Multiple frequency bioimpedance devices (BCM - Body Composition Monitor, BioScan 920-II, BioScan touch i8, InBody S10, and MultiScan 5000) for fluid management in people with chronic kidney disease having dialysis

Produced by Aberdeen Health Technology Assessment Group

Authors

Graham Scotland[2]
Moira Cruickshank[1]
Elisabet Jacobsen[2]
David Cooper[1]
Cynthia Fraser[1]
Michal Shimonovich[1]
Angharad Marks[3]
Miriam Brazzelli[1]

[1]Health Services Research Unit, University of Aberdeen, UK
[2]Health Economics Research Unit, University of Aberdeen, UK
[3]NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK

Correspondence to

Miriam Brazzelli
Senior Research Fellow
2nd Floor Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill, Aberdeen, AB25 2ZD
Email: m.brazzelli@abdn.ac.uk

Version Assessment Report

Date completed 7 December 2016

Source of funding: This report was commissioned by the NIHR HTA Programme as project number **15/17/07**

Declared competing interests of the authors

There are no competing interests.

Acknowledgements

The authors are grateful to Lara Kemp for her secretarial support.

The Health Services Research Unit, and Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen are both core-funded by the Chief Scientist Office of the Scottish Government Health Directorates.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the Chief Scientist Office of the Scottish Government Health Directorates or of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Scotland G, Cruickshank M, Jacobsen E, Cooper D, Fraser C, Shimonovich M, Marks A, Brazzelli M. Multiple frequency bioimpedance devices (BCM - Body Composition Monitor, BioScan 920-II, BioScan touch i8, InBody S10 and MultiScan 5000) for fluid management in people with chronic kidney disease having dialysis. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2016.

Contribution of authors

Moira Cruickshank (Research Fellow) reviewed and summarised the evidence on the clinical effectiveness of the bioimpedance devices; Michal Shimonovich (Research Assistant) contributed to the data extraction process and to the assessment of the risk of bias of included studies with assistance from Moira Cruickshank (Research Fellow) and from Miriam Brazzelli (Senior Research Fellow); David Cooper (Research Fellow) double checked the data extracted from the included randomised studies and conducted all statistical analyses; Elisabet Jacobsen (Research Assistant) reviewed the evidence on the cost-effectiveness of the bioimpedance devices and contributed to the economic evaluation under the supervision of Graham Scotland (Senior Health

Economist); Graham Scotland developed the economic model and conducted the economic evaluation. Cynthia Fraser (Senior Information Specialist) developed and ran the literature searches and provided information support; Angharad Marks (Clinician Scientist & Honorary Consultant Nephrologist) provided expert advice on the clinical aspects of this assessment. Miriam Brazzelli oversaw and co-ordinated all aspects of this assessment. All authors contributed to the writing of this report and approved its final version.

Table of contents

List of tables

List of figures

List of abbreviations

AFO	Acute fluid overload (Huan-Sheng)/Absolute fluid overload (Onofriescu)
AG	Assessment Group
Aix	Augmentation index
APD	Automated peritoneal dialysis
APKD	Adult polycystic kidney disease
BCM®	Body composition monitor
BMI	Body mass index
BIA	Bioimpedance analysis
CAPD	Continuance ambulatory peritoneal dialysis
CI	Confidence interval
CV	Cardiovascular
DDD	Defined daily dose
DM	Diabetes mellitus
DV	Dialysis vintage
ECW	Extracellular water
ESRD	End-stage renal disease
EuClid ®	European clinical database
FO	Fluid overload
FOR	Relative fluid overload
HD	Haemodialysis
HDF	Haemodiafiltration
ICER	Incremental cost effectiveness ratio
ICW	Intracellular water
LVMI	Left ventricular mass index
MHD	Maintenance haemodialysis
NT-proBP	N-terminal proB-type natriuretic peptide
NICE	National Institute for Health and Care Excellence
NRS	Non-randomised study
OH	Overhydration
PD	Peritoneal dialysis
PDTW	Post-dialysis target weight
PWV	Pulse wave velocity

QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Risk ratio
RRF	Residual renal function
SD	Standard deviation
SEM	Standard error of the mean
TBW	Total body water

1 Scientific summary

Background

Chronic kidney disease (CKD) is a long-term condition in which the kidneys do not function effectively. In the most severe stage of CKD, the kidneys operate at 15% or less of their normal function, and treatment in the form of conservative management, kidney transplantation or dialysis will be required. Dialysis involves removing waste products and excess fluid from the bloodstream, and there are two main types: (i) haemodialysis, where the person is connected to a dialysis machine which uses a semi-permeable membrane to filter out excess salts and water in the blood. Haemodialysis is commonly prescribed for four hours, three times per week, administered either in hospital, in a satellite unit or at home; (ii) peritoneal dialysis, in which dialysis fluid is passed into the peritoneal cavity through a permanent catheter and waste products and excess fluid are drawn from the blood into the dialysis fluid by the blood vessels lining the cavity. The process of fluid exchange can either be carried out overnight by a machine (automated peritoneal dialysis) or conducted manually, four times daily, taking 30 to 40 minutes for each fluid exchange (continuous ambulatory peritoneal dialysis). To optimise the volume of fluid to be removed during dialysis (to avoid underhydration or overhydration, both of which are associated with potentially serious complications), people are assigned a 'target weight', which is commonly assessed using clinical methods, such as weight gain between dialysis sessions, pre- and post-dialysis blood pressure and patient-reported symptoms. However, these methods are not precise, and measurement devices based on bioimpedance technology, which are non-invasive, simple and relatively inexpensive, are increasingly used in dialysis centres. There is currently limited evidence on the clinical and cost-effectiveness of bioimpedance devices compared with standard clinical assessment for fluid management in people with CKD having dialysis.

