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Research Article

Cost-effectiveness of bioimpedance-guided fluid management in patients undergoing haemodialysis: the BISTRO RCT

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Abstract

Background: The BioImpedance Spectroscopy to maintain Renal Output randomised controlled trial investigated the effect of bioimpedance spectroscopy added to a standardised fluid management protocol on the risk of anuria and preservation of residual kidney function (primary trial outcomes) in incident haemodialysis patients. Despite the economic burden of kidney disease, the cost-effectiveness of using bioimpedance measurements to guide fluid management in haemodialysis is not known.

Objectives: To assess the cost-effectiveness of bioimpedance-guided fluid management against current fluid management without bioimpedance.

Design: Within-trial economic evaluation (cost–utility analysis) carried out alongside the open-label, multicentre BioImpedance Spectroscopy to maintain Renal Output randomised controlled trial.

Setting: Thirty-four United Kingdom outpatient haemodialysis centres, both main and satellite units, and their associated inpatient hospitals.

Participants: Four hundred and thirty-nine adult haemodialysis patients with > 500 ml urine/day or residual glomerular filtration rate > 3 ml/minute/1.73 m^2.

Intervention: The study intervention was the incorporation of bioimpedance technology-derived information about body composition into the clinical assessment of fluid status in patients with residual kidney function undergoing

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haemodialysis. Bioimpedance measurements were used in conjunction with usual clinical judgement to set a target weight that would avoid excessive fluid depletion at the end of a dialysis session.
Main outcome measures: The primary outcome measure of the BioImpedance Spectroscopy to maintain Renal Output economic evaluation was incremental cost per additional quality-adjusted life-year gained over 24 months following randomisation. In the main (base-case) analysis, this was calculated from the perspective of the National Health Service and Personal Social Services. Sensitivity analyses explored the impact of different scenarios, sources of resource use data and value sets.
Results: The bioimpedance-guided fluid management group was associated with £382 lower average cost per patient (95% CI −£3319 to £2556) and 0.043 more quality-adjusted life-years (95% CI −0.019 to 0.105) compared with the current fluid management group, with neither values being statistically significant. The probability of bioimpedance-guided fluid management being cost-effective was 76% and 83% at commonly cited willingness-to-pay threshold of £20,000 and £30,000 per quality-adjusted life-year gained, respectively. The results remained robust to a series of sensitivity analyses.
Limitations: The missing data level was high for some resource use categories collected through case report forms, due to COVID-19 disruptions and a significant dropout rate in the informing BioImpedance Spectroscopy to maintain Renal Output trial.
Conclusions: Compared with current fluid management, bioimpedance-guided fluid management produced a marginal reduction in costs and a small improvement in quality-adjusted life-years. Results from both the base-case and sensitivity analyses suggested that use of bioimpedance is likely to be cost-effective.
Future work: Future work exploring the association between primary outcomes and longer-term survival would be useful. Should an important link be established, and relevant evidence becomes available, it would be informative to determine whether and how this might affect longer-term costs and benefits associated with bioimpedance-guided fluid management.
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Background

Maintenance of residual kidney function (RKF) in patients commencing dialysis has been linked to notable benefits, including improved survival, better quality of life and lower risk of intradialytic hypotension, cardiac stunning and death due to removal of high fluid volumes.[1–4] However, there is little evidence on the effectiveness of interventions to maintain RKF in patients undergoing haemodialysis; where trials have been undertaken, they have been limited by their small sample sizes (< 50 participants).[5–7] This issue is also confounded by inconsistency in the design and application of dialysis unit protocols to guide fluid management, which was evident in the findings of a recent UK-wide survey of practices.[8]

Of the approximately 68,000 people in the UK treated with kidney replacement therapies for end-stage kidney disease in 2019, about one-third (24,000) received centre-based haemodialysis at an annual cost of 0.5% of the NHS budget, excluding additional costs, such as travel, drugs, access procedures and inpatient episodes.[9,10]

A key objective of kidney replacement therapies is to regulate the body's fluid or 'volume' status. Getting this wrong leads to either volume excess or depletion, and both can be very harmful. In this high-cost setting, bioimpedance spectroscopy devices have been developed and are frequently used in haemodialysis units, where they have the potential to enhance the productivity of care by helping clinicians make appropriate and safe treatment decisions. For example, improved accuracy in the assessment of a patient's fluid status when compared to clinical judgement alone may reduce the risk of volume depletion which may, in turn, help to preserve RKF. The anticipated benefit to patients would be a change in clinical practice in which a more balanced approach to the bidirectional risks of volume status is taken that is associated with improved well-being, fewer dialysis-related symptoms, possibly less dialysis in those commencing treatment in an incremental fashion, and potentially better survival.[11–15] Through these benefits, bioimpedance also has potential to address several of the NHS Outcomes Framework domains. These include prevention of premature death, improving outcomes by addressing a number of National Institute for Health and Care Excellence (NICE) chronic kidney disease standards, such as cardiovascular risk, blood pressure and avoidance of acute illness episodes[16,17] and enhancing the quality of life for people on dialysis, and contributing through improved engagement and activation to a more positive patient experience.[18,19]

In making recommendations for the use of bioimpedance, NICE considered that there was insufficient evidence to recommend its routine application[20] and called for rigorous evidence on its clinical effectiveness and cost-effectiveness. In response, the National Institute for Health and Care

Research (NIHR) funded the BioImpedance Spectroscopy to maintain Renal Output (BISTRO) randomised controlled trial (RCT), through its Health Technology Assessment (HTA) programme. The trial demonstrated that bioimpedance added to a standardised fluid management protocol does not significantly improve preservation of RKF in patients on incident haemodialysis.[21] Recognising that the correct fluid status of a person with kidney failure will have an influence on a broader range of outcomes than just residual kidney function, it is appropriate that the cost-effectiveness of bioimpedance incorporating these outcomes is undertaken. To date, the cost-effectiveness of bioimpedance-informed haemodialysis is unknown. For example, it is unclear whether the extra cost of bioimpedance would be balanced out by reduced use of resources (e.g. because of a possible reduction in serious adverse events, hospital admissions) and/or improved outcomes in terms of quality-adjusted life-years (QALYs).

Aim of the bioimpedance spectroscopy to maintain renal output economic evaluation

The overarching aim of the BISTRO economic evaluation was to determine the costs, outcomes and overall cost-effectiveness of bioimpedance-guided fluid management (BGFM), compared with current fluid management (CFM). The primary (base-case) analysis was conducted from the perspective of the NHS and Personal Social Services (PSS). For each of the comparators, costs included use of healthcare resources associated with the intervention and care received in the primary care and hospital settings. Outcomes were expressed in terms of QALYs. Sensitivity analyses were carried out to present results based on different scenarios and sources of data.

Bioimpedance spectroscopy to maintain renal output trial methods

Trial design and participants

The economic evaluation was embedded into the BISTRO RCT. The trial's protocol and clinical effectiveness results are reported in detail elsewhere.[21,22] In brief, BISTRO was an open-label, pragmatic, randomised, multicentre UK wide trial of patients having incident haemodialysis, comparing current best practice in setting the post-dialytic target weight with the same assessment guided by serial bioimpedance measurements. In terms of inclusion criteria, potential participants were adult patients undergoing haemodialysis, aged > 18 years, within 3 months of commencing centre-based maintenance haemodialysis due to advanced kidney disease (CKD stage 5). Patients required evidence of RKF > 500 ml urine volume/day or residual glomerular filtration rate > 3 ml/minute/1.73 m^2. Participants should have entered the study on outpatient treatment. Exclusion criteria were the inability or unwillingness to give informal consent, or inability to comply with trial procedures, and either high risk of death or expected transplantation within 6 months.

Intervention

The study intervention was the incorporation of bioimpedance-derived information about body composition into the clinical assessment of fluid status of dialysis patients. In essence, the intervention was the availability of this additional information, specifically the normally hydrated weight reported by the device, which could then be used in conjunction with clinical judgement. Clinicians whose usual role was to assess fluid status were trained in the use of the fluid assessment proforma and asked to set the post-dialysis target weight to avoid excessive volume depletion, where possible. For patients in the control arm, the target weight was set using clinical judgement only. To achieve blinding, bioimpedance measurements were taken in both study groups but the results were concealed from the clinical teams and trial participants in the control group. To minimise performance bias and information bias, the bioimpedance measurements were taken independently of the fluid assessments by trained nurses. In an independent selection process, overseen by Kidney Research UK, the Fresenius body composition monitor (BCM) was selected and used for measuring bioimpedance.[22] All participating centres received bespoke training at the site during visits prior to enrolling patients, which included a standardised approach to taking bioimpedance measurements by the research nurses. Full bioimpedance data sets were downloaded on to the computers at participating renal centres and, throughout the trial, regular blinded quality control assessments of submitted readings were undertaken by the study team.

Randomisation and follow-up

Randomisation was one to one for the bioimpedance intervention and control groups, with random permuted blocks stratified by centre. All participants were followed up until the point when the first of the following events occurred: the participant became anuric, died, had a kidney transplantation, or withdrew from the study due to stopping dialysis (e.g. recovery of function), patient choice or investigator exclusion (e.g. medical condition) or reached the end of the trial with a maximum study follow-up period of 24 months. In those patients who reached the end point before 24 months, data on quality of life and health-related costs were collected while they remained in the study.

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Bioimpedance spectroscopy to maintain renal output economic evaluation methods

The economic evaluation took the form of a cost–utility analysis using, as a primary outcome, incremental costs (or cost savings) per QALY gained. The perspective of the base-case analysis was that of the UK NHS and PSS as recommended by NICE reference case for appraising health technologies.[23] Additional analyses were undertaken to explore different sources of data for particular cost categories, including broader costs, different health-related quality of life (HRQoL) instruments and value sets. The time horizon of this within-trial analysis matched the length of the BISTRO follow-up, that is, 24 months following randomisation. In line with recommendations,[23] costs and QALYs accruing beyond the first year were discounted at 3.5% per annum.

Analyses were carried out in accordance with the aims and methods specified in the BISTRO trial protocol and the health economics analysis plan (HEAP). The latter detailed the objectives to be pursued and the methods to be followed for the BISTRO economic evaluation. Deviations from the protocol were minor and served the purposes of meeting the study's objectives when obstacles were presented. The most noteworthy deviation was the additional use of Hospital Episode Statistics (HES) data when available data on resource use collected through case report forms were limited. The trial protocol and the HEAP were reviewed and approved by the BISTRO independent trial steering committee.

As specified in the study's HEAP, a decision model would be considered to extend the time horizon beyond 2 years, if findings suggested significant differential costs and outcomes as a result of the intervention accruing beyond the trial follow-up period. Analysis of the study's effectiveness carried out subsequently found the interventions to be equivalent (small, non-statistically significant effect of BGFM compared with CFM in terms of risk of anuria and rate of loss of RKF),[21] which was not anticipated to change beyond the 2-year period. This, and the paucity of reliable evidence linking BGFM-related effects to long-term outcomes,[24] suggested limited value (and caution) in extrapolating beyond the trial follow-up period.

Health outcomes

The main measure of health outcome in the BISTRO economic evaluation was QALYs. The QALY is a widely used and recommended[23] metric that combines quantity (length) of life and preference-based HRQoL into a single value. HRQoL was obtained through participants' responses to the EuroQol EQ-5 dimension-5 level (EQ-5D-5L)[25] and Short-Form 12 (SF-12) instruments[26] at baseline and 3-monthly thereafter, until month 24. The EQ-5D-5L consists of two parts: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system asks respondents to indicate their health state by ticking boxes next to the statement that represents the level of health (no problems, slight problems, moderate problems, severe problems and extreme problems) across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The EQ VAS asks respondents to rate their health on a vertical visual analogue scale, where the end points are labelled 'The best health you can imagine' and 'The worst health you can imagine'.[25] The SF-12 status description instrument asks respondents to answer 12 questions about their perceived status in relation to seven dimensions (physical activities, social activities, usual activities, pain, mental health, energy and fatigue, and general health).[26] Each participant's responses to the EQ-5D-5L and SF-12 status description instruments can be translated into a single, preference-based HRQoL index score (utility value) using appropriate value sets. Although a new UK specific EQ-5D-5L value set exists,[27] it has been a subject of controversy[28] and, currently, NICE recommends[29] the use of the Hernandez Alava *et al*. algorithm.[30] Therefore, 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 Hernandez Alava *et al*. value set for the EQ-5D-5L.[30] SF-12 was converted to the Short-Form 6 Dimensions (SF-6D) quality of life instrument and utility values[31] (presented in sensitivity analysis). QALYs were calculated as the area under the curve connecting utility scores reported at different time points.[32] Deceased patients were assigned a utility of zero from the date of death.

Resource use and costs

Key healthcare resource use and costs for both comparators were obtained from two primary resources: (1) patient-level data collected within the BISTRO trial and (2) routinely collected data for care received within a hospital through HES. As per the BISTRO protocol, the latter source was used to provide more accurate information on episodes of care provided in hospital (i.e. scheduled and unscheduled inpatient admissions, critical care admissions and hospital outpatient visits). Data collected as part of the BISTRO trial were captured through case report forms (CRFs) and a client services receipt inventory for chronic kidney disease questionnaire.[33] CRFs were completed at baseline and 3-monthly thereafter until month 24 (bioimpedance and haemodialysis sessions were also completed at months 1 and 2). A table listing information about the type of data

TABLE 1 Source of resource use and cost data for base-case analysis

Resource use or cost category	Base-case analysis
Bioimpedance sessions	CRF
Haemodialysis sessions	CRF
Inpatient admissions	
Scheduled	HES (incl. EL, DC, RP)
Unscheduled	HES (incl. NES, NEL)
Nursing home	CRF
Critical care admissions	HES
Outpatient appointments	
Hospital outpatient visits	HES
Nursing home	CRF
Primary and community care services	CRF

CRF, case report form; DC, daycase care; EL, elective care; HES, Hospital Episode Statistics; NEL, non-elective long stay; NES, non-elective short stay; RP, regular day/night.

collected from CRFs and the schedule of data collection can be found in *Appendix 1*, *Table 12*. Administrative hospitalisation data (HES) for BISTRO participating sites were obtained from NHS Digital in England, Public Health in Scotland, NHS Informatics Service in Wales and by the site research teams in Northern Ireland. HES data were cleaned (e.g. cancellations and duplicates removed) and checked against randomisation date, analysis date, event type, date of 2-year follow-up and trial end date. *Table 1* gives the source of data for each key resource use category in the base-case analysis.

