. This is likely to be because it does not result in an improvement in setting of the target weight when a standardised proforma and protocol are used to support this complex decision. BISTRO was associated with a remarkably slow rate in RKF decline when compared to previous studies[21–26] and thus supports the concept that avoiding excessive fluid removal during dialysis, where possible, is the optimal approach.

Health economic evaluation

The BISTRO economic evaluation was published in the *Health Technology Assessment* journal in 2024.[4] This article provides detailed information of the BISTRO economic evaluation. The overarching aim of the health economic evaluation was to evaluate the costs, benefits and overall cost-effectiveness of bioimpedance-guided fluid management (BGFM;BI intervention) compared to the control group using a standardised proforma, from an NHS and Personal Social Services (PSS) perspective.[27] This economic evaluation was made alongside the multicentre RCT (BISTRO). The time horizon of this within-trial analysis matched the length of the BISTRO follow-up (i.e. 24 months following randomisation).

Key healthcare resource use and costs for both groups were obtained from two primary resources: (1) patient-level data collected within the BISTRO trial via CRFs and (2) routinely collected data for care received within a hospital through Hospital Episode Statistics (HES). CRFs were completed at baseline and 3-monthly thereafter, until month 24, including after participants had reached the primary outcome, anuria. HES data were obtained from NHS Digital for BISTRO participating sites in England, Public Health Scotland, Wales and Northern Ireland.

Health-related quality of life (HRQoL) was obtained through participants' responses to the EQ-5D-5L[28] and Short Form questionnaire-12 items (SF-12)[29] instruments at baseline and 3-monthly thereafter, until month 24. For the base-case analysis, each participant's responses to the instrument's health status classification system were translated into a single, preference-based (utility) index

score using the Hernández Alava *et al*. value set for the EQ-5D-5L.[30] Quality-adjusted life-years (QALYs) were calculated as the area under the curve connecting utility scores reported at different time points.[31]

Descriptive analyses of missing data were carried out to investigate the patterns of missing data (through graphs) and the likely mechanism of missingness. Missing utility and costs data were then imputed using fully conditional multiple imputation by chained equations implemented through the multivariate imputation via chained equations package in Stata® 17 (StataCorp LP, College Station, TX, USA).[32]

The main outcomes of the economic evaluation were total per-patient cost, total per-patient QALYs and incremental cost per QALY gained. The primary analysis was complemented by a series of additional sensitivity analyses carried out to explore the impact of different sources of data (i.e. BISTRO CRFs, HES), specifications and assumptions in the cost-effectiveness analysis. Base-case and sensitivity analyses are described in *Table 1*.

Overall, 439 adult haemodialysis patients were initially recruited from 34 centres. Randomisation led to well-balanced study arms according to prespecified baseline patient characteristics.[2] Key information regarding unit cost, resource use and EQ-5D-5L data at each time point are given in the *Appendix 1*, *Tables 4–6*. The BI intervention group resulted in £382 lower average cost per patient (95% CI −£3319 to £2556) and 0.043 more QALYs (95% CI −0.019 to 0.105) compared to the control group, with neither values being statistically significant (*Table 2*).

Figure 6 depicts the results of 5000 bootstrap replications plotted on the cost-effectiveness plane. Each point represents a pair of incremental cost and incremental effectiveness estimates for the comparison between

TABLE 1 Description of base-case and sensitivity analyses conducted as part of the BISTRO economic evaluation

Analysis	Description
Base-case analysis (ITT)	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use QALY derivation: through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 1 (available complete data)	Data: available complete data, non-imputed Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use QALY derivation: through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: unadjusted
Sensitivity analysis 2 (CRF rather than HES for resource use)	Data: missing data imputed using multiple imputation Data source: HES for critical care admissions; CRF for other resource use QALY derivation: Through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 3 (unadjusted ITT)	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use QALY derivation: through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: unadjusted ITT
Sensitivity analysis 4 (EuroQol-5 Dimensions using Devlin)	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use QALY derivation: through EQ-5D-5L using a value set by Devlin *et al.* Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 5 [Short Form questionnaire-6 Dimensions (SF-6D)]	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use QALY derivation: through SF-12 (converted to SF-6D) using Brazier and Roberts algorithm Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility

TABLE 1 Description of base-case and sensitivity analyses conducted as part of the BISTRO economic evaluation (*continued*)

Analysis	Description
Sensitivity analysis 6 (excluded nursing home, and primary/community care)	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use, excluding nursing home, and primary and community care services QALY derivation: through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 7 (included patients' family-incurred costs)	Data: missing data imputed using multiple imputation Data source: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use, including patients' family-incurred costs to adopt a broader perspective than NHS and PSS QALY derivation: through EQ-5D-5L using a value set by Hernández Alava *et al.* Statistical model specification: GLM: costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility

GLM, generalised linear model; ITT, intention to treat.

TABLE 2 Cost–utility results of base-case analysis at 24 months (£, 2020)[a]

	BI group		Control group				
Parameter	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (BI vs. controls) (£ per QALY)
Base-case analysis	51,648.86	1.009	52,030.51	0.966	−381.65 (−3318.97 to 2555.67)	0.043 (−0.019 to 0.105)	BI group less costly and more effective

BI, bioimpedance-guided fluid management; control, protocol fluid management, blinded to BI measurements; ICER, incremental cost-effectiveness ratio.

a Estimates derived from bootstrapping using 1000 replications; cost adjusted for baseline covariates; QALYs adjusted for baseline covariates, including baseline EQ-5D-5L scores.