Objectives

The specific objectives of this assessment were to:

- Systematically review the evidence on the clinical-effectiveness of multiple frequency bioimpedance devices (i.e. BCM, MultiScan 5000, BioScan 920-II,

BioScan touch i8, InBody S10) compared with standard clinical assessment for fluid management in people with CKD receiving dialysis treatment;

- Systematically review existing economic evaluations on multiple frequency bioimpedance devices for people with CKD receiving dialysis treatment;
- Develop a *de novo* economic model to assess the cost-effectiveness of multiple frequency bioimpedance technologies (using BCM, MultiScan 5000, BioScan 920-II, BioScan touch i8, InBody S10) for fluid management in people with CKD receiving dialysis treatment versus standard clinical assessment.

Methods

Clinical effectiveness

Comprehensive electronic searches were undertaken to identify relevant reports of published studies up to 10th October 2016. Evidence was considered from randomised controlled trials (RCTs) assessing multiple frequency bioimpedance devices versus standard clinical assessment, and non-randomised cohort studies. The population was people with CKD being treated with haemodialysis or peritoneal dialysis. The comparator was standard clinical assessment, consisting of blood pressure, presence of oedema, changes in weight, residual renal function, pre-existing cardiovascular conditions and/or patient-reported symptoms of overhydration or underhydration.

Data on clinical outcomes, intermediate outcomes and patient-reported outcomes were extracted from the included studies. Binary and continuous data were meta-analysed (where appropriate) as pooled summary effect sizes using standard inverse variance methods.

Cost effectiveness

A Markov model was developed to simulate the progression of the prevalent dialysis cohort through a set of mutually exclusive health states capturing mortality, CV and other causes of hospitalisation, transplantation (for those listed), and graft failure post-transplant. The model included costs to the health service of providing dialysis treatment, costs of inpatient hospitalisation, costs of outpatient attendance, costs of kidney transplantation, post-transplant follow-up and immunosuppressant costs, and costs of dialysis following transplant graft failure. Health state utility multipliers were

identified and incorporated for the dialysis and post-transplant states in the model, allowing cumulative QALYs to be estimated. Further proportional reductions in health state utility were modelled in the short-term for all hospitalisation events and in the long-term following incident CV hospitalisation events.

The added costs and plausible effects of bioimpedance guided fluid management (based on four tests per year) were added to the baseline model, and the cumulative costs and QALYs were simulated over the lifetime of the cohort in the alternative arms of the model. In the base case clinical effectiveness scenarios, proportional reductions in all-cause mortality and CV or all-cause hospitalisation were applied in the bioimpedance guided arm of the model. Given the limited direct evidence from the clinical effectiveness review, these effects (incorporated as hazard ratios) were primarily estimated by linking effects on surrogate endpoints (arterial stiffness (PWV) and hydration status) to plausible effects on the final outcomes using secondary published sources.

Results

Clinical effectiveness

A total of six RCTs, analysing a total of 1039 participants, and eight non-randomised studies (published in nine papers), analysing a total of 4915 participants, were included in the review of clinical effectiveness. All included studies investigated the use of the BCM - Body Composition Monitor in the relevant population, all of which were adults. Of the RCTs, one trial was assessed as being at Low risk of bias, one at High risk of bias and four trials did not provide sufficient information to make a robust judgement. We further identified four ongoing trials.

The results of the meta-analyses conducted for this assessment showed that using the BCM - Body Composition Monitor, as compared with standard clinical methods, for fluid management in people with chronic kidney disease significantly reduced systolic blood pressure (mean difference -3.48, 95%CI -5.96 to -1.00, p=0.006) and arterial stiffness (mean difference -1.53, 95%CI -3.00 to -0.07, p=0.04) but had no significant effects on mortality (HR 0.689, 95%CI 0.23 to 2.08, p=0.51). Both absolute overhydration and relative overhydration were significantly lower in the BCM - Body Composition Monitor group compared with the standard clinical assessment group

(WMD=--0.39, 95%CI -0.62 to -0.15, p=0.001 and WMD=-1.54, 95%CI -3.01 to -0.07, p=0.04, respectively).

Evidence from non-randomised studies suggested no statistically differences of blood pressure between the following subgroups: patients in whom overhydration was reduced within 6 months compared with those whose overhydration was not reduced within 6 months; patients having short versus long dialysis; and patients who were normohydrated compared with those overhydrated.

Cost-effectiveness

Six main clinical effectiveness scenarios were explored in the cost-effectiveness modelling, with hazard ratios of varying magnitude applied to all-cause mortality and CV or all-cause hospitalisation rates. One of the scenarios also explored the impact of modelling a reduction in the use (cost) of blood pressure medication with bioimpedance guided fluid management. There was insufficient evidence to justify the inclusion of effects on dialysis requirements (number and duration of sessions), residual renal function, and the health related quality of life of dialysis patients (independent of effects on hospitalisation).

When dialysis costs were included in the model, the incremental cost-effectiveness ratios for bioimpedance guided fluid management ranged from £58,723 to £66,007 per QALY gained. These ICERs related to incremental costs that varied between £4,518 and £35,676, and corresponding incremental QALY gains that varied from 0.07 to 0.58. The costs of dialysis in added years made up the vast majority of the incremental costs. When dialysis costs were excluded from the model, the base case ICERs ranged from £15,215 to £21,201.

Sensitivity analyses

The cost-effectiveness results were found to be most sensitive to the effect of bioimpedance guided fluid management on all-cause mortality. When dialysis costs were included in the model, the ICER was most favourable (~£22,000) when the hazard ratio for all-cause mortality was set equal to one; i.e. no effect mortality leading to no extra dialysis costs, but retained benefits on non-fatal hospitalisation events. With dialysis costs and an effect on mortality included in the model, there

would need to be an accompanying effect of bioimpedance monitoring on the cost of dialysis and/or health state utility over the lifetime of patients on dialysis. There is currently limited available evidence to justify such scenarios.
When dialysis costs were excluded from the model, the ICER for bioimpedance guided fluid management remained below £20,000 in most scenarios assessed. Given the relatively low cost of adding bioimpedance testing four times a year, the ICERs remained favourable with modest effects on mortality and hospitalisation rates.

Discussion

Strengths, limitations of the analyses and uncertainties

The methods used to conduct this assessment were detailed and thorough. The main limitation was the lack of evidence on any of the specified devices, with the exception of the BCM - Body Composition Monitor, and on children receiving dialysis.