Healthcare resources were translated into costs using unit cost values taken from up-to-date national sources, including the Unit Costs of Health and Social Care 2020 [Personal Social Services Research Unit (PSSRU)][34] and the National Schedule of NHS Costs 2019–20.[35] Monetary values throughout the study were expressed in Great British pounds using 2019–20 as the base year. Service use over the 24-month period was multiplied by unit costs to arrive at total cost for each patient in each of the alternative comparators.

Bioimpedance sessions

The cost of a bioimpedance device was obtained from the manufacturer Fresenius Medical Care (UK) Ltd (www.freseniusmedicalcare.co.uk), and the additional, bioimpedance-related cost per session over the duration of the study was calculated taking into account the device cost, necessary disposables, maintenance costs, device depreciation, personnel training and staff cost associated with measurements and interpretation (see *Appendix 2*, *Tables 13* and *14*).

Haemodialysis sessions

Haemodialysis sessions took place in outpatient haemodialysis centres, within main or satellite units and in their associated inpatient renal units.[22] For each participating patient, the number of haemodialysis sessions was recorded in CRFs and, for the period between CRFs, this number was assumed to be fixed. The unit cost of a haemodialysis session was taken from the National Schedule of NHS Costs 2019–20[35] (*Table 2*).

TABLE 2 Unit cost of resource use services

Service	Unit cost (£)	Source
Bioimpedance session (CRF)	25.10[a]	Fresenius Medical Care (UK) Ltd, Unit Costs of Health and Social Care 2020[34]
Haemodialysis sessions (CRF)		
Catheter or line for hospital/satellite	165[b]	National Schedule of NHS Costs 2019–2020[35]
Fistula or graft for hospital/satellite	163.50[b]	
Inpatient admissions		
Scheduled (HES)	See *Appendix 3*, *Table 15*	National Schedule of NHS Costs 2019–2020[35]
Unscheduled (HES)	See *Appendix 3*, *Table 16*	
Scheduled (CRF)	4168[c]	Unit Costs of Health and Social Care 2020[34]

continued

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TABLE 2 Unit cost of resource use services (*continued*)

Service	Unit cost (£)	Source
Unscheduled (CRF)	See *Appendix 4*, *Table 17*	National Schedule of NHS Costs 2019–2020[35]
Nursing home (CRF)	184[d]	Unit Costs of Health and Social Care 2020[34]
Critical care admissions (HES)	See *Appendix 5*, *Table 18*	National Schedule of NHS Costs 2019–2020[35]
Outpatient appointments		
Hospital outpatient visits (HES)	See *Appendix 6*, *Table 19*	National Schedule of NHS Costs 2019–2020[35]
Hospital outpatient visits (CRF)	135[e]	Unit Costs of Health and Social Care 2020[34]
Daycare 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[34]
Dietitian, 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]	

CRF, case report form; HES, hospital episode statistics; PSS, Personal Social Services.
a Per session (see *Appendix 2*, *Tables 13* and *14*).
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 PSSRU.

Inpatient admissions

Data on scheduled and unscheduled inpatient admissions were available from HES. Data sets were cleaned, checked and converted to the format accepted by HRG4 + 2020 National Costs Grouper[36] for admitted patient care. This was to check the healthcare resource group (HRG) codes attached to any of the inpatient admissions. A total of 17 different body system categories including 171 different HRG code types were defined for the scheduled admissions. Each of the scheduled HRG codes was then assigned a relevant elective, daycase or regular day/night average unit cost obtained from the NHS Reference Costs Guide[35] (see *Appendix 3*, *Table 15*). For the unscheduled admissions, 17 different body system categories including 236 different HRG code types were defined. According to the *NHS Data Model and Dictionary 2021* and the *Reference Costs Guidance 2015–16*, non-elective short stay is defined as any length of inpatient stay < 2 days and non-elective long stay defined as any length of inpatient stay of 2 days or more.[37,38] Based on these definitions, each of the unscheduled HRG codes was assigned a relevant non-elective short- or long-stay average unit cost obtained from the NHS Reference Costs Guide[35] (see *Appendix 3*, *Table 16*).

A limited amount of information regarding number and dates of admissions was made available through CRFs, and these were used in sensitivity analyses. There was no information available regarding the reason of scheduled admission to be able to provide exact unit cost for hospital inpatient ward. Therefore, an average unit cost per episode of an average elective HRG was attached to scheduled admissions[34] (*Table 2*). A unit cost per day was attached to nursing home admissions[34] (see *Table 2*). Unscheduled inpatient admissions due to serious adverse events that led to hospital admission were captured in CRFs and unscheduled admissions, whether or not due to serious adverse events, were available from HES. The former were costed using unit costs from NHS Reference Cost Schedules. The latter were costed as part of HES data costing.[35] Sixteen different body system categories including different Common Terminology Criteria for Adverse Events (CTCAE) Dictionary term types and their grades were defined within the serious adverse events collected through CRF. The CTCAE terms and their descriptions were linked to 44 best-possible HRG code types and currency description; they were assigned a non-elective short- or long-stay average unit cost[35] (see *Appendix 4*, *Table 17*).

Critical care admissions

Critical care admissions were obtained from HES. Files were cleaned, checked and converted to the format accepted by National Costs Grouper[36] for adult critical care, to attach HRG codes to each critical care admission episode. Six different critical care/HRG code types were defined and each of the adult critical care HRG codes was then assigned a relevant unit cost considering the number of supported organs (0, 1, 2, 3 or 4)[35] (see *Appendix 5*, *Table 18*).

Outpatient appointments

Outpatient appointments are captured by HES; thus, data on such appointments were available from this source. All files were cleaned, checked and converted to the format accepted by National Costs Grouper[36] for non-admitted consultation (i.e. hospital outpatient visits). This was to attach HRG codes to any of the outpatient appointments. 139 different outpatient services/HRG code types were defined. Each of the outpatient HRG codes was then assigned a relevant face-to-face, first or follow-up attendance or telephone/telemedicine, first or follow-up, consultation unit cost[35] (see *Appendix 6*, *Table 19*).

Limited information about outpatient hospital appointments was collected through CRF. This information was used in a sensitivity analysis. There was no information available regarding the reason for outpatient visits, so an average unit cost[34] was assigned (see *Table 2*). In addition, a question about nursing home visits in the CRF made available nursing home (daycare centre) attendances, which were assigned a unit cost from the PSSRU Unit Costs of Health and Social Care report[34] (see *Table 2*).

Primary and community care services

Primary and community care services, including appointments with general practitioners and nurses, were collected through CRFs. Unit costs for costing of different professions were taken from the PSSRU Unit Costs of Health and Social Care report[34] (see *Table 2*).

Time devoted to caring by unpaid carers

Data were also collected on time devoted to caring by unpaid carers through a relevant question in the Client Services Receipt Inventory. These data were used to calculate costs incurred by patients' family to be included in a sensitivity analysis. These included help patients had received from friends or family members as a result of their illness, including personal care (e.g. bathing), help with medical procedures (e.g. taking medication), help inside the home (e.g. cooking), help outside the home (e.g. shopping), and time spent 'on call'. Cost of these forms of unpaid carer work were calculated according to the replacement cost method[39] (see *Table 2*).

Missing data

Missing data are a common occurrence in studies collecting patient-level data. The choice of analytic method to be used for accounting for missing data

depends on the extent of missing information and the likely underlying mechanism through which data were missing. Descriptive analyses of missing data were carried out to investigate the patterns of missing data (through graphs) and the likely mechanism of missingness. Utility values and cost values for deceased participants were imputed by zero from the time of their death. Additionally, a cost of zero was attached to bioimpedance sessions (in the intervention group) and haemodialysis (in both groups) after transplantation or recovery of sufficient kidney function to allow the patient to stop dialysis. The remaining missing utility and costs data were imputed under the missing at random assumption, at each time point for utility and for year 1 and 2 for different cost components, using fully conditional multiple imputation by chained equations implemented through the MICE package in STATA® version 17 (StataCorp LP, College Station, TX, USA).[40] The appropriateness of using missing at random was evaluated by investigating the missing data patterns and comparing attributes with and without missing utility data at each follow-up time point; and cost components data at years 1 and 2. The multiple imputation model used covariates and utility scores collected at baseline. The imputation was conducted separately by trial arm.[41]

Statistical and cost–utility analyses

In line with recommended practice for the analysis of RCT data, the intention-to-treat (ITT) principle was adopted.[42] The ITT data set comprised all randomised patients, analysed according to randomised groups, and including those deviating from protocol, switching treatment, withdrawn or lost to follow-up. The unadjusted calculated mean total per-patient values were given for the intervention and control arms alongside mean difference and 95% confidence intervals (CIs) obtained through non-parametric bootstrap (bias corrected and accelerated) methods using 1000 replications.[43] The distributions of the calculated costs and QALYs were interrogated using graphs and skewness statistics and generalised linear regression models (GLM) were used.[44] Adjustment for baseline utility and for the same covariates (*Table 5*) as for the primary outcome was made. Cost–utility is presented as an incremental cost-effectiveness ratio (ICER), calculated as difference in costs between comparators over difference in QALYs between comparators.[45] The use of bioimpedance was selected as the intervention and current management without bioimpedance as control. Measures of uncertainty were calculated for the mean difference estimates through bootstrap methods using 1000 replications.[43] For the base-case analysis, to account for the inherent uncertainty in the results due to sampling variation, the joint distribution of differences in cost and QALYs was derived using 5000 of non-parametric bootstrap simulations/iterations.[46] The simulated cost and QALYs pairs were depicted on a cost-effectiveness plane and were plotted as cost-effectiveness acceptability curves (CEACs).[47] A CEAC shows the probability of the bioimpedance-guided and standard fluid management options being cost-effective across a range of possible values of willingness to pay (WTP) for an additional QALY. Net monetary benefits (NMB) for each compared option, as well as incremental net monetary benefits (BGFM vs. CFM), were estimated for a range of different WTP thresholds, where a positive incremental NMB would indicate that BGFMI is cost-effective compared with CFM. Data management tasks and statistical analyses were carried out in STATA version 17. Findings of this economic evaluation were reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement.[48]

Base-case and sensitivity analyses

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. The base-case and sensitivity analyses are described in *Table 3*.

Detail information regarding resource use data sources used in sensitivity analyses are given in *Table 4*.

Results

Participants characteristics

The study recruitment process is summarised in the Consolidated Standards of Reporting Trials diagram, which has been published elsewhere.[21] Overall, 439 patients were initially recruited from 34 centres, for a maximum follow-up period of 24 months. Randomisation led to well-balanced study arms according to prespecified baseline patient characteristics (*Table 5*).

Data completeness

The availability of key economic data (healthcare resource use, EQ-5D-5L and SF-12) by comparator is provided in *Appendix 7*, *Table 20*. At each point in time, EQ-5D-5L data were considered incomplete if the health status classification part of the questionnaire was not completed or it was partially completed (i.e. fewer than its five domains were completed), which precluded the calculation of utility values. Similarly, resource use and costs were considered missing if an item or answer was not available (i.e. it was not recorded in the CRF or it was unavailable through HES).

TABLE 3 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[40] *Data source*: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use (see *Table 1*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *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[49] *Data source*: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *Statistical model specification*: unadjusted
Sensitivity analysis 2 (CRF rather than HES for resource use)	*Data*: missing data imputed using multiple imputation[40] *Data source*: HES for critical care admissions; CRF for other resource use (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *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[40] *Data source*: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *Statistical model specification*: unadjusted ITT
Sensitivity analysis 4 (EQ-5D using Devlin)	*Data*: missing data imputed using multiple imputation[40] *Data source*: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Devlin *et al.*[27] *Statistical model specification*: GLM – costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 5 (SF-6D)	*Data*: missing data imputed using multiple imputation[40] *Data source*: HES for scheduled and unscheduled inpatient admissions, critical care admissions, and hospital outpatient visits; CRF for other resource use (see *Table 4*) QALY *derivation*: through SF-12 (converted to SF-6D) using Brazier and Roberts algorithm[31] *Statistical model specification*: GLM – costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility
Sensitivity analysis 6 (excluded nursing home and primary/community care)	*Data*: missing data imputed using multiple imputation[40] *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 (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *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[40] *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 than PSS (see *Table 4*) QALY *derivation*: through EQ-5D-5L using a value set by Hernandez Alava *et al.*[30] *Statistical model specification*: GLM – costs adjusted for relevant covariates; QALYs adjusted for both relevant covariates and baseline utility

CRF, case report form; GLM, generalised linear model; HES, Hospital Episode Statistics; QALY, quality-adjusted life-year.

As anticipated, there was a high level of completeness of HES data (only 14 missing data from HES England). As expected, the amount of missing data increased with time in trial and the level of completeness was markedly low for particular resource use data collected via CRFs (e.g. completeness of bioimpedance sessions, haemodialysis sessions, and primary and community care services dropped to 22%, 22% and 13%, respectively, at year 2: 12–24 months). In a similar fashion, completion of EQ-5D dropped to levels below 60% from month 6 onwards, with less than one-third of the expected completed questionnaires returned at the 18-month follow-up point.