Note

For base-case analysis description, refer to *Table 1*.

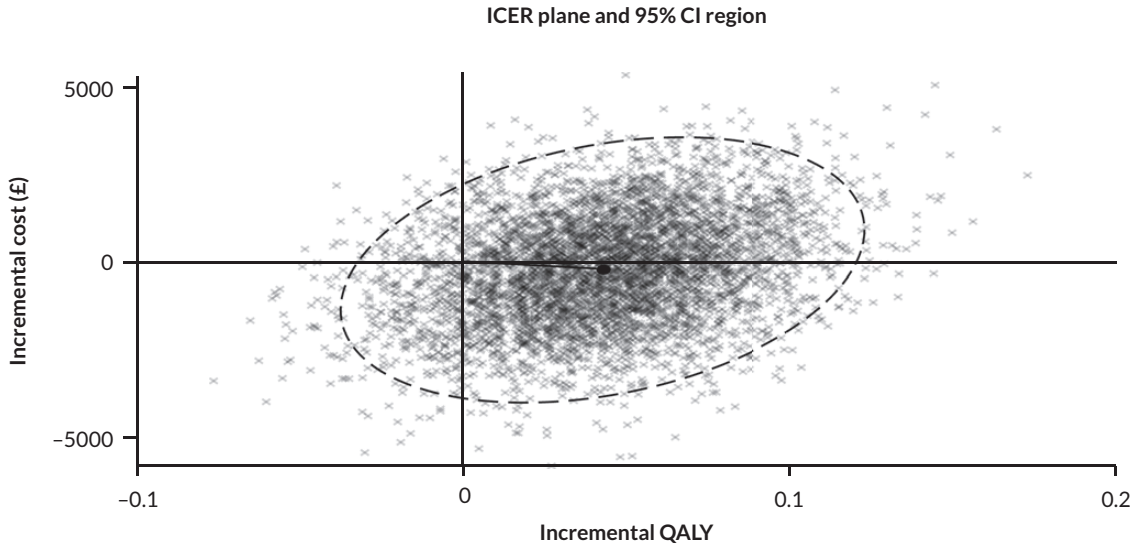


FIGURE 6 Cost-effectiveness plane depicting the distribution of simulated cost and QALY pairs. ICER, incremental cost-effectiveness ratio.

the BI and control groups. Overall, 48% of the simulated estimates are located in the south-east quadrant, indicating that BI is less costly and more effective than in controls.

The probability of BGFM being cost-effective was 76% and 83% at commonly cited willingness-to-pay threshold of £20,000 and £30,000 per QALY gained, respectively, suggesting that BI intervention is likely to be a cost-effective option (*Figure 7*).

The results remained robust to a series of sensitivity analyses (*Table 3*).

Overall, we conclude that the lack of precision in our estimates does mean that there is low certainty in the cost-effectiveness of this low-cost intervention. Since the BISTRO trial commenced, the research group that undertook the previous NICE review[33] has updated its findings.[34] Their conclusions were somewhat similar in

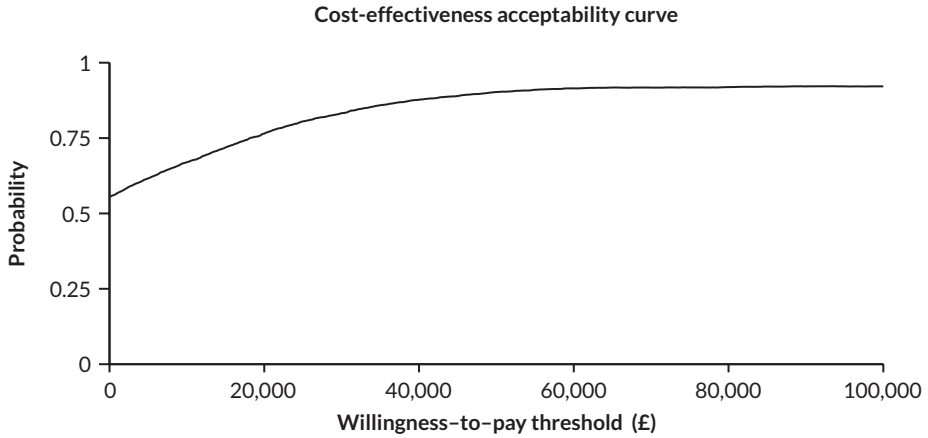


FIGURE 7 Cost-effectiveness acceptability curve showing the probability of BI being cost-effective at different values of willingness to pay for a QALY.