In light of the limited available clinical effectiveness evidence, the economic modelling relied on estimated effects on surrogate endpoints (hydration status, arterial stiffness and blood pressure) to model plausible reductions in all-cause mortality and CV/all-cause hospitalisation. Critically, there were no ideal sources of evidence to link intervention induced changes in the relevant surrogates to effects on mortality and hospitalisation rates. Therefore, the possible effects were informed by reference to cross-sectional prognostic studies, leading to great uncertainty in the robustness of the cost-effectiveness findings.

Generalisability of the findings

The included trials involved only the BCM - Body Composition Monitor and it is not known if the effects of this device generalise across the other multiple frequency bioimpedance devices specified for this appraisal. None of the included studies were conducted in the UK or involved paediatric populations, so the applicability of our findings in those contexts is unclear. The generalisability of the modelled cost-effectiveness scenarios is also dependent on the generalisability of the estimated pooled effects of bioimpedance guided management on arterial stiffness (pulse wave velocity), or inferred effects on hydration status. Since all the included RCTs were conducted outside the UK, this remain uncertain.

Conclusions

Our findings indicate that use of the BCM - Body Composition Monitor for fluid management in people with CKD having dialysis may significantly reduce systolic blood pressure and arterial stiffness but the current evidence does not demonstrate a significant effect on mortality. In addition, both absolute overhydration and relative overhydration appear to be significantly lower among people assessed using the BCM - Body Composition Monitor compared with those assessed by standard clinical methods. There is currently no evidence to indicate that these findings are generalisable to paediatric populations or across other multi-frequency bioimpedance devices. With possible effects on mortality and hospitalisation rates modelled indirectly through estimated pooled reductions in surrogate endpoints (PWV or overhydration), it appear unlikely that the ICER for bioimpedance guided fluid management will fall below standard thresholds for cost-effectiveness with dialysis costs included in the model. However, if dialysis costs are excluded from the model, the ICER may feasibly fall below £20,000 with modest effects on mortality and/or hospitalisation rates. The economic modelling is subject to substantial uncertainty given the limitations in the clinical evidence base.

Implications for service provision

The current evidence suggests the BCM - Body Composition Monitor use in addition to routine clinical assessment improves intermediate outcomes such as systolic BP but significant effects on mortality have not been demonstrated.

Services that are currently, or subsequently, routinely using the BCM - Body Composition Monitor to augment routine clinical assessment should report their long-term outcomes before and after introduction of the bioimpedance device to extend the current evidence base.

Services that plan to introduce the routine use of the BCM - Body Composition Monitor to augment routine clinical assessment should adopt a protocol that is transparent and reproducible.

Suggested research priorities

The ultimate aim of introducing multiple frequency bioimpedance device measurement in addition to standard clinical assessment into clinical practice is to reduce clinically important events such as mortality, cardiovascular events and hospital admissions, whether this is through reduction in overhydration- or underhydration-related events. However, the clinical effectiveness of introducing this assessment into clinical practice on these clinically important outcomes has not been demonstrated. The effects of introducing multiple frequency bioimpedance device measurement on intermediate outcomes such as systolic BP control and arterial stiffness have been documented. The timeline from these intermediate endpoints to those clinically relevant, however, may not demonstrate an effect within the timeframe of the identified clinical trials. The studies were generally short-lived and the sustainability of introducing a change in routine practice has yet to be established.

We recommend that those centres that have introduced routine multiple frequency bioimpedance device measurement to augment clinical assessment of dialysis patients do investigate and report their clinically relevant and intermediate outcomes both before and after the introduction of the device; and also the sustainability of the measurement and its use in clinical practice over a sustained period.

We recommend that currently ongoing and future clinical trials are adequately powered to identify any clinical benefit (not just intermediate benefits) and, in particular, that the likely timeline of how any benefit (e.g. thorough better BP control) is considered and factored in to allow such studies to truly demonstrate whether an important clinical effect exists.

We recommend that future trials adopt protocols that are likely to be clinically applicable in multiple areas (e.g. three-monthly testing to allow use at routine review appointments).

Future trials should carefully match their included population to the outcomes of interest. For example, if the primary outcome is a reduction in blood pressure, an appropriate clinical population would be patients who had high blood pressure and were fluid overloaded post-HD, as they would be likely to have overhydration-related

hypertension. Removing fluid from patients with hypertension who are not overhydrated may result in harm to some participants.

2 Background and definition of the decision problem(s)

2.1 Condition(s) and aetiology(ies)

Brief statement describing the health problem

Chronic kidney disease (CKD) is a long-term condition in which the kidneys do not function effectively. There are many causes of CKD, including hereditary disease and autoimmune disorders, but the most common causes are high blood pressure or diabetes.[1] The progression of CKD can be measured according to 5 stages of severity. In the most severe stage of the disease, stage 5, the kidneys will be working at 15% or less of their normal function. At this point, the person will need to start treatment in the form of conservative management, dialysis or kidney transplantation.[2]

Collectively these treatments are referred to as renal replacement therapy (RRT). Dialysis involves removing waste products and excess fluid from the bloodstream.[3] There are two types of dialysis treatment: haemodialysis (HD) and peritoneal dialysis (PD). To calculate the amount of fluid to be removed during dialysis, a person will be assigned a target weight, which is the amount a person should weigh in the morning if they have PD, or at the end of an HD session. Maintaining the correct amount of fluid in the body is essential for people having dialysis.[4] Multiple frequency bioimpedance devices, which measure the fluid status of people having dialysis for CKD, have been proposed for the monitoring of fluid status and for assisting the decision about the optimum target weight for people receiving dialysis.