TABLE 4 Sources of resource use information in sensitivity analyses

Resource use or cost category	Sensitivity analysis no. 2	All other sensitivity analyses[a]
Bioimpedance sessions	CRF	CRF
Haemodialysis sessions	CRF	CRF
Inpatient admissions		
Scheduled	CRF (incl. EL)	HES (incl. EL, DC, RP)
Unscheduled	CRF (incl. SAEs: NES, NEL)	HES (incl. NES, NEL)
Nursing home	CRF	CRF
Critical care admissions	HES	HES
Outpatient appointments		
Hospital outpatient visits	CRF	HES
Nursing home	CRF	CRF
Primary and community care services	CRF	CRF

CRF, case report form; DC, day case; EL, elective; HES, Hospital Episode Statistics; NEL, non-elective long stay; NES, non-elective short stay; RP, regular day/night; SAEs, serious adverse events.
a Sensitivity analysis no. 6 excludes nursing home, and primary and community care services; sensitivity analysis no. 7 includes patients' family incurred cost as well.

Overall, there were entirely complete data for all resource use categories for only 40 participants (9.15% of all participants; 22 in BGFM group, 18 in CFM group) and only for 48 participants (10.98% of all participants; 28 in BGFM group, 20 in CFM group) for all EQ-5D-5L measurements. The low availability of data over the 24 months made imputation of missing data highly necessary. Further information on data completion is given in *Appendix 7*.

Costs

Imputed costs for each resource use category and assessed comparator for the base-case analysis are given in *Table 6*. Findings show BGFM to be associated with greater costs for the cost categories of primary and community care (£201.22), bioimpedance (£185.86), critical care (£71.92), outpatient consultations (£41.32) and unscheduled inpatient admissions (£9.93). Conversely, BGFM was associated with cost savings for the cost categories of haemodialysis (−£494.48), inpatient nursing home admissions (−£54.39), outpatient nursing home visits (−£11.92) and scheduled inpatient admissions (−£4.10). Differences in costs for bioimpedance, inpatient stay and outpatient visits in nursing homes, and care received in primary and community settings were statistically significant ($p < 0.00$).

The total costs and the difference between the assessed options for the base-case analysis are given in *Table 7*. Overall, over 24 months, the mean per-patient cost with

TABLE 5 Prespecified baseline patient characteristics of the BGFM and CFM groups at randomisation

		BGFM (n = 222)	CFM (n = 213)[a]
Sex; male/female (% male)		157/65 (70.7)	149/63 (69.3)
Age, mean (SD)		60.06 (14.3)	62.7 (13.7)
Ethnicities, *n* (%)	White	174 (78.4)	173 (81.2)
	Black/Black British	6 (0.3)	0 (0)
	Asian/Asian British	7 (0.3)	2 (0.4)
	Other	35 (15.8)	38 (17.8)
Planned/unplanned start, *n* (%)		180 (81.1)/42 (18.9)	184 (86.4)/29 (13.6)
Comorbidities, *n* (%)	Malignancy	14 (6.3)	14 (6.6)
	Ischaemic heart disease	41 (18.4)	47 (22.1)
	Peripheral vascular disease	19 (8.5)	33 (15.3)
	Left ventricular dysfunction	31 (14.0)	25 (11.2)
	Diabetes mellitus	107 (48.2)	91 (42.3)
	Systemic collagen vascular disease	6 (2.7)	7 (3.3)

TABLE 5 Prespecified baseline patient characteristics of the BGFM and CFM groups at randomisation (*continued*)

	BGFM (*n* = 222)	CFM (*n* = 213)[a]
Comorbidity score, median (IQR)	1 (0, 2)	1 (0, 2)
Patients on diuretics, *n* (%)	115 (51.8)	111 (51.6)
Patients on RAAS inhibition, *n* (%)	61 (27.4)	49 (22.7)
Patients on calcium antagonists, *n* (%)	103 (46.4)	117 (52)

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; IQR, interquartile range; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation.
a Two of the 215 patients in the control groups did not have baseline data. However, as part of the multiple imputation, these data were imputed.

TABLE 6 NHS 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 £,[a] mean difference (95% CI)	*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

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; CRF, case report form; HES, Hospital Episode Statistics; PSS, Personal Social Services.
a Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.

BGFM was £382 lower (non-significant, 95% CI −3319 to 2556) than that with CFM.

Health outcomes

Table 8 summarises the imputed health outcomes (EQ-5D-5L utility scores) and between group mean differences at each time point and across the follow-up period for the base-case analysis. EQ-5D utility scores from follow-up time point 12 suggest a small non-significant gain for the BGFM group.

The total QALYs and the difference between the assessed options for the base-case analysis are given in *Table 9*. Overall, over 24 months, there was a small, non-significant QALY gain for the BGFM group 0.043 (95% CI −0.019 to 0.105).

Cost–utility results

Results for the base-case analysis are presented in *Table 10*. Over 24 months BGFM was associated with a slightly lower total per-patient cost, giving an estimated total per-patient cost-saving of £382 (non-statistically significant, 95% CI −£3319 to £2556). In terms of QALYs gained, BGFM appeared to be slightly more effective than CFM, resulting in a gain of 0.043 QALYs (non-statistically significant, 95% CI −0.019 to 0.105). On average, BGFM was found to be less costly and more effective than CFM.

Figure 1 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 BGFM and CFM. Approximately 90% of the simulated

TABLE 7 Mean total cost per patient for BGFM compared with CFM

	Total cost			95% CI[a]	
Comparators	Mean	SD	Difference[a]	Lower CI	Upper CI
CFM	52,030.51	17,041.81	−381.65	−3318.97	2555.67
BGFM	51,648.86	13,668.27			

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; SD, standard deviation.
a Generated through bootstrapping using 1000 replications and is adjusted for baseline covariates.

TABLE 8 EQ-5D utility scores (base-case analysis)

EQ-5D-5L[a]	BGFM (*n* = 222), mean (SD)	CFM (*n* = 215), mean (SD)	BGFM–CFM, mean difference[b] (95% CI)	*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

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; SD, standard deviation.
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.

TABLE 9 Mean QALY per patient for BGFM vs. CFM

	Total QALYs[a]			95% CI[b]	
Comparators	Mean	SD	Difference[b]	Lower CI	Upper CI
CFM	0.966	0.438	0.043	−0.019	0.105
BGFM	1.009	0.443			

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; SD, standard deviation.
a Total QALYs estimated as the area under the curve.
b Generated through bootstrapping using 1000 replications and is adjusted for baseline covariates, including baseline EQ-5D-5L scores.

TABLE 10 Cost–utility results of base-case analysis at 24 months (£, 2020)[a]

	BGFM		CFM				
Parameter	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (BGFM vs. CFM) (£ 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)	BGFM less costly and more effective

BGFM, bioimpedance-guided fluid management; CFM, current fluid management.
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 3*.

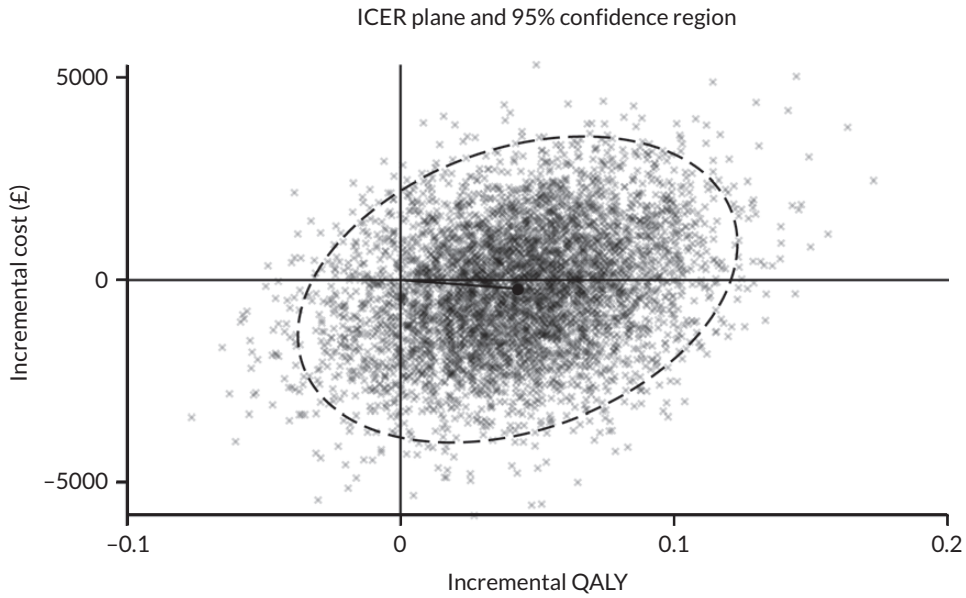

FIGURE 1 Cost-effectiveness plane depicting the distribution of simulated cost and QALY pairs.

pairs are located in the east half of the plane, indicating that BGFM is likely to be more effective than CFM. Simulated estimates are fairly split between the north and south halves of the plane, with 44% being located in the north half and 56% in the south. Overall, 48% of the simulated estimates are located in the south-east quadrant, indicating that BGFM is less costly and more effective than CFM. Of the remaining simulated estimates, 42% are in the north-east quadrant, 8% in the south-west and 2% in the north-west.

The probability that BGFM is cost-effective at different WTP thresholds, representing the (hypothetical) amount decision-makers may be willing to pay for an additional QALY, is shown in *Figure 2*. At £0, the probability that BGFM is cost-effective is 57%. At £20,000 per QALY, this rises to 76% and, at £30,000 per QALY, it further increases to 83% (see *Figure 2*).

Incremental NMBs, which measure the difference in NMB between alternative interventions, are plotted in *Figure 3*. At the WTP threshold of £20,000 per additional QALY the incremental NMB is £1091, and it increases to £1519 at the WTP threshold of £30,000 per additional QALY. A positive incremental NMB indicates that, at a particular WTP threshold, BGFM is cost-effective.

Overall, the findings suggest that the BGFM is likely to be cost-effective, although the incremental cost savings and QALY gains were marginal.

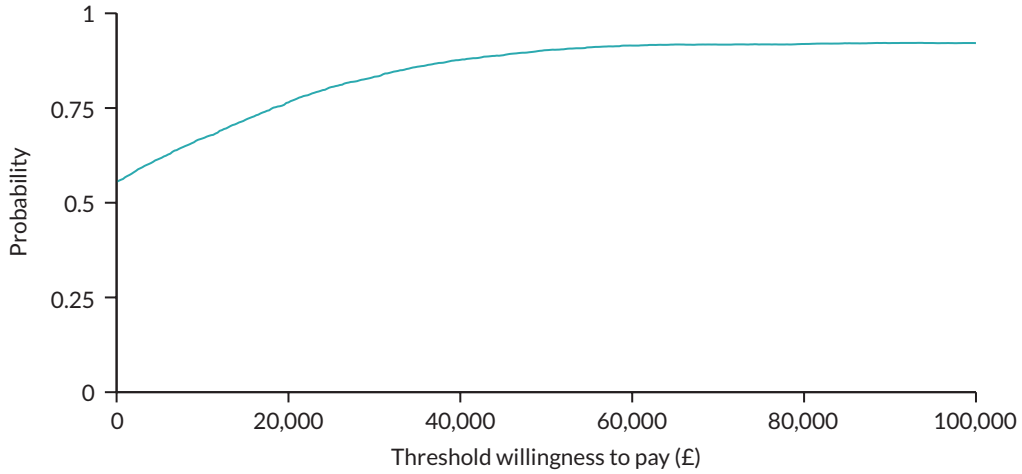

FIGURE 2 Cost-effectiveness acceptability curve showing the probability of BGFM being cost-effective at different values of WTP for a QALY.

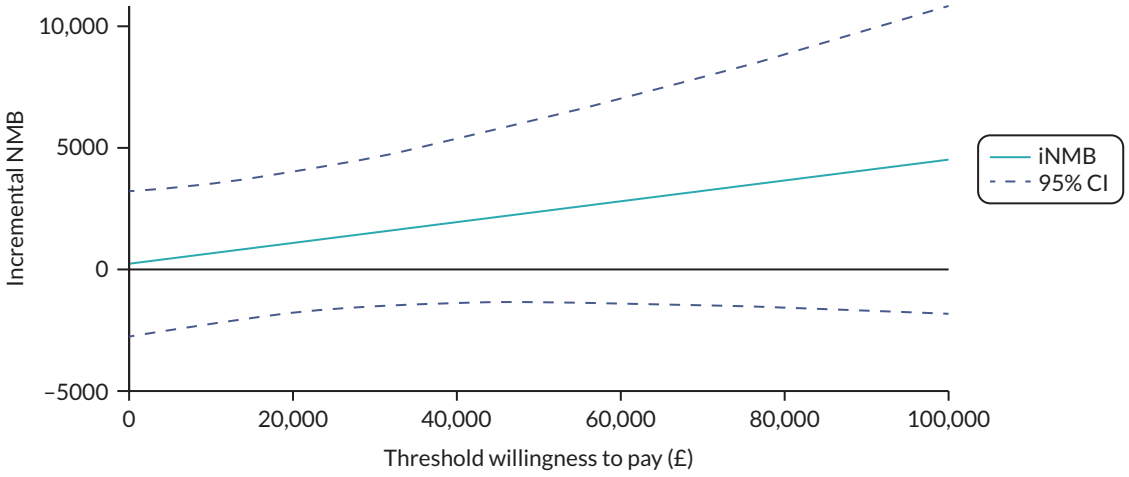

FIGURE 3 Incremental net monetary benefit (NMB) across different WTP values for a QALY. iNMB, incremental net monetary benefit.