TABLE 3 Cost–utility results of sensitivity analyses at 24 months (£, 2020)[a]

Parameter	BI group		Control group		Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (BI vs. controls) (£ per QALY)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
Sensitivity analysis 1	43,305.38	0.972	41,392.45	0.858	1912.93 (−14,298.08 to 18,123.95)	0.114 (−0.230 to 0.458)	16,780
Sensitivity analysis 2	48,341.43	1.009	48,410.83	0.966	−69.40 (−2373.58 to 2234.77)	0.043 (−0.019 to 0.105)	BI less costly and more effective
Sensitivity analysis 3	51,809.74	0.993	51,864.37	0.985	−54.63 (−2850.65 to 2741.40)	0.008 (−0.072 to 0.091)	BI less costly and more effective
Sensitivity analysis 4	51,648.86	1.174	52,030.51	1.118	−381.65 (−3318.97 to 2555.67)	0.056 (−0.007 to 0.119)	BI less costly and more effective
Sensitivity analysis 5	51,648.86	1.139	52,030.51	1.101	−381.65 (−3318.97 to 2555.67)	0.038 (−0.011 to 0.088)	BI less costly and more effective
Sensitivity analysis 6	50,943	1.009	51,447.73	0.966	−504.73 (−3444.15 to 2434.69)	0.043 (−0.019 to 0.105)	BI less costly and more effective
Sensitivity analysis 7	52,355.80	1.009	52,794.28	0.966	−438.48 (−3405.78 to 2528.82)	0.043 (−0.019 to 0.105)	BI less costly and more effective

BI, bioimpedance-guided fluid management; control, protocol fluid management, blinded to BI measurements; ICER, incremental cost-effectiveness ratio.

a Estimates derived from bootstrapping using 1000 replications; cost adjusted for baseline covariates; QALYs adjusted for baseline covariates, including baseline EQ-5D-5L scores.

Note

For base-case analysis description, refer to *Table 1*.

that they reported a 59% chance of the incremental cost-effectiveness ratio being below £20,000 per QALY, suggesting that bioimpedance testing may offer a cost-effective approach to improve fluid management in patients with kidney failure on dialysis. They recognise that further research is needed to reduce the current uncertainties, citing the BISTRO trial as an important future source.

Validation of the measurement of residual kidney function

Despite its apparent clinical importance, very few dialysis centres anywhere in the world, including the UK, measure RKF routinely in haemodialysis patients (in marked contrast to those treated with peritoneal dialysis). Of the 34 centres in the trial, between 20% and 30% did this as a matter of routine. It was, therefore, imperative for BISTRO to have a robust plan to train sites in this procedure, which included the development of teaching materials, and a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA)-based spreadsheet calculator was put in place to support calculation of the GFR. To assess the effectiveness of this approach, we audited this early on in the course of the trial. This validation process was published in the journal *Physiological Measurement* in 2022.[3]

The standard approach to measuring RKF in haemodialysis patients is cumbersome. It requires patients to collect all their urine between two dialysis sessions (i.e. a 48-hour period), and that three blood samples are taken, before and after the dialysis session before the urine collection, and again before the next dialysis session. It is, however, theoretically possible that the number of blood samples required can be reduced with the help of modelling that can estimate missing values using the steady-state assumption. We realised that being able to do this would reduce the number of failed measurements of RKF in the trial due to logistical challenges on a bust dialysis unit, such as forgetting to take samples or their going missing on the way to, or in, the pathology laboratory. In the event, patients were good at collecting their urine in BISTRO (see *Patient and public involvement* for a full discussion on how this was achieved), but there were significant logistic problems with blood samples.

Our audit and analysis of the BISTRO study data confirmed that the steady-state assumption can be used to estimate missing solute concentrations in plasma (i.e. both urea and creatinine, as it is the mean of the urea and creatinine clearance that is used to measure GFR). At GFR levels ranging between 0 and 20 ml/minute/1.73 m^2 (we included samples from those who failed screening for BISTRO in our validation), we found that for two different scenarios of missing samples, the difference between the modelled and measured GFR was 2% and −1.2%, respectively, and the absolute difference was < 0.5 ml/minute/1.73 m^2 in all but 2–3% of the 316 patients tested.

Practice patterns related to fluid management in the BISTRO participating centres

In designing BISTRO, it was recognised that it would be important to collect information from the participating sites on centre-level approaches to fluid management. Although these should not affect the trial outcomes directly, given that randomisation of participants was stratified by centre, we wanted to know whether they changed during the course of the trial and recognised that this was an opportunity to link these practices to patient-level fluid assessments and outcomes. A unit-level questionnaire was developed, and participating sites were asked to complete it early in the trial and again later towards the end. The full description of the survey, the survey results and the analysis of their relationship to clinical outcomes were presented at UK Kidney Week meetings in 2022 and 2023 and have since been published.[5]

The questionnaire was designed to cover a number of domains in centre-level practice that are associated with fluid management, including dialysate sodium concentration, dietary advice (including salt intake), strategies related to preservation of RKF, use of incremental dialysis, fluid assessment and management and the usual dialysate temperature used. Thirty-two out of 34 centres enrolled across the UK contributed survey data to the trial (2 centres dropped out early on). Twenty-six completed the first survey (with 5 centres entering the trial after the window for completion of the first survey had closed), and 31 competed the second survey. In 10 centres, it was completed by the same person, which allowed for assessment of consistency, and where this could be tested, this was excellent (e.g. numeric values for dialysate [Na^+] or answers to subquestions). Overall, practices did not change significantly between the two surveys, although they were substantially different from the pretrial survey that we conducted in 2016. Any differences between the two surveys could largely be accounted for by the additional five centres in the second survey (e.g. a higher proportion of these centres routinely measured RKF); there was, overall, a trend in favour, a reduced use of blanket unit-wide policies (e.g. in the first survey, 92% reported having a fluid restriction policy, dropping to 55% on the second survey), perhaps suggesting the evolution of an increasingly person-centred approach. Similarly, in the second survey, more centres reported reducing dialysis frequency if RKF was present. Generally, protocols

and policies for fluid management were lacking across all centres.