Aetiology, pathology and prognosis

The primary function of the kidneys is to remove waste products from the blood and expel them into the urine. The kidneys are also involved in maintaining blood pressure, regulating the levels of chemicals in the body, and producing vitamin D and erythropoietin. Chronic kidney disease (CKD) is a long-term condition in which the ability of the kidney(s) to function is reduced[3, 4] and is defined as either kidney damage (i.e. abnormalities of kidney function or structure; albuminuria) or glomerular filtration rate (GFR) of less than 60 ml/min per 1.73m^2 for at least three months.[5-9] In healthy people, the level of GFR varies according to age, sex, and body size. Normal GFR in young adults is approximately 120 to 130 mL/min per 1.73m^2 and declines

with age.[6, 10] Therefore, a GFR of less than 60 ml/min per 1.73m^{2,} represents loss of at least half of the normal adult kidney function and, below this level, the prevalence of CKD complications increases.[6] Glomerular filtration rate is the "gold standard" for assessment of kidney function but its measurement is awkward and calculated creatinine clearance is often used as a proxy measure of GFR for practical purposes.[11]

Risk factors for CKD lie within the following categories: i) factors that increase the risk of kidney damage, for example, age, diabetes, hypertension, family history, ii) factors that initiate kidney damage, for example, diabetes, hypertension, autoimmune diseases, primary glomerulopathies, or iii) factors that cause progressive decline in renal function after onset of kidney disease, for example, persistent activity of underlying disease, elevated blood pressure or blood glucose, high protein/phosphate diet, hyperlipidaemia, anaemia, cardiovascular disease, smoking.[6, 11]

Chronic kidney disease is classified into a continuum of five stages, based on renal function:[5, 6, 11]

1. Normal or increased GFR
2. Early renal insufficiency
3. Moderate renal failure
4. Severe renal failure
5. Kidney failure.

In the early stages, kidney disease is often asymptomatic and can be reversible. Most diseases evolve slowly over time but rapidly progressive diseases can result in kidney failure within months.[12] Kidney failure is considered to be the most serious outcome of CKD, with symptoms generally caused by reduced kidney function. Kidney failure is defined as GFR less than 15 ml/min per 1.73m^2, which is accompanied, in most cases, by signs and symptoms of uraemia, or the need to start kidney replacement therapy (dialysis or transplantation).[6, 13-16]

The two main types of dialysis that are available are haemodialysis and peritoneal dialysis. The key factors in determining what type of dialysis people receive are patients' preference, availability of options and clinical contraindications.[17]

In **haemodialysis**, the patient is connected to a dialysis machine containing a semi-permeable membrane and dialysis fluid. The patient's blood is passed into the machine, where electrolytes, water and metabolic waste products in the blood pass across the semi-permeable membrane and the waste products are retained in the dialysis fluid. The most common haemodialysis prescription is for four hours, three times per week. Haemodialysis can be given in hospital, in a satellite unit or at home.[18]

Peritoneal dialysis involves dialysis fluid (usually containing glucose) being passed into the peritoneal cavity (via a permanent catheter), where blood vessels lining the cavity draw waste products and excess fluid from the blood into the dialysis fluid, which is then drained from the cavity. Changing the fluid takes around 30 to 40 minutes and is repeated four times daily (continuous ambulatory peritoneal dialysis; CAPD). Alternatively, the process of fluid exchange can be carried out by a machine overnight (automated peritoneal dialysis; APD).[3, 4, 19] It is also possible to have a combination of manual and automatic exchanges.

Incidence and/or prevalence

The UK Renal Registry 18th Annual Report indicates that the prevalence of renal replacement therapy in 2014 was 913 per million population (pmp).[20] Prevalence rates were observed to increase in all of the UK countries in 2014. The median age of prevalent patients was 59 years (haemodialysis 67 years, peritoneal dialysis 64 years, transplant 53 years). It is worth noting that while half of all patients on renal replacement therapy continued to be aged 40-69 years, the prevalent population is becoming more elderly with 16% of patients being over 75 years old. For all ages, the prevalence rate in men exceeded that in women. The proportion of patients treated with peritoneal dialysis, which has been falling since the early 1990s, was reported to be just 6% in 2014. In general, large variations in prevalence were observed between centres across UK. This variation is likely to be explained by the proportion of patients requiring renal replacement therapy but also by the type and quality of clinical care delivered by renal centres.[20]

Impact of health problem: significance for patients in terms of ill-health (burden of disease) and significance for the NHS

In replacing normal renal function, dialysis needs to remove any excess fluid. Where haemodialysis is used, this is fluid that has accumulated in the body since the last dialysis session. In people receiving dialysis, it is vital to balance fluid status as both overhydration (also referred to as hypervolaemia or fluid overload) and underhydration (also referred to as hypovolaemia) are associated with negative outcomes, such as mortality, intradialytic morbidity and long-term cardiovascular complications.[19, 21-26] Removal of an appropriate volume of fluid is required to minimise complications caused by being either 'overhydrated' or 'underhydrated'. Determining when a person is 'overhydrated' or 'underhydrated' varies depending on the parameter used to determine fluid status, and also the cut-off points used to designate overhydration or underhydration, which differ between studies. When clinical assessment is used, fluid status is classified qualitatively. Individuals are classified as overhydrated or underhydrated if any corresponding symptoms are present and normohydrated (or 'euvolaemic') when they are absent.

Overhydration resulting from removal of too little fluid during dialysis contributes to hypertension, cardiovascular complications, mortality, oedema and left ventricular hypertrophy.[21, 22, 26-32] A negative association between higher diastolic blood pressure and residual renal function has also been reported.[33]

Complications associated with overhydration can be asymptomatic. Oedema, for example, may not be detectable until interstitial fluid volumes rise to approximately 30% above normal.[28] The use of blood pressure as a surrogate measure for fluid status is not entirely reliable as factors such as age and comorbidities may cause volume-independent hypertension.