Additional sensitivity analyses

Findings of sensitivity analyses can be found in *Table 11*, with more detailed information given in *Appendix 8* (*Tables 21* and *22*) and *Appendix 9* (*Tables 23* and *24*). Findings were largely similar to the base-case analysis, showing that, under different assumptions, BGFM is likely to be slightly less costly and modestly more effective than CFM. As an exception, a sensitivity analysis that took into account only 40 patients (9.15% of the sample) with complete data across all resource use categories and EQ-5D-5L measurements, showed an ICER of £16,780 per QALY, suggesting that the BGFM is more costly and more effective than CFM. Complete case analysis (with 90.85% missing data) was carried out for completeness. In this analysis, all cost categories apart from total outpatient visits cost and outpatient nursing home visits presented a small, non-significant increase of cost with BGFM group at 24 months (see *Appendix 8*, *Table 21*). However, findings of this analysis should be considered with caution, as they are calculated on the basis of a small number of complete data. Overall,

TABLE 11 Cost–utility results of sensitivity analyses at 24 months (£, 2020)[a]

	BGFM		CFM				
Analyses[b]	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (BGFM vs. CFM) (£ per QALY)
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)	BGFM 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)	BGFM 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)	BGFM 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)	BGFM 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)	BGFM 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)	BGFM less costly and more effective

BGFM, bioimpedance-guided fluid management; CFM, current fluid management.
a Estimates derived from bootstrapping using 1000 replications; cost adjusted for baseline covariates; QALYs adjusted for baseline covariates, including baseline EQ-5D-5L scores.
b Sensitivity analysis (SA) 1: available complete data; SA 2: CRF rather than HES for resource use; SA 3: unadjusted ITT; SA 4: EQ-5D using Devlin *et al.* algorithm; SA 5: using SF-6D; SA 6: excluding nursing home and primary community care; SA 7: including patient family incurred costs. For a detailed description of all sensitivity analyses, refer to *Table 3*.

all sensitivity analyses showed that use of bioimpedance is likely to be cost-effective at a cost-effectiveness threshold of £20,000–30,000 per QALY in the population studied.

Discussion

Patient and public involvement

The BISTRO trial was supported by patient and public involvement (PPI) from inception and design to delivery and dissemination of the results. It was co-led by a patient with lived experience of dialysis and expertise in research on devices who was a funded co-applicant, employed by NIHR Devices for Dignity. This co-applicant was a full member of the trial management group and led the patient advisory group that supported trial design, delivery and dissemination. He designed all the patient-facing communications. Deciding the optimal amount of fluid removal on dialysis is a complex clinical decision and measuring the primary outcome, RKF is a complex procedure. PPI was key in ensuring that the patient perspective was considered in all aspects of the trial, which resulted in excellent adherence to trial procedures.

Equality, diversity and inclusion

BioImpedance Spectroscopy to maintain Renal Output was an inclusive trial and the proportions of patients from minority groups are reported in the report of the primary findings[21] where they are compared with contemporary data reported to the UK Renal Registry.

Principal findings

Compared with CFM, the addition of bioimpedance measurements was associated with slightly lower costs and slightly higher QALYs. Apart from an additional analysis that used only the small number of complete data sets available, which found costs to be marginally higher in BGFM, sensitivity analyses also lent support to this option being slightly less costly and more effective than CFM. It is observed that the 95% CIs for incremental costs and incremental QALYs were wide both in base-case and sensitivity analyses. This indicated uncertainty around the estimate of the incremental costs and QALYs. Although the CIs for the ICERs were wide, BGFM remains likely to be cost-effective, as the simulated estimates were largely in the south-east (48%) and north-east (42%) quadrants and the probability of BGFM being cost-effective at the WTP threshold of £20,000 per QALY is 76%.

Bioimpedance spectroscopy to maintain renal output effectiveness findings versus cost-effectiveness findings

The results need to be considered jointly with findings of the BISTRO effectiveness analysis. The latter found that the primary outcome (time to anuria) despite a hazard ratio of 0.74, did not differ significantly between the BGFM and the CFM (control) groups, with a 95% CI that spanned one. The primary outcome event rate was half that predicted prior to trial design and the difference between the normally hydrated weight and the target weight set by clinicians did not differ by group. Findings of the BISTRO economic evaluation, on the other hand, suggest that the intervention is likely to be cost-effective, being slightly less costly and more effective than CFM. In interpreting these results, it is useful to keep a number of considerations in mind. First, the economic evaluation seeks to answer a question about BGFM's cost and effectiveness, which has a broader evaluative space. Given this, the primary outcome of the economic evaluation differs from that of the clinical study: it is a composite measure of differences in costs per difference in QALYs (with the latter being a broader measure, combining time in a health state and generic HRQoL), and hence there is always a possibility that findings about effectiveness will differ in direction from findings about cost-effectiveness. Second, the BISTRO RCT was not powered to estimate costs, QALYs or cost per QALY ratios with a desired precision. With this in mind, the question of interest is whether, despite appearing to be cost-effective, an intervention should be rejected for not reaching significance levels using common rules of inference. Such inference, it has been argued, is irrelevant for decision-making: if the aim is to maximise health benefits from a given budget, one should select the alternative that is shown to be the most cost-effective.[50] In this particular case, failing to do so would mean that an average cost-saving of approximately £380 per patient (which equates to as much as £9 million in total) and a slight increase of 0.04 QALYs would be forfeited.

Key strengths and limitations

This is the first study evaluating the cost-effectiveness of BGFM using patient-level data collected within a pragmatic, RCT. Strengths of the BISTRO trial, in which this economic evaluation is embedded, include a larger sample size compared with studies on the topic,[5–7] a 24-month follow-up period and frequent collection of data useful for the economic analysis (resource use and HRQoL). Additionally, data collected as part of the BISTRO trial were complemented by detailed data on care provided in hospital from HES (e.g. inpatient admission, critical care admissions, outpatient appointments), which offered more granular and complete information. Given this, BISTRO provides detailed new evidence on a range of relevant cost components. A number of sensitivity analyses were carried out to generate results on the basis of different sources of data (i.e. CRFs, HES), cost categories and HRQoL instruments and value sets. Finally, methods used throughout the economic analysis, including the base-case

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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

and additional analyses, were in line with 'good practice' recommendations and requirements for the allocation of healthcare resources in the UK.[23,45,51]

Despite these strengths, this study has certain limitations. First, BISTRO was not able to recruit to the initial target within the funding period, despite a funded extension and our attempt to compensate for this by extending the follow-up period. This would have resulted in a larger sample size for both the effectiveness and cost-effectiveness analyses. Second, the level of missing data was high for some resource use categories collected via CRFs, largely as a result of COVID disruptions and a significant dropout rate during the trial. Third, limited data on use of medications were collected through CRFs (at baseline only, to facilitate statistical adjustment), which precluded the inclusion of costs of medications (chiefly antihypertensives) provided outside the hospital setting (medications costs are incorporated in inpatient admission recorded in HES data). Additionally, costs beyond the NHS and PSS were limited to the opportunity cost of time devoted by unpaid carers. However, given no differential effectiveness of BGFM and CFM, it is not anticipated that medication use and broader costs accruing outside the NHS (e.g. time off work) attributable to BGFM and CFM would differ in a systematic way across the compared options. It is also worth noting that data completeness for the EQ-5D data was markedly reduced at 6 months and, as a result, the value of total QALYs over the 24-month period is influenced, at least to some extent, by the results of multiple imputation. Reassuringly, the direction and pattern of EQ-5D results generated by multiple imputation were in agreement with those of the complete case analysis based on available observations only (see *Appendix 9*, *Table 23*). It must be also noted that the results of this analysis are applicable to the patient population of interest in BISTRO (see *Trial design and participants*) and may not be generalisable to other populations.

Future research

Ongoing analysis as part of the trial is exploring the association between primary outcomes and longer-term survival. Should an important link be established, it would be informative to determine whether and how this might affect longer-term costs and benefits associated with BGFM.

Conclusions

The results of this economic evaluation demonstrate that BGFM results in modestly lower per-patient costs and a slightly higher number of QALYs than current fluid management. We anticipate that these findings offer further insights and useful evidence to support a decision about the wider use of bioimpedance spectroscopy in the particular patient population and setting.

Additional information

CRediT contribution statement

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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 corresponding author.

Ethics statement

The study had UK Integrated Research Ethics approval: 206213 (date of approval: 18 August 2016) and 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: https://www.keele.ac.uk/legalgovernancecompliance/legalandinformationcompliance/informationgovernance/ or by e-mail dpo@keele.ac.uk.

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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.

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This article 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.

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This article 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.

List of abbreviations

BCM	body composition monitor
BGFM	bioimpedance-guided fluid management
BISTRO	BioImpedance Spectroscopy to maintain Renal Output
CC	Charlson comorbidity
CEAC	cost-effectiveness acceptability curve
CFM	current fluid management
CRF	case report form
EQ-5D-5L	EuroQol EQ-5 dimension-5 level
EQ VAS	EQ visual analogue scale
GLM	generalised linear regression models
HEAP	health economic analysis plan
HES	Hospital Episode Statistics
HRG	healthcare resource group
HRQOL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
NEL	non-elective long stay
NES	non-elective short stay
NHW	normally hydrated weight
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	net monetary benefits
PPI	patient and public involvement
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RKF	residual kidney function
SF-12	Short-Form 12 Dimensions
SF-6D	Short-Form 6 Dimensions
WTP	willingness to pay

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Appendix 1

TABLE 12 Collection of health economics data through BISTRO CRFs

Category	Baseline	M 1	M 2	M 3	M 6	M 9	M12	M 15	M 18	M 21	M 24
HD[a]	x	x	x	x	x	x	x	x	x	x	x
BI[b]	x	x	x	x	x	x	x	x	x	x	x
Hospital and nursing home inpatient elective[c]				x	x	x	x	x	x	x	x
Inpatient SAEs[d]	x[e]										
Hospital and nursing home outpatient appointments[f]				x	x	x	x	x	x	x	x
Primary and community care[g]				x	x	x	x	x	x	x	x
Patients' family costs[h]				x	x	x	x	x	x	x	x
Quality of life	x			x	x	x	x	x	x	x	x

BI, bioimpedance; CRF, case report form; HD, haemodialysis; M, month; SAEs, serious adverse events.
a Date of dialysis prescription and number of dialysis sessions per week were obtained. These were completed by research nurses.
b Dates of bioimpedance measurements, which reflected sessions that took place, were collected. These were completed by research nurses.
c Hospital and nursing home inpatient elective services, and their number of admission days were collected. These were completed by patients.
d SAEs were collected which were completed by research nurses and clinicians. All information regarding SAEs including number, type (related, unrelated), body system, term, grade, description (diagnosis) and which group the patient was randomised to were reported.
e Data on SAEs were collected when SAE occurred.
f Hospital and nursing home outpatient appointments, and their number of attendances were collected. These were completed by patients.
g Primary and community care services (e.g. GP) and their number of contacts and average duration time (minutes) were collected. These were completed by patients.
h Information regarding time devoted to caring by unpaid carers and their number of hours were collected. These were completed by patients.

Appendix 2

Calculation of bioimpedance spectroscopy cost. Detail information of cost of BCM machine, related accessories, training and staff time.

For the purposes of this economic evaluation, it is necessary to determine the per-session cost of bioimpedance. The key steps in calculating this are explained below.

1. Average number of bioimpedance sessions.

The majority of patients had one measurement every 3 months (four sessions per year).

2. Determine the average number of patients served by bioimpedance device.

Also, for calculating bioimpedance costs per session, it was necessary to estimate the average number of

patients per haemodialysis unit on haemodialysis. Looking at the latest UK renal annual report,[9] the total adult patients receiving kidney replacement therapy for end-stage kidney disease was 68,111. Of these patients, 35.8% (*n* = 24,383) were on haemodialysis.[9] Therefore, dividing the total number of patients on haemodialysis in the UK (24,383) by total number of haemodialysis units in the UK (274) gives an average of 89 patients per unit were on haemodialysis.[52] This number, which was considered in our calculations, was very similar to the average 70–80 patients per unit of the BISTRO trial which we received from Leeds Teaching Hospital NHS Trust.

3. Costs of bioimpedance device and related equipment.

The costs of the bioimpedance device (BCM) and related accessories (2020), which were available through Akeso NHS Supply Chain, were received from the Fresenius Medical Care (UK) Ltd.
The cost of the BCM devices (the BCM machine plus first electrode cable, card reader and carry case was £5177.36). This cost was annuitised over effective lifetime of BCM of 10 years (£622.53) using an annual depreciation rate of 3.5%.[23,24] The effective lifetime of BCM was decided by consulting with Leeds Teaching Hospital NHS Trust. Estimated costs of BCM equipment maintenance were provided at £666.36 for annual maintenance, including spare electrode cable and batteries by Fresenius Medical Care (UK) Ltd. In terms of consumables, four electrodes were used per session and the price of each electrode was £0.75; each card was usable for 5 years and the price of each card was £6.28.