We undertook a post hoc analysis to determine whether there were any associations between some of these centre-level practices and the trial participants' fluid status (defined as before in this report as the difference between the TW_{POST} and the NHW, except that here it was the magnitude of the difference in either direction) and their pre- or postdialysis BP readings. Prior to inclusion of practice patterns and demographic adjustment in the model, centre-level intraclass correlations were extremely low for all five outcomes studied, whereas significant patient-level correlations were observed. To investigate the effect of the practices, we conducted a multilevel analysis of the data to account for repeated measures clustering and centre size, adjusted for age, comorbidity score and gender. The two surveys were analysed independently. The practice patterns interrogated were the usual dialysate sodium concentration used in the centre, the usual dialysate temperature, having a standard fluid assessment protocol in place for new patients, and the routine use of additional methods of assessing fluid status (e.g. bioimpedance, echocardiograms, chest X-ray, central vein diameter monitoring, blood volume monitoring or lung ultrasound).

We were not able to demonstrate clear associations with any of the practice patterns and the outcomes of interest. For example, across the range of dialysate sodium concentrations used by different centres, which ranged from 135 to 140 mmol/l, no differences were seen. A lower predialysis diastolic BP was significantly and consistently associated with being older, male and having more comorbidities. There was a signal suggesting that in the very few centres using a very low dialysate temperature (35 °C), fluid status was less close to NHW when compared to those using 36 °C or 36.5 °C. No association with BP was observed. No consistent associations with the routine use of a protocol for new patients or additional methods of assessing fluid status were observed.

This secondary analysis is reassuring in that for the duration of the BISTRO trial, no major changes in centre-level practices related to fluid management occurred that might have affected the results. It also indicates that that patient-level factors are more important determinants of fluid status and BP than currently identifiable centre practices, lending further weight to the argument that these are more associated with comorbidity, age and other patient-level factors. However, BISTRO was not designed or powered to establish the importance of centre-level practices, especially when considering harder clinical outcomes such as cardiovascular events. This requires much larger trials with a cluster randomised design when implementing interventions across the dialysis unit, such as the currently recruiting international RESOLVE trial, ClinicalTrials.gov Identifier: NCT02823821, which is testing two concentration of dialysate sodium. Nevertheless, our findings are in keeping with the recent trial, MyTEMP[35] showing no difference in cardiovascular outcomes according to two different dialysate temperatures.

Secondary analysis of medium-term impact of preservation of residual kidney function on survival

It is well established that preservation of RKF is associated with better survival in patients treated with peritoneal dialysis. It is likely that this is also the case for those treated with haemodialysis, but because RKF is not routinely measured in the dialysis unit, this is less well established. Three previous analyses have suggested that it is important. The first, a secondary analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis, which was a national incident cohort study of all Dutch patients starting dialysis in the early 2000s, found that when repeated measures of RKF were included in a Cox survival model of haemodialysis patients, there was a strong association with better survival – an effect that completely swamped any effects of differences in dialysis small solute clearance between individuals when RKF was present. A single-centre study in the UK also found that patients surviving longer on haemodialysis have better preserved RKF. More recently, an analysis undertaken by a large dialysis provider in the USA (DaVita, Denver, CO, USA) of data from 6000 patients, who had their RKF measured at the start of treatment, was able to show that the better this was maintained at 12 months, the better the subsequent survival over the next 2–3 years. This suggests that it is not just having RKF at any time on dialysis that is important (which may be dictated by the starting level) but that the individual's rate of decline in RFK, calculated from two time points, is also important.

Data from the BISTRO trial provided the opportunity to investigate this further, especially as, on average, the number of measurements in RKF after starting dialysis was far more than in the DaVita study, which had, by definition, also excluded patients who died within the first year of treatment.[6] To do this post hoc analysis, we took data collected during the trial and linked them to longer-term timeline data obtained from the UK Renal Registry (UKRR). This included time to death, transplantation or loss of follow-up. This allowed us to extend the follow-up

period for 2 to almost 5 years and increase the power of our survival models as the number of deaths over this period of time increased from 32 to between 84 and 104 depending on the model.

Cox proportional hazards regression survival models, including those incorporating change in GFR from baseline as a time-varying variable, and joint regression models for longitudinal and survival data (longitudinal models for GFR or urine volume) were used to explore the relationship of RKF preservation with survival. Analyses were adjusted for age, sex, comorbidity and ethnicity.

Higher age and comorbidity score were associated with increased mortality in all models. Baseline GFR reduced the risk of death, hazard ratio (HR) 0.918 (95% CI 0.844 to 0.999) per ml/minute/1.73 m^2. A greater fall in GFR and urine volume from baseline was associated with a non-significant increased risk of death as visualised on spline plots. In the joint survival models, higher GFR (adjusted HR 0.88, 95% CI 0.80 to 0.97) or urine volume (adjusted HR 0.75, 95% CI 0.57 to 0.95 per l) at any time point associated with better survival.[6] This implies that the benefits of RKF for survival are not just dictated by the level of RKF at the start of dialysis and that interventions designed to slow the rate of decline in RKF should be actively sought and investigated.