Underhydration, which is caused by excessive amounts of fluid being removed during dialysis, can result in cramps, intra-dialytic hypotension and increased recovery time following dialysis.[34-37] In addition, there is an association between reduction of fluid volume in people commencing haemodialysis and loss of residual kidney function, along with a related increase in the risk of morbidity and mortality.[38, 39]

In the UK, on 31 December 2014, there were 58,968 adults receiving renal replacement therapy (49,842 in England, 2,842 in Wales). Of these, 27,804 people were on dialysis (23,734 in England, 1,308 in Wales). In particular, 86.9% received haemodialysis (38.6% in hospital, 44% in satellite units and 4.3% at home,); 5.8% received continuous ambulatory peritoneal dialysis; and 7% received automated peritoneal dialysis.[20, 40] In addition, 190 children and young people under the age of 18 years were on dialysis (103 haemodialysis and 87 peritoneal dialysis).[20, 40]

The Hospital Episode Statistics for England for the 2014-2015 period[41] reported 40 finished consultant episodes and 6 outpatient attendances for renal dialysis (code X40.1), 2265 finished consultant episodes and 931 outpatient attendances for peritoneal dialysis (code X40.2), 44457 finished consultant episodes and 16941 outpatient attendances for haemodialysis (code X40.3) and 570 finished consultant episodes and 1 outpatient attendance for automated peritoneal dialysis (code X40.5). There is a possibility, however, that the outpatient data are not complete as procedure/intervention is not a mandated field in the outpatients' dataset and coverage within this field is poor.

Measurement of disease

To enable an assessment of the amount of fluid to be removed during dialysis – the so called 'ultrafiltration volume',[19] - people are assigned a 'dry weight' or 'target weight' (i.e. euvolaemic), which is commonly defined as the lowest tolerated post-dialysis weight at which there are minimal signs or symptoms of underhydration or overhydration. This is achieved via gradual change in post-dialysis weight.[21, 24, 42, 43] It can also be defined as how much a person should weigh in the morning, if receiving peritoneal dialysis, or at the end of a haemodialysis session.[4] While the terms 'dry weight' and 'target weight' are often used interchangeably in clinical practice and in the published literature, hereafter the term 'target weight' will be used in this report. Target weight is commonly estimated using methods such as weight gain between dialysis sessions, pre-dialysis and post-dialysis blood pressure and subjective symptoms.[34] However, methods for assessing target weight are not precise and it has been reported that approximately one-half of people who achieve their 'ideal target weight' are actually overhydrated.[44] Dialysis centres are now increasingly using

measurement devices based on bioimpedance technology, as they are non-invasive, simple and relatively inexpensive.[23, 45, 46]

2.2 Description of technology(ies) under assessment

Summary of the multiple frequency bioimpedance devices under assessment

Bioimpedance technology involves assessment of fat-free mass and total body water in people without significant fluid and electrolyte abnormalities.[47] Extracellular water (ECW) and intracellular water (ICW) contain ions and, therefore, conduct, so their volume measurement is based on their resistance, or impedance, as cell membranes may act as capacitors at low or intermediate frequencies. There are various bioimpedance methods, depending on the frequency of current involved and body site of measurement. Single frequency bioimpedance analysis uses only one single current (e.g. 50 kHz), multiple frequency bioimpedance analysis uses currents of multiple frequencies (e.g. 5, 50 and 100 kHz) and bioimpedance spectroscopy uses a range of frequencies (5 to 1000 kHz).[29, 48] In particular, bioimpedance spectroscopy uses an electrical circuit of tissues with parallel resistances and a conductivity theory to take account of non-conducting elements to measure ECW and ICW volumes.[45] In a simple direct current electrical circuit, resistance is the determining factor of flow at a given voltage. However, when an alternating current is applied, there is a second factor causing resistance (or 'reactance') to flow and it is this factor that provides the additional metric to enable fluid compartments to be characterised. When an alternating current is applied to tissue, the resistance measurement is inversely proportional to the total content (ICW and ECW) between two electrodes on the skin; the reactance, a measure of electrical capacitance, is proportional to the cell mass in this tissue volume. The various methods of capturing and interpreting this information all obtain indirect measures of tissue water content and the proportion contained in the intracellular and extracellular spaces.[23, 49] The limbs provide a disproportionate amount of information (>80%), as compared to the trunk, by way of bioimpedance analysis, due to the neurovascular bundles and high muscle content in proportion to their cross-sectional area. As a result, measuring segments of the body, such as the lower leg[50] or chest wall[51] is sometimes preferred. [23]

The technologies relevant to this assessment are the BCM - Body Composition Monitor; the MultiScan 5000, the BioScan 920-II, the BioScan touch i8, and the InBody S10. Characteristics of these devices are reported below.

The **BCM - Body Composition Monitor** (Fresenius Medical Care, Bad Homburg, Germany) is a portable, stand-alone device, which uses bioimpedance spectroscopy to estimate a person's fluid and nutritional status. The person is placed in a supine position and four electrodes are attached: two to the back of one hand and two to the foot on the same side of the body. The electrodes are connected to the BCM - Body Composition Monitor device via a cable. The device passes a painless alternating current at 50 different frequencies (5 to1000kHz) through the body and measures the impedance between the hand and foot, giving relative impedance values for each frequency. This range of measurements determines the electrical resistances of the total body water and extracellular water and allows distinction of extracellular water and intracellular water.[23, 52] The software also calculates fluid overload using two physiological models. The amount of extracellular water that should be present based on the identified amounts of lean and adipose tissue is calculated and compared with the measured volume of extracellular fluid.[53, 54] The resulting volume difference between predicted and actual extracellular fluid is used as a measure of a person's overhydration volume and is reported by the device in litres.

The BCM - Body Composition Monitor is intended to be used as an objective measure of fluid imbalance, to complement clinical judgement. The associated software uses two validated physiological models to obtain the clinically relevant parameters: overhydration, lean tissue mass and adipose tissue mass.[4, 52] There are no restrictions on the age of the person that this device can be used on. Results from the BCM - Body Composition Monitor are available within two minutes and are stored on a "PatientCard" automatically, from which it can be loaded onto a database. Cards are reusable and can be reprogrammed for a new patient or can have a patient's data deleted if it becomes full and remain programmed for that patient.