4. Cost of training.

Training resources were provided free of charge by the manufacturer, but the cost of NHS personnel's time is incurred by the NHS. The unit costs of staff involved in bioimpedance training (as well as measurement and interpretation) were taken from the Unit Costs of Health and Social Care 2020.[34] Total training costs (opportunity cost of time) for a typical haemodialysis centre were estimated based on the number of staff (two hospital nurses, band 6, and two clinical support workers, band 4) trained, multiplied by their costs per contract hour (£50 and £31, respectively) and the number of hours of training attended. They attended training 2 hours initially and then 15 minutes every year over 10 years. The total training

TABLE 13 Cost of bioimpedance device and related accessories

Description	Unit cost (£)	Source
Body composition monitor[a]	4500	Fresenius Medical Care (UK) Ltd
BCM skin electrodes – pack of 40[b]	30.00	
BCM patient card – pack of 10[c]	62.80	
BCM electrode cable[d]	156.98	
BCM card reader[e]	40.38	
BCM carry case[f]	480.00	
Purchase price of BCM + first electrode cable + card reader + carry case	5177.36	Fresenius Medical Care (UK) Ltd
Annual maintenance cost of BCM	666.36	Fresenius Medical Care (UK) Ltd
Cost per electrode	0.75	Fresenius Medical Care (UK) Ltd
Cost per card	6.28	Fresenius Medical Care (UK) Ltd

BCM, body composition monitor.
a One BCM machine per unit for the trial duration.
b One pack of electrodes per patient for the trial duration.
c One card per patient for the trial duration.
d Recommended units to buy a spare electrode cable in case of damage.
e One card reader per site for the trial duration.
f One carry case per site for the trial duration.

investment was spread over 10 years, and the equivalent annual cost was divided by the number of patients in the centre (n = 89) to give a cost per patient per year. For each centre the total training costs were estimated to be £672.30. Divided by 10 years, this comes to £67.23 and £0.76 per patient per year.

5. Cost of bioimpedance testing and interpretation.

Staff costs associated with the time required to conduct each test were estimated based on 10 minutes of direct patient contact with a band 6 hospital nurse or band 4 clinical support worker. Therefore, an average of these two was considered (£11.75). This was further multiplied by four to estimate the staff costs per patient per year (£47). The added hospital nurse (band 6) and consultant time required to interpret the findings of each bioimpedance test as part of clinical management were assumed to be 5 minutes and 1 minute, respectively, giving £6.14 per session and £24.56 per year.

TABLE 14 Unit cost of bioimpedance per patient year and per session

Description	Unit cost per patient year (£)	Unit cost per session (£)
BCM equivalent annual cost	6.99	1.75
Annual maintenance cost	7.49	1.87
Cost of electrodes	12.00	3.00
Card estimated annual cost of purchase	1.25	0.31
Training cost (opportunity cost of time)	0.76	0.19
Staff costs associated with the time required to conduct/measure	47.00	11.75
Staff costs associated with the time required to interpret	24.56	6.14
Total	100.05	25.10

BCM, body composition monitor.

Appendix 3

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost)

		Scheduled admissions unit cost (£)[35]		
Body system	HRG code and currency description	Elective	Day case	Regular day/night
Blood and lymphatic disorders	Sickle-cell anaemia with crisis, with CC score 2–5	3243	383	
	Sickle-cell anaemia with crisis, with CC score 6 +	5301	321	
	Plasma cell disorders with CC score 2–4		341	
	Plasma cell disorders with CC score 5–7		343	
	Other red blood cell disorders with CC score 2–5		369	
	Other red blood cell disorders with CC score 6–9		384	
	Other red blood cell disorders with CC score 10–13		356	
	Single plasma exchange or other intravenous blood transfusion, 19 years and over		584	

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

Body system	HRG code and currency description	Scheduled admissions unit cost (£)[35]		
		Elective	Day case	Regular day/night
Cardiac disorders	Arrhythmia or conduction disorders, with CC score 4–6	1173		
	Arrhythmia or conduction disorders, with CC score 13 +		1087	
	Actual or suspected myocardial infarction, with CC score 4–6	1625		
	Actual or suspected myocardial infarction, with CC score 7–9	1760		
	Cardiac valve disorders with CC score 5–8	2962		
	Explanation or attention to, cardiac pacemaker or cardioverter defibrillator, with CC score 6 +		1906	
	Implantation of dual-chamber pacemaker with CC score 6–8		2097	
	Implantation of electrocardiography loop recorder with CC score 0–2		1508	
	Implantation of electrocardiography loop recorder with CC score 3 +		1646	
	Other acquired cardiac conditions with CC score 0–2		540	207
	Other acquired cardiac conditions with CC score 3–5	2100	523	234
	Other acquired cardiac conditions with CC score 6–8	2539	576	
	Other acquired cardiac conditions with CC score 9–12	3023	673	
	Other acquired cardiac conditions with CC score 13 +	4805	802	
	Complex cardiac catheterisation with CC score 4–6		1525	
	Transient ischaemic attack with CC score 0–4			328
	Complex cardiac catheterisation with CC score 7 +	5325	1362	
	Complex percutaneous transluminal coronary angioplasty with CC score 4–7	4101		
	Standard cardiac catheterisation with CC score 2–3		1174	
	Standard cardiac catheterisation with CC score 4–6		1227	
	Standard cardiac catheterisation with CC score 7–9		1292	
	Standard cardiac catheterisation with CC score 13 +	10,074		
	Standard, other operations on heart or pericardium, with CC score 10 +	7196		
	Standard percutaneous transluminal ablation of heart with CC score 3 +		2138	
	Standard, coronary artery bypass graft with single heart valve replacement or repair, with CC score 11 +	18,309		
	Complex echocardiogram		652	
	Percutaneous transluminal angioplasty of single blood vessel with CC score 0–2	1768		
	Percutaneous transluminal angioplasty of single blood vessel with CC score 3–5	2280	1280	
	Percutaneous transluminal angioplasty with insertion of single metal stent into peripheral blood vessel, with CC score 6 +	4682		
	Complex repair of aortic root with CC score 7 +	21,785		

continued

This article should be referenced as follows:
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TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

		Scheduled admissions unit cost (£)[35]		
Body system	**HRG code and currency description**	**Elective**	**Day case**	**Regular day/night**
Dermatology	Skin disorders without interventions, with CC score 0–1	1009	360	279
	Minor skin procedures 19 years and over		672	
Gastrointestinal disorders	Diagnostic colonoscopy with biopsy, 19 years and over		692	
	Diagnostic flexible sigmoidoscopy, 19 years and over		417	
	Diagnostic endoscopic upper gastrointestinal tract procedures with biopsy, 19 years and over		551	561
	Non-malignant gastrointestinal tract disorders without interventions, with CC score 3–5	1809		
	Non-malignant gastrointestinal tract disorders with single intervention, with CC score 5–8	5295		
	Malignant gastrointestinal tract disorders with multiple interventions, with CC score 3–6	6595		
	Malignant gastrointestinal tract disorders without interventions, with CC score 3–4		342	
	Diagnostic flexible sigmoidoscopy 19 years and over		417	
	Very major small intestine procedures, 19 years and over, with CC score 5–7	10,436		
	Major therapeutic endoscopic, upper or lower gastrointestinal tract procedures, 19 years and over, with CC score 3 +	4073		
	Therapeutic colonoscopy, 19 years and over		703	
	Complex therapeutic endoscopic, upper or lower gastrointestinal tract procedures		848	
	Radiological insertion of gastrostomy tube, 19 years and over		700	
	Complex, oesophageal, stomach or duodenum procedures, 19 years and over, with CC score 4 +	13,539		
	Intermediate anal procedures, 19 years and over, with CC score 3 +		1503	
	Inflammatory bowel disease without interventions, with CC score 5 +	3793		
	Gastrointestinal bleed with multiple interventions, with CC score 0–4	2811		
General disorders	Special screening, examinations or other genetic disorders			533
	Abnormal findings without diagnosis without interventions with CC score 1 +			223
	Diagnostic flexible cystoscopy, 19 years and over		488	
	Major general abdominal procedures, 19 years and over, with CC score 6–9		1520	
	Major general abdominal procedures, 19 years and over, with CC score 10 +	10,580		
	Open operations, on other or unspecified blood vessels, with CC score 2 +	7139		
	Abdominal hernia procedures, 19 years and over, with CC score 4 +	6367		
	Inguinal, umbilical or femoral hernia procedures, 19 years and over, with CC score 3–5	3304		
	Unspecified chest pain with CC score 5–10		397	
	Intermediate therapeutic general abdominal procedures, 19 years and over, with CC score 1–2	4241		

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

Body system	HRG code and currency description	Scheduled admissions unit cost (£)[35]		
		Elective	Day case	Regular day/night
Gynaecology	Diagnostic hysteroscopy		1083	
	Diagnostic hysteroscopy with biopsy and implantation of intrauterine device		1208	
Hepatobiliary	Appendicectomy procedures, 19 years and over, with CC score 3–4	5133		
	Endoscopic ultrasound examination of hepatobiliary or pancreatic duct	1379		
	Percutaneous punch biopsy of lesion of liver, 19 years and over		713	
	Major therapeutic endoscopic retrograde cholangiopancreatography with CC score 5 +		1178	
	Non-malignant, hepatobiliary or pancreatic disorders, without interventions, with CC score 0–1	1165		
	Non-malignant, hepatobiliary or pancreatic disorders, without interventions, with CC score 8 +	3037		
Injury/poison/procedure (vascular access)	Attention to arteriovenous fistula, graft or shunt	2053	1217	916
	Attention to central venous catheter, 19 years and over		283	
	Coagulation defect with CC score 5 +		637	
	Open arteriovenous fistula, graft or shunt procedures	3290	2300	1152
	Procedure not carried out, for other or unspecified reasons	640	345	428
	Procedure not carried out, for medical or patient reasons	735		
	Removal of central venous catheter, 19 years and over		423	
	Major endoscopic, kidney or ureter procedures, 19 years and over, with CC score 0–2	3523		
	Intermediate endoscopic ureter procedures 19 years and over		1246	
	Insertion of tunnelled central venous catheter, 19 years and over	1405	889	
	Insertion of non-tunnelled central venous catheter, 19 years and over	1533	800	
	Peripheral insertion of central venous catheter, 19 years and over		524	
	Thrombocytopenia with CC score 5–7			325
	Thrombocytopenia with CC score 8 +			351
Infections and infestations	Infections of bones or joints, with CC score 0–1	3704		
	Lobar, atypical or viral pneumonia, without interventions, with CC score 4–6	2206		
	Sepsis with single intervention, with CC score 0–4	5878		
	Sepsis with multiple interventions, with CC score 9 +	16,817		
	Infections or other complications of procedures, without interventions, with CC score 0–1	1588		
	Infections or other complications of procedures, with single intervention, with CC score 0–1	3848		
Metabolism and nutrition disorders	Nutritional disorders without interventions, with CC score 2–5	2317		
	Parathyroid procedures with CC score 2 +	4035		

continued

This article should be referenced as follows:
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

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

		Scheduled admissions unit cost (£)[35]		
Body system	**HRG code and currency description**	**Elective**	**Day case**	**Regular day/night**
Musculoskeletal and connective tissue disorders or fractures	Diagnostic bone marrow extraction		423	
	Single, amputation stump or partial foot amputation procedure, for diabetes or arterial disease, with CC score 0–4	3772		
	Major shoulder procedures for non-trauma with CC score 2–3		2937	
	Minimal foot procedures		768	
	Denervation or injection around spinal facet, for pain management		905	
	Degenerative spinal conditions without interventions, with CC score 3–5		1533	
	Single, amputation stump or partial foot amputation procedure, for diabetes or arterial disease, with CC score 5–7		1674	
	Single, amputation stump or partial foot amputation procedure, for diabetes or arterial disease, with CC score 8 +	5448		
	Single, amputation stump or partial foot amputation procedure, for diabetes or arterial disease, with imaging intervention, with CC score 8 +	11,413		
	Epidural under image control for pain management		839	
	Extraction of multiple teeth, 19 years and over		979	
	Multiple trauma with diagnosis score 24–32, with intervention score 0	4849		
	Very major hip procedures for non-trauma with CC score 6–7	8250		
	Very major knee procedures for non-trauma with CC score 6–7	7921		
Neoplasms (other)	Other or unspecified neoplasm, without interventions, with CC score 2 +	3659		
Nervous system disorders	Muscular balance cranial or peripheral nerve disorders epilepsy or head injury with CC score 9–11	4076		
	Cerebrovascular accident, nervous system infections or encephalopathy, with CC score 5–7	3066		
	Stroke with CC score 0–3	2475		
	Syncope or collapse, with CC score 0–3	508		
	Syncope or collapse, with CC score 4–6	940		
	Syncope or collapse, with CC score 7–9	1190		
Ophthalmology	Non-surgical ophthalmology without interventions, with CC score 0–1		433	
	Intermediate, cataract or lens procedures, with CC score 0–1		1056	
	Intermediate vitreous retinal procedures, 19 years and over, with CC score 0–1		267	
	Intermediate vitreous retinal procedures, 19 years and over, with CC score 2 +		275	
	Phacoemulsification cataract extraction and lens implant, with CC score 0–1		967	
	Phacoemulsification cataract extraction and lens implant, with CC score 2–3		1008	
	Phacoemulsification cataract extraction and lens implant, with CC score 4 +		1048	
	Complex vitreous retinal procedures, 19 years and over, with CC score 2 +	3082	1606	
	Complex, cataract or lens procedures, with CC score 0–1		1583	
	Very complex vitreous retinal procedures, 19 years and over, with CC score 0–1		2385	
	Very complex vitreous retinal procedures, 19 years and over, with CC score 2 +	3894		
	Very major, cataract or lens procedures, CC score 2 +		1192	
	Very major, glaucoma or iris procedures, CC score 0–1		2134	
	Very major vitreous retinal procedures, 19 years and over, with CC score 2 +		1766	