Patient and public involvement

The role of patient and public involvement (PPI) in the design, execution and dissemination of the BISTRO trial has been described in detail, using the Guidance for Reporting Involvement of Patients and the Public 2 criteria, in a separate publication because of its importance to the trial.[36] For several reasons, it was clear that PPI would be crucial to the trial's success. Setting the optimal target weight on dialysis is something that directly affects the lives of dialysis patients and should, where possible, be a shared decision. The main outcome of interest, RKF, would require patients to collect their urine samples on a regular basis, and there was real concern that this might not be feasible. In contrast to many trials that require a single, one-off intervention, BISTRO requires multiple interventions over a prolonged period.

Our objectives for PPI at the start of planning the trial were to develop an effective PPI participation model, ensure the patient's voice was heard by the Trial Management Group (TMG) and undertake coproduction of all participant-facing documents and communications, including dissemination of the trial results, with the main purpose of maximising participant engagement in the study.

To achieve this, we adopted the following PPI methodology: we developed an effective PPI working model that was represented within the TMG, contributing to protocol design, selection of bioimpedance device, coproduction of all participant-facing communications, including dissemination of trial findings. The PPI group was co-led (with the chief investigator) by the patient co-applicant, who has experience of haemodialysis and of supporting research through his paid position at the NIHR Devices for Dignity MedTech Co-operative. He was a full member of the TMG, and his time was reimbursed from the research grant. The PPI outcomes of interest were: contributions prior to trial initiation, description of the participant-facing communications, participant adherence to trial procedures, participant dropout, and dissemination of trial findings to participants and the wider dialysis population.

An effective working model for the PAG was developed using social media, specifically a WhatsApp group, that enabled participation from geographically diverse regions. This was developed prior to COVID-19, at which point it became invaluable. The PAG coproduced with the TMG a series of communication postcards and newsletters and a web page to support participants and disseminate the trial results. Although the trial only recruited to 85% of its intended target, this was not due to lack of willingness of patients to participate, with 50% of eligible patients agreeing (compared to a projected 25%). Rather, this failure to recruit to target was due to differences in levels of support from Hospital Trust Research and Development Departments and staffing challenges. Participant adherence to the main trial outcomes was excellent (137% urine collections obtained, i.e. more than required because of repeat requests). Potentially, avoidable dropout was moderate at 14.4%, although only 3.6% were clearly attributable to inability or unwillingness to comply with trial procedures. There were no dropouts attributable to the national pause in non-COVID-19-related research during the pandemic other than those directly due to the infection.

The main limitation in PPI was the failure to collect real-time data from which the assessment of the impact of PPI might have supported a causal link between PPI interventions and the successful delivery of the trial.

In conclusion, PPI played an important role in the design, delivery and dissemination of the BISTRO trial. Key to this success was the close relationship between the PAG and the TMG. Given the complexity of the intervention, dropout was reasonably low and did not compromise trial findings, but reasons were not always clear.

Equality, diversity and inclusivity

BISTRO was intended as a pragmatic trial that could be generalisable to the wider incident dialysis haemodialysis population. We recruited from almost half of the dialysis centres across the UK, including both main and satellite units. There were deliberately few exclusion criteria, and the proportion of eligible patients willing to take part in the trial was higher than we planned for. Patients with failing kidney transplants could be included. On the advice of the PAG, we extended the enrolment period to the first 3 months of dialysis treatment, in recognition of the fact that starting dialysis is a traumatic time for patients and that they may need time to consider participation in a trial that involved a significant commitment. To establish if we were successful in our aspiration for inclusivity, we compared the demographic characteristics of those enrolled into the trial with those of the whole dialysis population commencing treatment in 2019, that is, midway through the trial, as reported to the UKRR.[2,37] Compared to registry data, BISTRO participants were a little younger (median age 62 vs. 64 years), more likely to be male (70% vs. 65.5%) and a little more likely to be white (79% vs. 75%). They were more likely to have diabetes (44% vs. 30.4%), although it is recognised that comorbidities are under-reported to the UKRR, and gratifyingly, there was a very similar proportion of patients starting dialysis in an unplanned manner (16% vs. 16.4%). Of note, in the multivariable analysis of the rate of decline in RKF, this was significantly slower in white people compared to some ethnic groups, and tended to be slower in older patients, whereas the effect of comorbidity was not significant.

It should, however, be noted that the initial collection of ethnicity data via the clinical report forms returned a significant number of patients allocated to the 'other' category. Although the research staff were encouraged to provide a text description of what is meant by this category, they, in fact, did not do so. To clarify this issue when we obtained the data download for the long-term effects of RKF on survival from the UKRR, we requested the ethnicity data reported to the registry to allow us to cross-check validity and establish whether we could allocate the 'other' category. Where ethnicities had been recorded on the trial CRFs, there was good agreement with the UKRR data (only three individuals differently classified). However, whereas the CRFs classified 70 as 'other', the UKRR classified 36 as Asian, 28 as black, 2 as mixed, 3 as white and 1 as 'other' (3 could not be matched). In fact, this means that the trial population was actually more representative of the UK dialysis population that we originally thought, and, as a result, we used the UKRR classification of ethnicity for the survival analyses.[6] There are still some limitations in the UKRR classification that should be addressed given that it does not distinguish between South and East Asian ethnicity, although it is known that the South Asian population dominates this category. One important learning point is that when collecting ethnicity data via CRFs, this is open to significant error, and this likely needs to be addressed in the training of research staff with appropriate improvement in the design of CRFs. In retrospect, we provided too many options for ethnicity, which apparently led to confusion and thus opting for the 'other' category.