Good agreement has been shown between BCM - Body Composition Monitor and current standard methods for measuring extracellular and total body volumes, intracellular volume, total fat, fat free mass and fluid overload in adults and urea

distribution volume in children.[55, 56] The evidence for the association between BCM - Body Composition Monitor assessment and improved patient outcomes is mixed. The Canadian Agency for Drugs and Technology in Health Rapid Response Report published in 2015[49] identified two RCTs of 131 and 189 participants, respectively,[57, 58] and one observational study of 110 participants, which assessed the use of the BCM - Body Composition Monitor in people receiving haemodialysis.[59] The report concluded that there was improvement in some patient outcomes such as decreased blood pressure and reduced fluid overload with patient management guided by BCM - Body Composition Monitor assessments but that the evidence base was limited. A study of people receiving peritoneal dialysis compared the assessment of overhydration status using BCM - Body Composition Monitor with a standard protocol. Results showed that extracellular volume and extracellular volume to intracellular volume ratio decreased steadily over the three-month follow-up in the BCM - Body Composition Monitor group but increased in the group assessed using standard methods. In addition, systolic blood pressure decreased significantly in the BCM - Body Composition Monitor group but increased significantly in the standard group.[60]

Further information on the BCM - Body Composition Monitor is available from the company's website.[52]

The **MultiScan5000** (Bodystat, Douglas, Isle of Man) is a portable device that uses bioimpedance spectroscopy to measure at 50 frequencies (ranging from 5kHz to 1000kHz), which are used to calculate body composition and hydration by a mathematical model called Cole-Cole analysis (also used in the BCM - Body Composition Monitor models). Values for extracellular water, intracellular water, total body water, and volume of over/underhydration are obtained from the same physiological models as used in the BCM - Body Composition Monitor analysis.[53, 54]

The volume of overhydration output is recommended for the assessment of hydration status in people 18-70 years old. Outside of this age range, this output can be used to track relative changes over time. In addition, the ratio of total body to extracellular water calculated by the device (called the 'prediction marker') can be used as an additional marker to track hydration status over time in all age groups. The device can

measure body segments, depending on the placement of the electrodes[61] and provide a bioelectrical impedance vector analysis (BIVA). Additional parameters related to body composition such as fat weight, lean weight, skeletal muscle mass and body cell mass can also be estimated. These parameters can be used to estimate nutritional status and therefore help to identify malnutrition status in people with chronic kidney disease who are treated with dialysis. Further information on the MultiScan 5000 device can be found on the product webpage.[61]

The **BioScan 920-II** (Maltron International, Essex, UK) is a portable multiple frequency bioimpedance analysis device which measures at 5, 50, 100 and 200 kHz. The eight electrodes allow monitoring of fluid changes in the whole body, thorax, trunk, legs or arms. All data are recorded and displayed immediately for analysis by the system. Alongside the standard output parameters related to hydration status [target water (min/max), target weight, target weight (min/max), extracellular fluid, ECW volume, ICW volume, total body water volume, ECW (%), ICW (%), total body water (%), extracellular/intracellular water, plasma-fluid (intravascular), fat free mass hydration], the device estimates additional parameters related to body composition (including body mass index, body density, body cell mass, protein mass, fat mass, fat free mass, and glycogen mass) and mineral content.

These parameters can be used to evaluate nutritional status and help to identify malnutrition in people with chronic kidney disease who are on dialysis. Further information can be found on the product webpage.[62] The use of the BioScan 920-II is recommended for people aged 5-99 years. A version of the BioScan 920-II device (the BioScan 920-II-P) is also available for monitoring hydration status in preterm, neonatal and paediatric patients (for use from 23 weeks gestational age up to 18 years).

According to the manufacturer, an updated version of the BioScan 920-II device, the **BioScan touch i8** with an updated user interface, is due to be released during the course of this assessment. As with the BioScan 920-II, it is anticipated that there will be two versions, one suitable for people aged 0-18 years and one suitable for people aged 5-99 years.

The **InBody S10** (InBody, Seoul, Korea) is a portable device that uses a direct multiple frequency bioimpedance analysis method to provide measurements across six different frequencies (1, 5, 50, 250, 500 and 1000 kHz). Measurements of five segments of the body are available: right arm, left arm, trunk, right leg, left leg. Hydration related outputs include water volumes (extracellular water, intracellular water), ratio of extracellular to total body water, and history of body water condition.

These parameters are estimated along with a suggested standard range of values to facilitate identification of overhydrated or underhydrated individuals. In addition, the InBody S10 provides estimates related to body composition such as body cell mass, basal metabolic rate, bone mineral content, skeletal muscle mass, fat free mass, and BMI. These parameters can be used to evaluate nutritional status and help to identify malnutrition in people with chronic kidney disease who are on dialysis. A full list of outputs can be found on the product webpage (http://www.inbody.com/global/product/InBodyS10.aspx). The use of the InBody S10 device is recommended for people aged 3-99 years.

Identification of important sub-groups

This assessment focuses on people with chronic kidney disease (CKD) who are treated with haemodialysis or peritoneal dialysis.

Relevant patient subgroups may include:

- People who are treated with haemodialysis;
- People who are treated with peritoneal dialysis;
- People of different ethnic origins;
- People for whom recommended configurations of electrodes cannot be used or who cannot assume the required positions for measurements to be made;
- People at extremes of body composition measurements; and
- Children younger than 5 years who may require more frequent monitoring.

Current usage in the NHS

In the UK, multiple frequency bioimpedance devices are used in some renal centres alongside clinical judgement to estimate fluid levels in patients receiving

haemodialysis or peritoneal dialysis. The Leeds Teaching Hospitals NHS Trust, for example, has prepared a standard operating procedure document for using the BCM - Body Composition Monitor in UK clinical practice.[4, 63] However, there is currently no national guidance in England and Wales on the role and adoption of these devices in clinical practice.

2.3 Comparators

In UK clinical practice, standard clinical assessment (without the use of bioimpedance devices) is used to determine fluid status and set, or adjust, target weights for people with chronic kidney disease who are treated with dialysis. This may include the consideration of clinical parameters such as blood pressure measurements, changes in weight, the presence of oedema, assessment of residual renal function, any pre-existing cardiovascular conditions, and any patient reported symptoms, intradialytic or interdialytic, of overhydration or underhydration (such as cramps, fatigue, diarrhoea, nausea, dizziness, fainting, breathlessness, decreased appetite, visual disturbances).

It is worth pointing out that clinical assessment does not directly measure fluid levels in the body to identify if a person is over- or underhydrated, but rather relies on the presence of symptoms and signs of overhydration and underhydration. This approach could, therefore, miss individuals who are asymptomatic despite having an excess or deficit of body water. For example, symptoms such as oedema may not appear until individuals are substantially overhydrated and people with fluid overload do not always exhibit high blood pressure.