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

Body system	HRG code and currency description	Scheduled admissions unit cost (£)[35]		
		Elective	Day case	Regular day/night
Renal and urinary disorders	Fluid or electrolyte disorders, without interventions, with CC score 0–1	778		
	Fluid or electrolyte disorders, without interventions, with CC score 2–3	859		
	Fluid or electrolyte disorders, without interventions, with CC score 10 +	2713		
	Kidney transplant 19 years and over from cadaver heart-beating donor	14,411		
	Kidney transplant, 19 years and over, from cadaver non-heart-beating donor	13,461		
	Kidney transplant, 19 years and over, from live donor	12,787		
	General renal disorders without interventions, with CC score 3–5	1600		
	Minor or intermediate, urethra procedures, 19 years and over		1064	
	Intermediate endoscopic ureter procedures, 19 years and over	2112	1246	
	Ureteric or bladder disorders, without interventions, with CC score 0–1		478	
	Chronic kidney disease without interventions CC score 0–2	1679	476	357
	Chronic kidney disease without interventions, CC score 3–4	2083		
	Chronic kidney disease without interventions, CC score 5–7	2129	565	
	Chronic kidney disease without interventions, CC score 8–10	2813		
	Chronic kidney disease with interventions, CC score 0–2	4210		
	Chronic kidney disease with interventions CC score 3–5	4922	1793	
	Chronic kidney disease with interventions, CC score 6 +	7466		
	Renal replacement peritoneal dialysis associated procedures	2112	1057	
	Transurethral prostate resection procedures with CC score 0–2	3439		
	Transurethral prostate resection procedures with CC score 6 +	4030		
	Unspecified haematuria with interventions, with CC score 3–6	2766		
	Major, open or percutaneous, kidney or ureter procedures, 19 years and over, with CC score 2–3	7891		
	Major, open or percutaneous, kidney or ureter procedures, 19 years and over, with CC score 4–6	8777		
	Major endoscopic bladder procedures with CC score 7 +	3885		
Respiratory, thoracic and mediastinal disorders	Cystic fibrosis with CC	600	352	
	Fibrosis or pneumoconiosis, without interventions, with CC score 0–3	2034		
	Respiratory sleep study	809		
	Pulmonary oedema without interventions, with CC score 0–5	675		140
	Pleural effusion without interventions, CC score 0–5		297	
	Pleural effusion with multiple interventions, score 6–10	5120		
	Intermediate thoracic procedures, 19 years and over, with CC score 3–5	3921	1135	
	Intermediate thoracic procedures, 19 years and over, with CC score 6 +		1126	
	Endobronchial ultrasound examination of mediastinum		928	
	Diagnostic bronchoscopy, 19 years and over		847	

continued

TABLE 15 Hospital Episode Statistics inpatient HRG codes and currency description: scheduled (elective, day case, regular day/night unit cost) (*continued*)

Body system	HRG code and currency description	Scheduled admissions unit cost (£)[35]		
		Elective	Day case	Regular day/night
Vascular disorders	Hypertension		341	
	Peripheral vascular disorders with CC score 2–4	2105	523	
	Peripheral vascular disorders with CC score 8–10	2619	572	
	Single open procedure, on blood vessel or upper limb with CC score 0–4		2022	
	Percutaneous transluminal arteriography, of intracranial or extracranial blood vessel		1535	

HES, Hospital Episode Statistics; HRG, healthcare resource group.

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short- and long-stay unit cost)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
Blood and lymphatic disorders	Other red blood cell disorders with CC score 6–9	637	–
	Sickle-cell anaemia with crisis, with CC score 6 +	1451	4831
	Sickle-cell anaemia without crisis	810	4958
Cardiac disorders	Cardiac arrest with CC score 0–4	–	1986
	Cardiac arrest with CC score 9 +	–	3225
	Cardiac valve disorders with CC score 9–12	1122	–
	Complex percutaneous transluminal coronary angioplasty with CC score 4–7	2780	–
	Complex percutaneous transluminal coronary angioplasty with CC score 8–11	3186	–
	Chest pain with CC score 5–10	402	1420
	Chest pain with CC score 11 +	509	–
	Heart failure or shock, with CC score 4–7	605	–
	Heart failure or shock, with CC score 8–10	509	–
	Heart failure or shock with CC score 11–13	–	3146
	Actual or suspected myocardial infarction, with CC score 4–6	–	1967
	Actual or suspected myocardial infarction, with CC score 10–12	831	–
	Actual or suspected myocardial infarction, with CC score 13 +	1159	3450
	Angina with CC score 8–11	508	1739
	Angina with CC score 12 +	619	2223
	Arrhythmia or conduction disorders, with CC score 4–6	509	1808
	Arrhythmia or conduction disorders, with CC score 7–9	583	2076

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
	Arrhythmia or conduction disorders, with CC score 10–12	679	2538
	Arrhythmia or conduction disorders, with CC score 13 +	1051	3387
	Other acquired cardiac conditions with CC score 0–2	–	1982
	Other acquired cardiac conditions with CC score 3–5	733	2501
	Other acquired cardiac conditions with CC score 6–8	858	2949
	Other acquired cardiac conditions with CC score 9–12	982	3309
	Other acquired cardiac conditions with CC score 13 +	1523	4445
	Percutaneous transluminal angioplasty of single blood vessel, CC score 0–2	–	3970
	Percutaneous transluminal angioplasty of single blood vessel, CC score 6–8	–	2763
	Percutaneous transluminal angioplasty of single blood vessel, CC score 9 +	–	9184
	Percutaneous transluminal angioplasty, including stenting, of intracranial or extracranial blood vessel	–	9371
	Implantation of single-chamber pacemaker with CC score 6–8	2644	–
	Implantation of single-chamber pacemaker with CC score 9–11	–	5626
	Implantation of dual-chamber pacemaker with CC score 6–8	–	4707
	Implantation of biventricular pacemaker with CC score 6 +	–	8368
	Standard cardiac catheterisation with CC score 4–6	1673	3747
	Standard cardiac catheterisation with CC score 13 +	–	7959
	Standard, single heart valve replacement or repair, with CC score 0–5	–	12,424
	Standard percutaneous transluminal coronary angioplasty with CC score 12 +	–	6520
	Transient ischaemic attack with CC score 5–7	565	–
	Transient ischaemic attack with CC score 11 +	732	2913
	Very complex percutaneous transluminal coronary angioplasty, CC score 4–7	–	6045
Dermatology	Minor skin procedures 19 years and over	632	–
	Skin disorders without interventions, with CC score 2–5	474	2005
	Skin disorders without interventions, with CC score 6–9	634	–
	Skin disorders without interventions, with CC score 14–18	1016	3707
	Skin disorders without interventions, with CC score 19 +	–	4656
	Skin disorders with interventions, with CC score 4–7	–	4058
	Skin disorders with interventions, with CC score 8–11	–	5260
ENT	minor treatment of epistaxis, 19 years and over	–	1141
	Non-malignant, ear, nose, mouth, throat or neck disorders, without interventions, with CC score 5 +	556	2342
	Non-malignant, ear, nose, mouth, throat or neck disorders, with interventions, with CC score 5 +	2190	–

continued

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TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
Gastrointestinal disorders	Abdominal pain without interventions	415	–
	Diagnostic colonoscopy, 19 years and over	622	–
	Endoscopic insertion of luminal stent into gastrointestinal tract, CC score 4–6	–	5560
	Intermediate therapeutic endoscopic retrograde cholangiopancreatography with CC score 6 +	–	5902
	Major therapeutic endoscopic retrograde cholangiopancreatography CC score 5 +	6775	–
	Gastrointestinal bleed without interventions, with CC score 5–8	662	–
	Gastrointestinal bleed with single intervention, with CC score 5–7	–	2953
	Inflammatory bowel disease without interventions with CC score 5 +	–	3135
	Non-malignant gastrointestinal tract disorders without interventions, CC score 3–5	633	2425
	Non-malignant gastrointestinal tract disorders without interventions, CC score 6–10	–	3132
	Non-malignant gastrointestinal tract disorders with single intervention, CC score 9 +	–	5730
	Non-malignant gastrointestinal tract disorders with multiple interventions, CC score 3–4	–	5768
	Malignant gastrointestinal tract disorders without interventions, CC score 5–8	1010	2732
	Gastrointestinal bleed with multiple interventions, with CC score 5 +	–	5500
General disorders	Admission related to social factors without interventions, with CC score 0	513	–
	Abnormal findings without diagnosis, without interventions, with CC score 0	358	–
	Abnormal findings without diagnosis, without interventions, with CC score 1 +	–	2043
	Major general abdominal procedures 19 years and over with CC score 6–9	4623	–
	Special screening, examinations or other genetic disorders	–	2244
	Unspecified chest pain with CC score 0–4	304	–
Hepatobiliary	Laparoscopic cholecystectomy, 19 years and over, with CC score 4 +	–	6912
	Non-malignant, hepatobiliary or pancreatic disorders, with single intervention, with CC score 4–8	–	3897
Injury/poison/procedure (vascular access)	Attention to arteriovenous fistula, graft or shunt	1846	3050
	Attention to central venous catheter, 19 years and over	541	–
	Attention to suprapubic bladder catheter	–	1042
	Insertion of non-tunnelled central venous catheter, 19 years and over	1131	1938
	Insertion of tunnelled central venous catheter 19 years and over	1351	1832
	Removal of central venous catheter, 19 years and over	763	–
	Open arteriovenous fistula, graft or shunt procedures	2504	3412
	Major, open or percutaneous, kidney or ureter procedures, 19 years and over, with CC score 2–3	–	5146
	Poisoning diagnosis without interventions, with CC score 0–1	–	1366
	Procedure not carried out, for medical or patient reasons	577	–
	Procedure not carried out, for other or unspecified reasons	581	–
	Percutaneous transluminal, embolectomy or thrombolysis, of blood vessel, with CC score 0–4	2493	–
	Percutaneous transluminal embolization of peripheral blood vessel, CC score 6 +	–	9003

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
Infections and infestations	Fever of unknown origin without interventions, with CC score 4 +	634	2306
	Sepsis without interventions, with CC score 0–4	694	2273
	Sepsis without interventions, with CC score 5–8	–	2940
	Sepsis without interventions, with CC score 9 +	–	3694
	Sepsis with single intervention with CC score 0–4	–	3677
	Sepsis with single intervention, with CC score 9 +	–	5816
	Sepsis with multiple interventions, with CC score 5–8	–	7236
	Sepsis with multiple interventions, with CC score 9 +	–	9660
	Spinal infection without interventions, with CC score 3–5	–	4543
	Spinal infection without interventions, with CC score 10 +	–	5774
	Spinal infection with interventions, with CC Score 0–5	–	8093
	Gastrointestinal infections without interventions, with CC score 2–4	–	2061
	Gastrointestinal infections without interventions, with CC score 5–7	685	–
	gastrointestinal infections without interventions, with CC score 8 +	–	3342
	Infections of bones or joints, with CC score 0–1	–	3500
	Infections of bones or joints, with CC score 2–4	–	3949
	Infections of bones or joints, with CC score 9–12	–	5094
	Infections of bones or joints, with CC score 13 +	–	6092
	Lobar, atypical or viral pneumonia, with single intervention, with CC score 8–12	–	3910
	Lobar, atypical or viral pneumonia, with single intervention, with CC score 13 +	–	5118
	Lobar, atypical or viral pneumonia, without interventions, with CC score 0–3	518	1612
	Lobar, atypical or viral pneumonia, without interventions, with CC score 4–6	615	1964
	Lobar, atypical or viral pneumonia, without interventions, with CC score 7–9	–	2330
	Lobar, atypical or viral pneumonia, without interventions, with CC score 10–13	587	2984
	Lobar, atypical or viral pneumonia, without interventions, with CC score 14 +	1380	3872
	Lobar, atypical or viral pneumonia, with multiple interventions, CC score 9–13	–	6324
	Chronic obstructive pulmonary disease or bronchitis, without interventions, with CC score 5–8	–	2027
	Chronic obstructive pulmonary disease or bronchitis, without interventions, with CC score 9–12	–	2461
	Chronic obstructive pulmonary disease or bronchitis, without interventions, with CC score 13 +	–	3158
	Infections or other complications of procedures without interventions with CC score 0–1	516	2183
	Unspecified acute lower respiratory infection without interventions, with CC score 0–4	417	–
	Unspecified acute lower respiratory infection without interventions, with CC score 5–8	–	1978
	Unspecified acute lower respiratory infection without interventions with CC score 9–12	–	2492

continued

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
	Standard infectious diseases without interventions with CC score 4–6	712	2465
	Kidney or urinary tract infections, without interventions, with CC score 0–1	–	1587
	Kidney or urinary tract infections, without interventions, with CC score 2–3	561	1951
	Kidney or urinary tract infections, without interventions, with CC score 4–7	–	2535
	Kidney or urinary tract infections, with interventions, with CC score 3–5	–	3049
	Kidney or urinary tract infections, with interventions, with CC score 6–8	–	4058
Metabolism and nutrition disorders	Diabetes with hyperglycaemic disorders, with CC score 0–1	–	1309
	Diabetes with hyperglycaemic disorders, with CC score 8 +	–	3029
	Diabetes with lower limb complications, with CC score 5–8	–	3131
	Diabetes with lower limb complications, with CC score 9 +	–	4088
Musculoskeletal and connective tissue disorders or fractures	Low back pain without interventions, with CC score 6 +	697	–
	Inflammatory, spine, joint or connective tissue disorders, with CC score 3–4	–	2238
	Inflammatory, spine, joint or connective tissue disorders, with CC score 9–11	669	–
	Non-inflammatory, bone or joint disorders, with CC score 5–7	–	3174
	Complex, hip or knee procedures for trauma, with CC score 12 +	–	17,071
	Foot fracture without interventions, with CC score 8 +	–	4868
	Intermediate knee procedures for non-trauma, 19 years and over, CC score 4 +	–	10,699
	Musculoskeletal signs or symptoms, with CC score 4–7	–	2017
	Multiple trauma with diagnosis score ≥ 51, with intervention score 0	1756	–
	Multiple trauma with diagnosis score ≥ 51, with intervention score 9–18	–	10,826
	Musculoskeletal signs or symptoms, with CC score 12 +	883	3188
	Major foot procedures for trauma, 19 years and over, with CC score 4 +	–	10,540
	Very major foot procedures for non-trauma with CC score 4 +	–	15,762
	Major hip procedures for trauma with CC score 3–5	–	7972
	Major hip procedures for non-trauma, 19 years and over, with CC score 6–9	–	12,828
	Soft-tissue disorders with CC score 3–5	364	–
	Soft-tissue disorders with CC score 6–8	438	–
	Soft-tissue disorders with CC score 9–11	–	2949
	Soft-tissue disorders with CC score 12 +	–	4126
	Vertebral column injury without interventions, with CC score 6 +	–	4984
	Other injury, of rib or chest, without interventions, with CC score 2–3	423	–
	Rib or chest fracture, without interventions, with CC score 3–5	–	2743
	Tendency to fall, senility or other conditions affecting cognitive functions, without interventions, with CC score 0–1	–	2215
	Tendency to fall, senility or other conditions affecting cognitive functions, without interventions, with CC score 2–3	–	2421
	Vertebral column injury without interventions, with CC score 6 +	–	4984