Implications for clinical practice and decision-makers

Use of bioimpedance

There is no evidence that incorporating bioimpedance measurements into fluid assessments leads to a reduction in the rate of decline in RKF in people starting haemodialysis treatment. Equally, there was no evidence of harm associated with the use of BI. There is some evidence that incorporating bioimpedance measurements is associated with a slight reduction in the decline of QoL in people on dialysis and that the very modest costs associated with its use are more than offset by a reduction in dialysis-related costs. It should be recognised that the potential benefits of using bioimpedance are likely to extend beyond the preservation of RKF, providing additional information and possible reassurance during fluid assessments that could have a 'soft' impact on QoL, for example, improving well-being, benefits that would extend to those without RKF. However, this research clearly indicates that bioimpedance, at best, has an *adjunctive role* in assessing fluid status and should not be used as a tool that is the *main guide* when setting the optimal target weight. There is no reason to believe that these implications for how this technology is used are not generalisable to all currently manufactured bioimpedance devices.

Rate of decline in residual kidney function

More than any other study, BISTRO has shown that the rate at which RKF declines following the start of dialysis can be slower than has previously been appreciated. BISTRO has also confirmed that measuring this as part of routine clinical practice is a practical proposition, and the validation process embedded within the trial provides clinicians with a simplified method for this procedure, which we plan to make available via the UK Kidney Association website. The demonstration that RKF, especially its rate of decline,

is strongly associated with subsequent patient survival only strengthens the argument for its routine assessment in the clinic. Attempts to further slow down the rate of decline in RKF raise new therapeutic opportunities, such as incremental start of dialysis treatment, a reduction in dialysis treatment times for certain patient groups who find dialysis traumatic or the use of medications that have been shown to slow the progression of kidney failure pre dialysis.

Assessing the optimal postdialysis target weight

Perhaps, most significantly, BISTRO has developed and tested a standardised proforma that gives structure to fluid assessments in dialysis patients. It is well recognised that giving structure to medical assessments and procedures result in improved outcomes in many clinical situations, and the findings of BISTRO imply that this also applies to this setting. A fluid management strategy that avoids volume depletion during dialysis treatment is associated with good patient outcomes but cannot be causally linked with the excellent preservation of kidney function.

Research recommendations

BISTRO has set a new standard for the rate of decline of RKF in haemodialysis against which new interventions can now be investigated. Obvious candidates for this are medications known to slow the progression of RKF in predialysis patients, most notably the recent successes obtained with the gliflozins.[38,39]

Once patients have become anuric on haemodialysis, the strategy for fluid management potentially changes, and bioimpedance may still have a role in helping with this. Research into other devices designed to support fluid assessments (e.g. blood volume monitoring, lung ultrasound) as well as bioimpedance have failed to demonstrate clear advantages in this setting, although there are possible benefits in certain high-risk patient groups. This is likely because the optimal fluid status (TW_{POST}) is a function of many things that affect fluid balance and distribution in the body.[40] It is recommended that further research considers a stratified approach to fluid management that considers the treatment goals for individual patients, which may vary considerably.[41]

BISTRO uncovered substantial variation in centre-level clinical practices associated with fluid management but was not sufficiently powered or designed to determine their effect on clinical outcomes with certainty. In particular, we were not able to determine the effect of implementing unit-wide policies to guide fluid management. These would need to apply to all patients within a dialysis unit and thus may be better evaluated using adequately powered cluster randomised trials.

BISTRO found a faster rate of decline in RKF in non-white ethnic groups, which could not be explained by age or the burden of comorbid illnesses. This requires further research to understand why this is the case.

Conclusion

There is no evidence that the routine use of BI spectroscopy in dialysis units provides additional information when optimising the TW_{POST} to reduce the rate of loss of RKF in people new to haemodialysis. However, there may be other HRQoL benefits of this intervention, and its low cost is possibly outweighed by modest cost savings identified in the health economic evaluation. The rate of decline of RKF in new dialysis patients is slower than previously appreciated in the context of a structured approach to the assessment of fluid status and a management strategy that aims to avoid volume depletion during dialysis treatments.

Additional information

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

The trial data are available to investigators under the conditions of a data sharing agreement. This will include group- and individual-level fully anonymised data. Applications should be made to the chief investigator.

Ethics statement

The study had UK Integrated Research Ethics approval (206213), submitted 18 August 2016, granted on 23 August 2016 subject to conditions that were satisfied on 12 September 2016. The Health Research Authority gave its approval on 4 October 2016. All participants gave their written consent.

Information governance statement

Keele University is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Keele University is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.keele.ac.uk/legalgovernancecompliance/legalandinformationcompliance/informationgovernance/ or by e-mail dpo@keele.ac.uk.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/RHON2378.