Additionally, some clinical features are only surrogate markers for fluid overload and can, therefore, be the result of other unrelated causes. This could lead to fluid levels being inappropriately adjusted. For example, a response to high blood pressure assumed to be caused by fluid overload (but actually caused by other factors) may involve the removal of increasing amounts of fluid during dialysis, which, in turn, may lead to underhydration with potential loss of residual renal function.

2.4 Care pathways

Figure 1 illustrates the management of stage 5 CKD currently recommended by NICE.

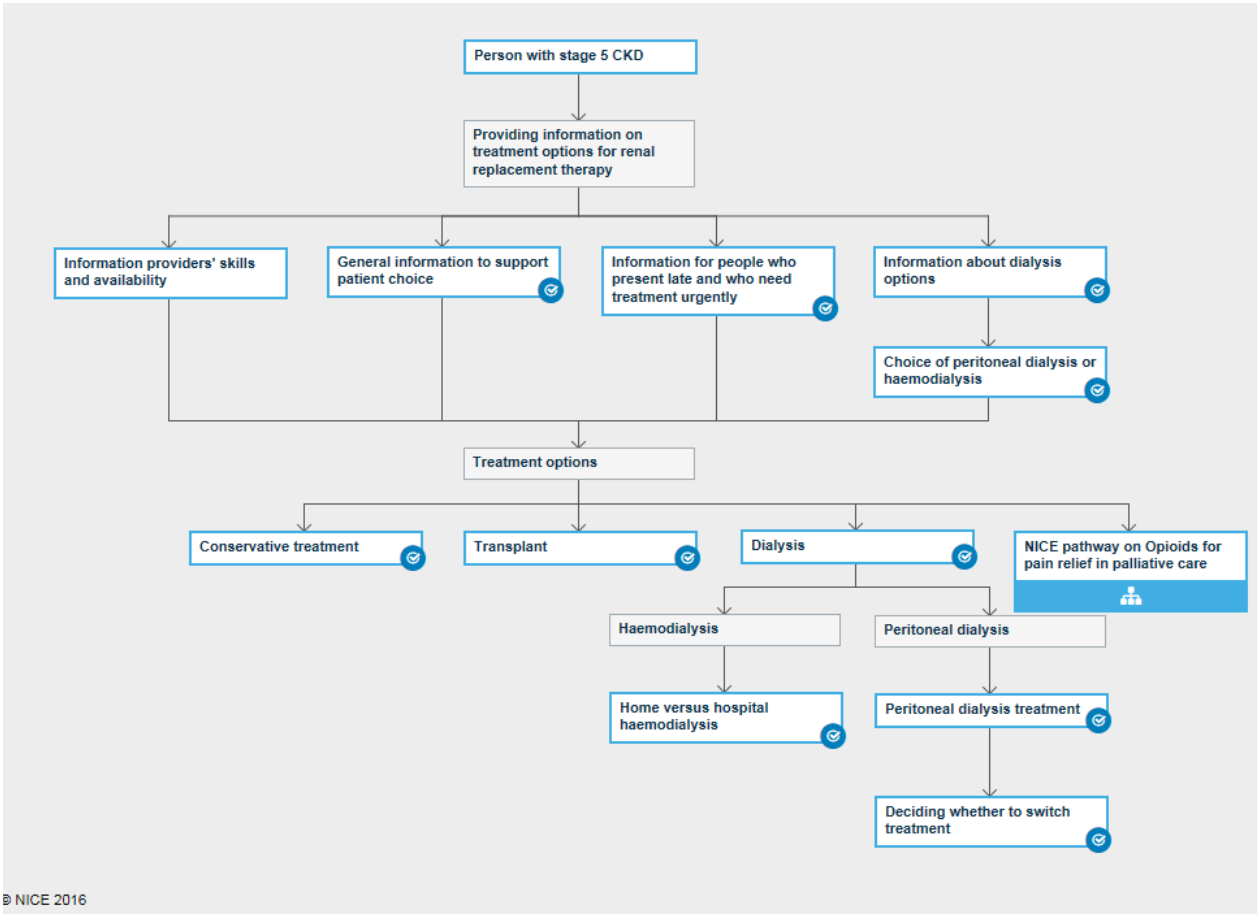

Figure 1 Management of stage 5 chronic kidney disease

3 Assessment of clinical effectiveness

3.1 Methods for systematic review of effectiveness

An objective synthesis of the evidence of the clinical effectiveness of multiple frequency bioimpedance devices in comparison with standard clinical assessment for fluid management in people with chronic kidney disease having dialysis. The evidence synthesis was conducted in accordance with the general principles of the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care[64] and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[65] and the NICE Diagnostics Assessment Programme manual.[66] The methods for this assessment were pre-specified in a research protocol (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016041785).

Identification of studies

Comprehensive electronic searches were conducted to identify relevant reports of published studies. Highly sensitive search strategies were designed, including appropriate subject headings and text word terms, to retrieve studies, which assessed the selected bioimpedance devices for CKD patients undergoing dialysis. Three facets were combined using the Boolean operator AND: CKD, renal replacement therapy and devices. There were no date or language restrictions. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, Science Citation Index and Cochrane Controlled Trials Register (CENTRAL) were searched for primary studies while the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the HTA database were searched for reports of evidence syntheses. The searches were undertaken during the period 27th June - 4th July 2016. The MEDLINE and EMBASE searches were rerun on 10th October 2016 to identify any recent reports. An additional search in MEDLINE and EMBASE was undertaken on 27th September 2016 to identify any published reports on validation of the devices which had not been identified by the main clinical effectiveness searches.

Reference lists of all included studies were perused in order to identify additional potentially relevant reports. The expert panel provided details of any additional potentially relevant citations.

Searches for recent conference abstracts (2014-2016) were also undertaken and included the following annual conferences: ERA-EDTA; Kidney Week (American Society of Nephrology) and the Annual Dialysis Conference.