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
Neoplasms (other)	Other or unspecified neoplasm, without interventions, with CC score 0–1	–	2407
	Malignant breast disorders with interventions, with CC score 7 +	–	6933
	Malignant gynaecological disorders without interventions, with CC score 7–9	–	4221
Nervous system disorders	Headache, migraine or cerebrospinal fluid leak, with CC score 0–6	383	–
	Headache, migraine or cerebrospinal fluid leak, with CC score 11 +	641	2424
	Syncope or collapse, with CC score 4–6	–	1638
	Syncope or collapse, with CC score 7–9	515	1963
	Syncope or collapse, with CC score 10–12	608	–
	Syncope or collapse, with CC score 13 +	–	3273
	Cerebrovascular accident, nervous system infections or encephalopathy, CC score 11–13	–	5419
	Cerebrovascular accident, nervous system infections or encephalopathy, CC score 14 +	–	6823
	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 3–5	506	2056
	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 9–11	–	2895
	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 12–14	–	3660
	Major intracranial procedures, 19 years and over, with CC score 12 +	8003	–
	Very major intracranial procedures 19 years and over with CC score 8–11	–	10,757
	Very complex intracranial procedures, 19 years and over, with CC score 12 +	18,492	–
	Stroke with CC score 4–6	857	–
	Stroke with CC score 7–9	980	3754
	Stroke with CC score 13–15	1475	5908
	Stroke with CC score 16 +	–	8104
	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 0–2	404	–
	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 6–8	–	2388
Ophthalmology	Non-surgical ophthalmology without interventions, with CC score 0–1	450	–
Renal and urinary disorders	Acute kidney injury without interventions, with CC score 4–7	–	2390
	Acute kidney injury without interventions, with CC score 8–11	–	2946
	Acute kidney injury without interventions, with CC score 12 +	1354	3728
	Unspecified haematuria without interventions, with CC score 0–3	380	–
	Unspecified haematuria without interventions, with CC score 8 +	–	2647
	Unspecified haematuria with interventions, with CC score 3–6	–	2389
	Unspecified haematuria with interventions, with CC score 7 +	–	3802

continued

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
	General renal disorders without interventions, with CC score 0–2	500	1577
	General renal disorders with interventions, with CC score 0–2	–	3295
	General renal disorders without interventions, with CC score 3–5	–	2172
	Kidney transplant, 19 years and over, from cadaver heart-beating donor	–	13,402
	Kidney transplant 19 years and over from cadaver non-heart-beating donor	–	15,572
	Major, open or percutaneous, kidney or ureter procedures, 19 years and over, with CC score 4–6	–	5359
	Major, open or percutaneous, kidney or ureter procedures, 19 years and over, with CC score 10 +	–	7538
	Transplant failure and rejection, without interventions, with CC score 0–1	–	2810
	Fluid or electrolyte disorders, without interventions, with CC score 0–1	361	–
	Fluid or electrolyte disorders, without interventions, with CC score 2–3	454	–
	Fluid or electrolyte disorders, without interventions, with CC score 4–6	550	1940
	Fluid or electrolyte disorders, without interventions, with CC score 7–9	644	2370
	Fluid or electrolyte disorders, without interventions, with CC score 10 +	866	–
	Fluid or electrolyte disorders, with interventions, with CC score 5 +	3843	–
	Chronic kidney disease without interventions, with CC score 0–2	967	2455
	Chronic kidney disease without interventions, with CC score 3–4	966	2691
	Chronic kidney disease without interventions, with CC score 5–7	1151	3075
	Chronic kidney disease without interventions, with CC score 8–10	1533	3776
	Chronic kidney disease without interventions, with CC score 11 +	–	4661
	Chronic kidney disease with interventions, with CC score 3–5	5532	5126
	Chronic kidney disease with interventions, with CC score 6 +	–	7483
	Ureteric or bladder disorders, with interventions, with CC score 4 +	–	3861
	Complex endoscopic bladder procedures with CC score 3 +	–	8401
Respiratory, thoracic and mediastinal disorders	Asthma without interventions, with CC score 3–5	514	1662
	Asthma without interventions, with CC score 6–8	586	–
	Allergy or adverse allergic reaction	356	–
	Cystic fibrosis with CC	–	3887
	Fibrosis or pneumoconiosis, with interventions, with CC score 0–6	2162	–
	Inhalation, lung injury or foreign body, with single intervention, CC score 10 +	–	6041
	Other respiratory disorders without interventions, with CC score 0–4	370	–
	Other respiratory disorders without interventions, with CC score 5–10	474	–
	Pulmonary embolus without interventions, with CC score 9–11	829	–
	Pulmonary oedema without interventions, with CC score 0–5	509	1800

TABLE 16 Hospital Episode Statistics inpatient HRG codes and currency description: unscheduled (non-elective short and long-stay unit cost) (*continued*)

Body system	HRG code and currency description	Unscheduled admissions unit cost (£)[35]	
		Non-elective short stay	Non-elective long stay
	Pulmonary oedema without interventions, with CC score 6 +	718	–
	Pleural effusion without interventions, with CC score 6–10	–	2168
	Pleural effusion without interventions, with CC score 11 +	–	2946
	Pleural effusion with single intervention, with CC score 11 +	–	4093
	Pleural effusion with multiple interventions, with CC score 11 +	–	6353
	Respiratory failure without interventions, with CC score 0–5	552	–
	Respiratory failure without interventions, with CC score 6–10	–	2430
	Respiratory failure with single intervention, with CC score 11 +	–	3948
	Unspecified acute lower respiratory infection without interventions CC score 5–8	587	–
	Unspecified acute lower respiratory infection without interventions CC score 13 +	–	3295
	Peripheral vascular disorders with CC score 5–7	801	3044
	Peripheral vascular disorders with CC score 8–10	–	3454
	Peripheral vascular disorders with CC score 15 +	–	5297
	Hypertension	394	1941

HES, Hospital Episode Statistics; HRG, healthcare resource group.

Appendix 4

TABLE 17 Case report forms' serious adverse events CTCAE terms, their best-possible HRG code and currency description, non-elective short and long-stay unit cost

Body system	CTCAE term/grade	HRG code and currency description[35]	Non-elective short-stay unit cost (£)[35]	Non-elective long-stay unit cost (£)[35]
Blood and lymphatic disorders	Haemolysis/G3	Sickle-cell anaemia with crisis, with CC score 6 +	1451	4831
Cardiac disorders	Atrial fibrillation because of cardiac valve disorders/G3	Cardiac valve disorders with CC sore 5–8	933	2989
	Chest pain: cardiac/G3–4	Chest pain with CC score 5–10	402	1420
	Atrioventricular block first degree/G3	Heart failure or shock, with CC score 8–10	714	2558
	Myocardial infarction/G3–4	Actual or suspected myocardial infarction, with CC score 7–9	762	2231
	Cardiac arrest/G4–5	Cardiac arrest with CC score 9 +	950	3225
	Bradycardia or ventricular arrhythmia/G3–4	Arrhythmia or conduction disorders, with CC score 7–9	583	2076
	Pericarditis/G3	Standard, other operations on heart or pericardium, with CC score 5–9	2478	4747
ENT	Vertigo/G3	Non-malignant, ear, nose, mouth, throat or neck disorders, without interventions, with CC score 1–4	423	1554

continued

This article should be referenced as follows:
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

TABLE 17 Case report forms erious adverse events CTCAE terms, their best-possible HRG code and currency description, non-elective short and long-stay unit cost (*continued*)

Body system	CTCAE term/grade	HRG code and currency description[35]	Non-elective short-stay unit cost (£)[35]	Non-elective long-stay unit cost (£)[35]
Gastrointestinal disorders	Visceral arterial ischaemic of bowel/G5	Non-malignant gastrointestinal tract disorders with multiple interventions, with CC score 8 +	8726	9099
	Vomiting, pain, nausea or diarrhoea/G3	Non-malignant gastrointestinal tract disorders with single intervention, with CC score 5–8	3691	4054
	Upper or lower gastrointestinal haemorrhage or bleed/G3	Gastrointestinal bleed with single intervention, with CC score 5–7	2821	2953
General disorders	Oedema limbs/G3	Oedema with CC score 2 +	488	2714
Hepatobiliary	Abdominal pain, cholecystitis/G3	Intermediate, hepatobiliary or pancreatic procedures, with CC sore 3 +	5342	8381
Injury/poison/procedure (vascular access)	33 Vascular access complications/thrombosis, 14 other procedures/G3	Other complications of, internal devices, implants or grafts, with CC score 6	1244	4138
Infections and Infestations	Sepsis/G3	Sepsis with single intervention, with CC score 5–8	2901	4687
	Enterocolitis infectious/G3	Gastrointestinal infections with single intervention, with CC score 5–7	4895	5011
	Bone infection/G3	Infections of bones or joints, with CC score 5–8	1158	4332
	Viremia because of diabetes/G3	Diabetes with lower limb complications, with CC score 5–8	753	3131
	Pleural infection/effusion/G3	Pulmonary, pleural or other tuberculosis, with interventions, with CC score 5–7	4988	6138
	Bacteraemia/G3	Bacteraemia with CC score 5–9	1469	4949
	Respiratory/lung infection (pneumonia)/G3–4	Lobar, atypical or viral pneumonia, with single intervention, with CC score 0–8	1511	2243
	Respiratory/lung infection (COPD)/G3	Chronic obstructive pulmonary disease or bronchitis, with single intervention, with CC score 5–8	1308	2680
	Wound infection/G4	Infection or inflammatory reaction, due to, internal devices, implants or grafts, with CC score 6 +	1768	7627
	Urinary tract infection/G3–4	Kidney or urinary tract infections, with interventions, with CC score 6–8	3868	4058
Metabolism and nutrition disorders	Diabetes (hyperglycaemia, hyperkalaemia)/G3	Diabetes with hyperglycaemic disorders, with CC score 5–7	599	2074
Musculoskeletal and connective tissue disorders or fractures	Arthralgia, trismus, chest-wall pain (non-cardiac), cramp, myalgia/G3	Musculoskeletal signs or symptoms, with CC score 4–8	487	2017
	Tendency to fall and/or bone fracture/G3	Tendency to fall, senility or other conditions affecting cognitive functions, with single intervention, with CC score 3 +	3936	4551
Neoplasms	Neoplasms benign, malignant or unspecified/G3	Other or unspecified neoplasm, with interventions, CC score 2 +	3885	6594
	Renal or prostate neoplasm/G3	Kidney, urinary tract or prostate neoplasms, with interventions, with CC score 6–8	4588	4747

TABLE 17 Case report forms erious adverse events CTCAE terms, their best-possible HRG code and currency description, non-elective short and long-stay unit cost (*continued*)

Body system	CTCAE term/grade	HRG code and currency description[35]	Non-elective short-stay unit cost (£)[35]	Non-elective long-stay unit cost (£)[35]
Nervous system disorders	Headache/G3	Headache, migraine or cerebrospinal fluid leak, with CC score 7–10	497	1873
	Syncope/G3	Syncope or collapse, with CC score 7–9	515	1963
	Cognitive disturbance/G5	Conditions affecting cognitive functions, with multiple interventions, with CC score 6 +	6204	8362
	Ischaemia cerebrovascular/G3–4	Cerebrovascular accident/ischaemia, with CC score 8–10	991	3824
	Seizure/G3	Muscular, balance, cranial or peripheral nerve disorders, epilepsy/seizure or head injury, with CC score 6–8	601	2388
	Intracranial haemorrhage/G5	Haemorrhagic cerebrovascular disorders with CC score 6–9	1040	4029
Psychiatric disorders	Delirium/G3	Delirium, treated by a non-specialist mental health provider	848	3777
Renal and urinary disorders	Haematuria/G3	Unspecified haematuria with interventions, with CC score 4–7	2043	2389
	Urinary tract pain/G3	Pain with CC score 1 +	696	3219
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema/G3	Pulmonary oedema with interventions, with CC score 6–8	886	4307
	Respiratory failure/G3	Respiratory failure with single intervention, with CC score 6–10	1074	2866
Vascular disorders	Hypotension or peripheral vascular disorders/G3–4	Peripheral vascular disorders with CC score 5–7	801	3044
	Hypertension/G3	Hypertension	394	1941
	Abdominal aortic aneurysm, critical ischaemia/G3	Standard endovascular repair of abdominal aortic aneurysm, with CC score 6 +	6988	11,946

CRF, case report form; HRG, healthcare resource group.

Note
Charlson comorbidity (CC) scores around 4–10 were considered for CTCAE terms grade categories 3–5: HRGs with lower CC scores and single intervention or without intervention for G: grade 3; HRGs with higher CC scores and multiple interventions for G: grades 4 and above.[35]

Appendix 5

TABLE 18 Unit cost of HES critical care admissions

	Adult critical care, organs supported (*n*)				
Service description for HRG	**0**	**1**	**2**	**3**	**4**
Unit cost of HRG code (£)					
Cardiac surgical adult patients predominate	–	1215	1520	–	2251
Non-specific, general adult critical care patients predominate	1185	1355	1862	2055	2242
Neurosciences adult patients predominate	–	–	–	–	1832
Renal adult patients predominate	733	1421	1398	–	–
Surgical adult patients (unspecified specialty)	–	1266	1632	–	–
Thoracic surgical adult patients predominate	–	–	–	1514	–

HES, Hospital Episode Statistics; HRG, healthcare resource group.