Primary conflicts of interest: David Keane: receipt of grants/contracts from Baxter Healthcare. Indranil Dasgupta: research grant/payments/support from Sanofi, Vifor, Astra Zeneca, and GSK. Leadership/fiduciary role: Secretary Renal Association UK, Chair of Research Committee British and Irish Hypertension Society, Co-Chair Association of British Clinical Diabetologists and UK Kidney Association Committee, Lead Division 2 of West Midlands Clinical Research Network. Paul Ormandy: Institutional Grant/contracts received from: Kidney Research UK – 06/2020–09/2023, NIHR (01/2022–03/2028), Development of a Social Prescribing Population Health Management Tool – Technology Strategy Board Knowledge Transfer Partnership – 08/2021–12/2022. Martin Wilkie: Institutional research grant from Baxter. Consulting fees: Baxter International 'My kidney Journey' and GSK Patient Advisory Board. Leadership/fiduciary role: Co-Chair Kidney Patient Involvement Network & Treasurer and Executive Member Association of Nephrology Nurses UK.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications

Davies SJ, Caskey FJ, Coyle D, Lindley E, Macdonald J, Mitra S, *et al*. Rationale and design of BISTRO: a randomized controlled trial to determine whether bioimpedance spectroscopy-guided fluid management maintains residual kidney function in incident haemodialysis patients. *BMC Nephrol* 2017;**18**:138. https://doi.org/10.1186/s12882-017-0554-1

Lindley E, Keane D, Belcher J, Fernandes Da Silva Jeffcoat N, Davies S. Monitoring residual kidney function in haemodialysis patients using timed urine collections: validation of the use of estimated blood results to calculate GFR. *Physiol Meas* 2022;**43**. https://doi.org/10.1088/1361-6579/ac80e8

Davies SJ, Coyle D, Lindley EJ, Keane D, Belcher J, Caskey FJ, *et al*. Bio-impedance spectroscopy added to a fluid management protocol does not improve preservation of residual kidney function in incident hemodialysis patients in a randomized controlled trial. *Kidney Int* 2023;**104**:587–98. https://doi.org/10.1016/j.kint.2023.05.016

(The results of the trial were presented at the European Renal Association's Conference at the Late Breaking Trials Session in May, 2022 in Paris and at the UK Kidney Association meeting in June 2022 held in Birmingham in a session organised by the UK Renal Trial Network.)

Zanganeh M, Belcher J, Fotheringham J, Coyle D, Lindley EJ, Keane DF, *et al*. Cost-effectiveness of bioimpedance-guided fluid management in patients undergoing haemodialysis: the BISTRO RCT [published online ahead of print September 25 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JYPR4287

(This analysis was presented at the UK Kidney Association Meeting in June 2024 in Edinburgh).

Coyle D, Ormandy P, Fernandes Da Silva Jeffcoat N, Davies SJ; on behalf of the BISTRO Investigators. Public and patient involvement (PPI) in the design, execution and dissemination of the BISTRO trial. [published online ahead of print January 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/DOTR5903

(This paper was, in part, presented at the UK Kidney Association Meeting in June 2022 held in Birmingham, at a session on the involvement of patients in research. The UKKA is a muti-disciplinary meeting attended by all members of the multi-professional team (e.g. doctors, nurses, technicians, dieticians, psychologists, social workers) alongside patients, their families and carers).

Johal N, Sharma R, Belcher J, Coyle D, Lindley EJ, Keane D, *et al*. Centre-level fluid management practices in the BISTRO trial and their lack of association with participant fluid status and blood pressure. *BMC Nephrol* 2024;**25**:398. https://doi.org/10.1186/s12882-024-03837-y

(These data were presented at the UK Kidney Association Meeting held in June 2023 at the Newport Conference Centre.)

Belcher J, Coyle D, Lindley EJ, Keane D, Caskey FJ, Dasgupta I, *et al*. Impact of the preservation of residual kidney function on hemodialysis survival: results from the BISTRO trial. *Kidney360* 2024;**6**(1):112–20. https://doi.org/10.34067/KID.0000000596

Trial registration

This trial is registered as ISRCTN11342007.

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This synopsis provided an overview of the research award *BioImpedance Spectroscopy to maintain Renal Output: the BISTRO Trial*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/14/216/01).

About this synopsis

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List of supplementary material

Report Supplementary Material 1
BISTRO statistical analysis plan

Report Supplementary Material 2
BISTRO health economics analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/RHON2378).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

BI	bioimpedance (spectroscopy)
BISTRO	BioImpedance Spectroscopy to maintain Renal Output
BGFM	bioimpedance-guided fluid management
BP	blood pressure
CI	confidence interval
CRF	case report form
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GFR	glomerular filtration rate
HES	Hospital Episode Statistics
HR	hazard ratio
HRQOL	health-related quality of life
NHW	normally hydrated weight
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PPI	patient and public involvement
PSS	Personal Social Services
QALY	quality-adjusted life-year
QOL	quality of life
RCT	randomised controlled trial
RKF	residual kidney function
SD	standard deviation
SF-12	Short Form questionnaire-12 items
TW_{POST}	postdialysis target weight
TMG	Trial Management Group
UKRR	UK Renal Registry

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Appendix 1

TABLE 4 Unit cost of resource use services

Service	Unit cost (£)	Source
Bioimpedance session (CRF)	25.10[a] See appendix 2, tables 13 and 14 in economic evaluation paper	Fresenius Medical Care (UK) Ltd,[35] Unit Costs of Health and Social Care 2020
Haemodialysis sessions (CRF)		
Catheter or line for hospital/satellite	165[b]	National Schedule of NHS Costs 2019–20
Fistula or graft for hospital/satellite	163.5[b]	

continued

TABLE 4 Unit cost of resource use services (*continued*)