This article should be referenced as follows:
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Appendix 6

TABLE 19 Unit cost of HES outpatient appointments

Service description	NAC_HRG code	First attendance face to face (WF01B)	Follow-up attendance face to face (WF01A)	First telephone or telemedicine consultation (WF01D)	Follow-up telephone or telemedicine consultation (WF01C)
Unit cost of HRG code (£)					
Accident and emergency	180	140	163	85	49
Adult mental illness	710	352	333	192	340
Anaesthetics	190	148	126	113	72
Cardiology	320	174	139	89	101
Cardiothoracic surgery	170	272	208	164	166
Chemical pathology	822	146	107	130	78
Clinical genetics	311	565	372	219	257
Clinical haematology	303	235	172	98	96
Clinical neurophysiology	401	251	354	215	43
Clinical oncology	800	166	151	53	95
Clinical physiology	304	129	54	135	82
Critical care medicine	192	236	269	195	80
Dental medicine specialties	450	151	187	76	58
Dermatology	330	131	123	56	72
Endocrinology	302	219	155	85	106
Ear, nose and throat	120	118	136	79	101
Gastroenterology	301	183	148	85	97
General medicine	300	233	201	47	109
General surgery	100	162	145	123	88
Geriatric medicine	430	341	253	148	151
Gynaecology	502	172	145	84	79
Infectious diseases	350	299	245	126	251
Medical oncology	370	253	200	396	136
Medical ophthalmology	460	126	108	62	58
Nephrology	361	221	171	86	113
Neurology	400	239	188	126	105
Neurosurgery	150	224	175	182	107
Nuclear medicine	371	177	99	68	71
Obstetrics	501	196	136	120	87
Ophthalmology	130	130	102	71	85
Oral surgery	140	149	120	138	118
Palliative medicine	315	376	241	378	167

TABLE 19 Unit cost of HES outpatient appointments (*continued*)

Service description	NAC_HRG code	First attendance face to face (WF01B)	Follow-up attendance face to face (WF01A)	First telephone or telemedicine consultation (WF01D)	Follow-up telephone or telemedicine consultation (WF01C)
Plastic surgery	160	138	110	98	83
Psychotherapy	713	469	168	580	252
Radiology	811	111	155	35	36
Respiratory medicine	340	198	154	109	86
Rheumatology	410	247	155	128	85
Trauma and orthopaedics	110	142	122	85	105
Urology	101	129	111	89	77

HES, Hospital Episode Statistics; HRG, healthcare resource group; NAC, non-admitted consultation.

Appendix 7

TABLE 20 Completeness of resource use (CRF, HES), EQ-5D and SF-12 data

	BGFM	CFM	Total
	n = 222	*n* = 215	*n* = 437
Parameter (months)	*N* (%)	*N* (%)	*N* (%)
Data obtained through CRFs			
Haemodialysis sessions			
0–12	97 (44)	86 (40)	183 (42)
12–24	55 (25)	41 (19)	96 (22)
Bioimpedance sessions			
0–12	93 (42)	82 (38)	175 (40)
12–24	53 (24)	44 (20)	97 (22)
Inpatient admissions (scheduled)			
0–12	67 (30)	57 (27)	124 (28)
12–24	44 (20)	34 (16)	78 (18)
Inpatient (unscheduled: SAEs)			
0–12	222 (100)	215 (100)	437 (100)
12–24	222 (100)	215 (100)	437 (100)
Inpatient nursing home admissions			
0–12	60 (27)	54 (25)	114 (26)
12–24	41 (18)	32 (15)	73 (17)
Outpatient (non-admitted consultation)			
0–12	51 (23)	42 (20)	93 (21)
12–24	38 (17)	30 (14)	68 (16)

continued

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TABLE 20 Completeness of resource use (CRF, HES), EQ-5D and SF-12 data (*continued*)

	BGFM	CFM	Total
	n = 222	*n* = 215	*n* = 437
Parameter (months)	*N* (%)	*N* (%)	*N* (%)
Outpatient nursing home appointments			
0–12	58 (26)	54 (25)	112 (25)
12–24	38 (17)	34 (16)	72 (16)
Primary and community care			
0–12	51 (23)	40 (19)	91 (21)
12–24	30 (13)	28 (13)	58 (13)
Caring by unpaid carers (non-NHS cost)			
0–12	41 (18)	36 (17)	77 (18)
12–24	34 (15)	25 (12)	59 (14)
Data obtained through HES			
Inpatient admissions (scheduled, unscheduled)			
0–12	215 (97)	208 (97)	423 (97)
12–24	215 (97)	208 (97)	423 (97)
Adult critical care (NHS)			
0–12	215 (97)	208 (97)	423 (97)
12–24	215 (97)	208 (97)	423 (97)
Outpatient (non-admitted consultation) (NHS)			
0–12	215 (97)	208 (97)	423 (97)
12–24	215 (97)	208 (97)	423 (97)
EQ-5D-5L			
Baseline	193 (87)	192 (89)	385 (88)
3	157 (71)	158 (73)	315 (72)
6	133 (60)	127 (59)	260 (59)
9	118 (53)	96 (45)	214 (49)
12	114 (51)	96 (45)	210 (48)
15	87 (39)	77 (36)	164 (37)
18	84 (38)	65 (30)	149 (34)
21	77 (35)	59 (27)	136 (31)
24	87 (39)	71 (33)	158 (36)
SF-12 (SF-6D)			
Baseline	189 (85)	183 (85)	372 (85)
3	154 (69)	156 (72)	310 (71)
6	128 (58)	127 (59)	255 (58)
9	114 (51)	94 (44)	208 (47)

TABLE 20 Completeness of resource use (CRF, HES), EQ-5D and SF-12 data (*continued*)

	BGFM	CFM	Total
	n = 222	*n* = 215	*n* = 437
Parameter (months)	*N* (%)	*N* (%)	*N* (%)
12	114 (51)	96 (45)	210 (48)
15	87 (39)	77 (36)	164 (37)
18	84 (38)	61 (28)	145 (33)
21	77 (35)	57 (27)	134 (31)
24	83 (37)	70 (33)	153 (35)

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; CRF, case report form; HES, Hospital Episode Statistics; SAEs, serious adverse events.
a Only 14 missing data from HES England.

Appendix 8

TABLE 21 NHS and PSS costs for resource use categories (complete cases), £ (2020)

Resource use category	*n*	BGFM, £, mean (SD)	*n*	CFM, £, mean (SD)	BGFM–CFM, £,[a] mean difference (95% CI)	*p*-value[a]
CRF haemodialysis	43	39,255.33 (15,626.66)	34	37,726.66 (17,062.8)	1528.67 (−5796.57 to 8853.91)	0.68
CRF bioimpedance	41	237.37 (70.15)	31	0 (0)	237.37 (217.15 to 257.59)	0.00
Inpatient	26	9322.61 (11,219.52)	19	5877.07 (7096.00)	3445.54 (−1653.64 to 8544.74)	0.18
HES inpatient (scheduled)	215	4455.31 (5609.89)	208	4442.08 (5954.61)	13.22 (−1087.52 to 1113.98)	0.98
HES inpatient (unscheduled)	215	5859.07 (7536.29)	208	5697.28 (8949.95)	161.78 (−1468.33 to 1791.89)	0.85
CRF inpatient, nursing home	29	0 (0)	19	0 (0)	0 (0 to 0)	0.00
HES adult critical care	215	300.61 (708.95)	208	219.27 (716.06)	81.34 (−47.65 to 210.33)	0.22
Outpatient	25	1690.43 (1247.58)	25	2564.34 (2333.64)	−873.90 (−1869.42 to 121.62)	0.08
HES outpatient consultation	215	1950.98 (2235.58)	208	1900.12 (1889.61)	50.86 (−346.94 to 448.67)	0.80
CRF outpatient, nursing home	27	0 (0)	25	4.04 (13.56)	−4.04 (−9.06 to 0.97)	0.11
CRF primary, community care	24	513.86 (574.56)	20	379.87 (298.90)	133.98 (−125.86 to 393.84)	0.31

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; CRF, case report form; HES, Hospital Episode Statistics; PSS, Personal Social Services; SD, standard deviation.
a Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.

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TABLE 22 NHS and PSS costs for resource use categories (second sensitivity analysis: imputed data) and additional non-NHS cost, £ (2020)

Resource use category	BGFM (*n* = 222) £, mean (SD)	CFM (*n* = 215) £, mean (SD)	BGFM–CFM £,[a] mean difference (95% CI)	*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	8105.52 (7634.56)	7875.60 (6380.60)	229.92 (−1047.94 to 1507.78)	0.72
CRF inpatient (scheduled)	5045.86 (4076.06)	4826.91 (2727.16)	218.94 (−429.95 to 867.84)	0.51
CRF inpatient (unscheduled)	3059.66 (5948.09)	2994.30 (5385.88)	65.36 (−956.78 to 1087.50)	0.90
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	644.22 (401.66)	1008.35 (552.95)	−364.14 (−454.50 to −273.77)	0.00
CRF outpatient consultation	644.22 (401.66)	996.43 (553.00)	−352.21 (−442.59 to −261.84)	0.00
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
Additional (non-NHS) cost	690.65 (799.08)	780.61 (717.47)	−89.96 (−233.48 to 53.55)	0.21

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; CRF, case report form; HES, Hospital Episode Statistics; PSS, Personal Social Services; SD, standard deviation.
a Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.

Appendix 9

TABLE 23 EuroQol EQ-5 dimension-5 level utility scores (first sensitivity analysis: complete cases)

EQ-5D-5L (months)[a]	*n*	BGFM, mean (SD)	*n*	CFM, mean (SD)	BGFM–CFM, mean difference[b] (95% CI)	*p*-value[b]
Baseline	193	0.554 (0.295)	192	0.601 (0.287)	−0.047 (−0.105 to 0.012)	0.12
3	157	0.553 (0.306)	158	0.563 (0.294)	−0.010 (−0.078 to 0.058)	0.78
6	133	0.538 (0.306)	127	0.568 (0.285)	−0.030 (−0.101 to 0.041)	0.41
9	118	0.532 (0.297)	96	0.525 (0.301)	0.007 (−0.073 to 0.087)	0.86
12	114	0.521 (0.296)	96	0.478 (0.316)	0.043 (−0.036 to 0.122)	0.29
15	87	0.513 (0.316)	77	0.453 (0.317)	0.060 (−0.034 to 0.154)	0.21
18	84	0.463 (0.308)	65	0.425 (0.325)	0.038 (−0.064 to 0.141)	0.46
21	77	0.411 (0.359)	59	0.372 (0.353)	0.039 (−0.079 to 0.157)	0.52
24	87	0.417 (0.347)	71	0.347 (0.349)	0.070 (−0.037 to 0.177)	0.20

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; SD, standard deviation.
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.

TABLE 24 EuroQol EQ-5 dimension-5 level and SF-6D utility scores (fourth and fifth sensitivity analyses)

Health status[a]	BGFM (*n* = 222) mean (SD)	CFM (*n* = 215) mean (SD)	BGFM–CFM,[b] mean difference (95% CI)	*p*-value[b]
EQ-5D-5L (months)[a]				
Baseline	0.639 (0.253)	0.681 (0.250)	−0.042 (−0.088 to 0.006)	0.08
3	0.623 (0.265)	0.637 (0.252)	−0.014 (−0.062 to 0.033)	0.55
6	0.626 (0.257)	0.650 (0.235)	−0.024 (−0.068 to 0.021)	0.31
9	0.604 (0.252)	0.596 (0.238)	0.008 (−0.038 to 0.053)	0.74
12	0.585 (0.250)	0.564 (0.260)	0.021 (−0.026 to 0.068)	0.38
15	0.591 (0.248)	0.552 (0.242)	0.039 (−0.004 to 0.084)	0.08
18	0.567 (0.243)	0.539 (0.253)	0.028 (−0.018 to 0.074)	0.24
21	0.528 (0.277)	0.486 (0.271)	0.042 (−0.009 to 0.093)	0.11
24	0.519 (0.266)	0.498 (0.264)	0.021 (−0.028 to 0.070)	0.40
SF-6D (months)[a]				
Baseline	0.627 (0.128)	0.636 (0.119)	−0.009 (−0.031 to 0.014)	0.46
3	0.618 (0.161)	0.619 (0.137)	−0.001 (−0.029 to 0.026)	0.93
6	0.617 (0.150)	0.603 (0.156)	0.014 (−0.015 to 0.043)	0.34
9	0.597 (0.164)	0.588 (0.175)	0.009 (−0.024 to 0.041)	0.61
12	0.584 (0.175)	0.551 (0.178)	0.033 (0.001 to 0.066)	0.05
15	0.564 (0.174)	0.534 (0.182)	0.030 (−0.002 to 0.062)	0.07
18	0.555 (0.185)	0.523 (0.173)	0.032 (−0.001 to 0.066)	0.06
21	0.522 (0.188)	0.498 (0.187)	0.024 (−0.012 to 0.060)	0.20
24	0.519 (0.189)	0.496 (0.194)	0.023 (−0.013 to 0.058)	0.21

BGFM, bioimpedance-guided fluid management; CFM, current fluid management; SD, standard deviation.
a EQ-5D-5L utility estimates using Devlin *et al*. value set, and SF-6D utility estimates.
b Mean difference (95% CI) and *p*-value calculated from bootstrapping using 1000 replications.

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