Service	Unit cost (£)	Source
Inpatient admissions		
Scheduled (HES)	See appendix 3, table 15 in economic evaluation paper	National Schedule of NHS Costs 2019–20
Unscheduled (HES)	See appendix 3, table 16 in economic evaluation paper	
Scheduled (CRF)	4168[c]	Unit Costs of Health and Social Care 2020
Unscheduled (CRF)	See appendix 4, table 17 in economic evaluation paper	National Schedule of NHS Costs 2019–20
Nursing home (CRF)	184[d]	Unit Costs of Health and Social Care 2020
Critical care admissions (HES)	See appendix 5, table 18 in economic evaluation paper	National Schedule of NHS Costs 2019–20
Outpatient appointments		
Hospital outpatient visits (HES)	See appendix 6, table 19 in economic evaluation paper	National Schedule of NHS Costs 2019–20
Hospital outpatient visits (CRF)	135[e]	Unit costs of Health and Social Care 2020
Day care centre (nursing home) (CRF)	64[e]	
Primary and community care services (CRF)		
General practitioner, NHS	184[f]	Unit costs of Health and Social Care 2020
Dietician, NHS	36[f,g]	
Social worker, PSS	45[f,g]	
Home care worker, PSS	24[f,g]	
Palliative care nurse, NHS	89[f]	
Dialysis nurse specialist, NHS	89[f]	
District nurse, NHS	89[f]	
Counsellor, NHS	48[f,g]	
Other		
Nurse (e.g. diabetic), NHS	89[f]	
Occupational therapist, NHS	36[f,g]	
Physiotherapist, NHS	36[f,g]	
Optician, NHS	36[f,g]	
Chiropodist, NHS	36[f,g]	
Podiatrist, NHS	36[f,g]	
Clinical support worker nursing higher level, NHS	52[f]	
Consultant medical, NHS	119[f,g]	
Consultant surgical, NHS	114[f,g]	
Clinical psychologist consultant, NHS	114[f,g]	

a Per session.
b Per session.
c Per episode.
d Per day.
e Per attendance.
f Per hour.
g In the absence of cost per hour of patient contact, cost per contracted hour for these professions was used based on advice via personal communication with Personal Social Services Research Unit.

TABLE 5 National Health Service and PSS costs for resource use categories (base-case analysis) (£, 2020)

Resource use category	BGFM (*n* = 222) £, mean (SD)	CFM (*n* = 215) £, mean (SD)	BGFM-CFM £, mean difference (95% CI)[a]	*p*-value[a]
CRF haemodialysis	38,338.58 (9963.56)	38,833.06 (9379.89)	−494.48 (−2199.08 to 1210.11)	0.57
CRF Bioimpedance	185.86 (78.63)	0 (0)	185.86 (175.46 to 196.27)	0.00
Inpatient	10,320.87 (744.32)	10,369.42 (756.34)	−48.55 (−2079.66 to 1982.554)	0.96
HES inpatient (scheduled)	4451.29 (5522.02)	4455.39 (5869.24)	−4.10 (−1103.56 to 1095.36)	0.99
HES inpatient (unscheduled)	5869.57 (7438.17)	5859.64 (9204.54)	9.93 (−1503.85 to 1523.72)	0.99
CRF inpatient, nursing home	0 (0)	54.39 (87.58)	−54.39 (−66.02 to −42.75)	0.00
HES adult critical care	306.23 (702.78)	234.31 (754.52)	71.92 (−65.78 to 209.62)	0.31
Outpatient	1946.53 (2200.46)	1917.13 (1869.96)	29.40 (−350.2878 to 409.09)	0.88
HES outpatient consultation	1946.53 (2200.47)	1905.20 (1867.28)	41.32 (−347.16 to 429.81)	0.83
CRF outpatient, nursing home	0 (0)	11.92 (12.79)	−11.92 (−13.69 to −10.16)	0.00
CRF primary, community care	711.68 (526.99)	510.45 (301.74)	201.22 (120.84 to 281.61)	0.00

CFM, current fluid management.
a Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.

TABLE 6 European Quality of Life measure-5 Dimensions utility scores (base-case analysis)

EQ-5D-5L[a]	BGFM (*n* = 222) mean (SD)	CFM (*n* = 215) mean (SD)	BGFM-CFM mean difference (95% CI)[b]	*p*-value[b]
Baseline	0.554 (0.278)	0.600 (0.276)	−0.046 (−0.099 to 0.006)	0.09
Month 3	0.541 (0.277)	0.549 (0.270)	−0.008 (−0.059 to 0.043)	0.75
Month 6	0.538 (0.266)	0.566 (0.248)	−0.028 (−0.075 to 0.019)	0.25
Month 9	0.513 (0.260)	0.529 (0.243)	−0.016 (−0.062 to 0.031)	0.50
Month 12	0.504 (0.256)	0.486 (0.265)	0.018 (−0.031 to 0.067)	0.47
Month 15	0.506 (0.247)	0.485 (0.239)	0.021 (−0.023 to 0.065)	0.35
Month 18	0.485 (0.246)	0.466 (0.252)	0.019 (−0.028 to 0.067)	0.42
Month 21	0.449 (0.276)	0.412 (0.262)	0.037 (−0.013 to 0.087)	0.15
Month 24	0.444 (0.263)	0.415 (0.255)	0.029 (−0.019 to 0.076)	0.25

CFM, current fluid management.
a EQ-5D-5L utility estimates using Hernandez Alava value set.
b Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.