Ongoing studies were identified through searching Clinical Trials.gov, EU Clinical Trials Register and WHO International Clinical Trials Registry. Websites of professional organisations and health technology agencies were checked to identify additional reports. Full details of the search strategies used are presented in Appendix 1.

Inclusion and exclusion criteria

Studies fulfilling the following criteria were eligible for inclusion in this assessment:

Population

People with chronic kidney disease treated with haemodialysis or peritoneal dialysis.

Interventions

The multiple frequency bioimpedance devices considered in this assessment were:

- BCM- Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany);
- MultiScan 5000 (Bodystat, Douglas, Isle of Man);
- BioScan 920-II and BioScan touch i8 (Maltron International, Essex, UK);
- InBody S10 (InBody, Seoul, Korea).

Comparator

The comparator considered in this assessment was standard clinical assessment, which takes account of the following parameters:

- Blood pressure;
- Presence of oedema;
- Changes in weight;
- Residual renal function;
- Pre-existing cardiovascular conditions;

- Any patient-reported symptoms of overhydration or underhydration, for example, cramps, fatigue, nausea, dizziness, breathlessness, decreased appetite, visual disturbances.

Outcomes

The following outcome measures were considered:

Intermediate measures, including:

- Number and length of haemodialysis sessions;
- Number of unplanned hospital visits/admissions due to fluid overload or dehydration;
- Use of antihypertensive medication;
- Incidence of anaemia;
- Blood pressure;
- Left ventricular hypertrophy;
- Left ventricular mass index;
- Arterial stiffness;
- Incidence of overhydration or underhydration;
- Changes of dialysis modality (from peritoneal dialysis to haemodialysis) because of fluid overload;
- Adherence with recommended fluid intake.

Clinical outcomes, including:

- Incidence of cardiovascular events (including stroke and heart attack);
- Mortality;
- Residual renal function;
- Incidence of oedema;
- Incidence of peritonitis;
- Adverse effects associated with hypotensive episodes (including cramps, fatigue, diarrhoea, nausea, dizziness, fainting).

Patient-reported outcomes, including:

- Post-dialysis recovery time and fatigue;
- Health-related quality of life.

One further relevant outcome not specified in the scope or protocol was also considered, due to its clinical importance: achievement of target weight.

Study design

Priority was given to RCTs assessing multiple frequency bioimpedance devices versus standard clinical assessment and RCTs comparing the effectiveness of one device and another. To supplement the evidence provided by RCTs, we also included non-randomised evidence, solely consisting of observational/cohort studies. As there was a large body of non-randomised evidence, which was not manageable in the timeframe of this assessment, we decided to focus exclusively on non-randomised studies with a sample size of at least 100 participants, which assessed hydration status of people with CKD having dialysis.

Of the non-randomised studies, which were excluded based on these latter criteria, three studies (published in four papers) with less than 100 participants focused on paediatric populations.[56, 67-69] Appendix 2 presents the characteristics of these studies. No UK-based studies, studies, which included any of the specified devices (other than the BCM - Body Composition Monitor) or studies which reported relevant outcomes not reported elsewhere in the report, were identified among the list of non-randomised studies that were not deemed suitable for inclusion based on the above criteria.

The following types of studies were also excluded from this assessment:

- Narrative reviews, editorials and opinions;
- Case reports;
- Conference abstracts for which a full publication or further methodological information could not be found;
- Non-English language reports for which a translation could not be organized;
- Studies reporting cross-sectional data only.

Data extraction strategy

One reviewer (MC) screened the titles and abstracts identified by the search strategies. A second reviewer (MB) independently screened a random sample of 10% of the titles and abstracts. Due to time constraints, this strategy differed from that detailed in the protocol, which stated that two reviewers would independently screen all titles and abstracts.

A data extraction form was designed and piloted specifically for this assessment (Appendix 3). One reviewer (MC or MS) extracted information on characteristics of studies and participants, details of interventions and comparators (where applicable), and relevant outcome measures. All extracted data were cross-checked by a second reviewer (DC, MC, MB or MS). Any disagreements were resolved by discussion between reviewers.

Assessment of risk of bias in included studies

The standard Cochrane Risk of Bias tool was used to assess the risk of bias in randomised trials (Appendix 4).[65] One reviewer (MC) assessed risk of bias in each included RCT and the results of these assessments were cross-checked by a second reviewer (DC or MS). There were no disagreements between reviewers. Studies were not included or excluded based on the assessment of their risk of bias. The Cochrane Risk of Bias tool incorporates the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Assessment of other sources of bias was based mainly upon the source of funding for the conduct of the study and potential links with the manufacturers of the devices under investigation. Individual risk of bias domains were assessed as being at High, Low or Unclear risk of bias.

Overall classification of studies was based on the assessment of three key domains: sequence generation, allocation concealment and blinding of outcome assessor. Studies were classified as high risk of bias if one or more key domains were judged to be at high risk; unclear risk of bias if one or more key domains were judged to be at unclear risk; or low risk of bias if all key domains were judged to be at low risk. Risk of bias of cohort studies was assessed using a modified version of a 17-item checklist previously developed by our research team (Appendix 5). The checklist was

originally adapted from several sources and developed through a partnership with the Review Body for Interventional Procedures (ReBIP) for NICE. The case series tool assessed the following domains: bias and generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of statistical analyses. Individual items were rated as 'yes', 'no' or 'unclear'. A rating of 'yes' indicated a low risk of bias.

Data analysis

The general approach recommended by the Cochrane Collaboration was used for data analysis and synthesis.[65] Where possible, for binary outcomes, the DerSimonian and Laird method was used to pool hazard ratios derived from each study, with the estimate of heterogeneity taken from the Mantel-Haenszel model. A random effects model was used to calculate the pooled estimates of effect. For continuous outcomes, mean differences between groups were pooled.

The statistical analyses focused on the five separate outcome measures for which consistent data were reported by at least two studies and were suitable for combining across studies: mortality, systolic blood pressure, arterial stiffness, absolute overhydration and relative overhydration. Other relevant outcomes that were reported but not meta-analysed because inconsistently reported across studies were: achievement of target (dry) weight,[57, 58, 70] hospitalisation,[58, 70, 71] left ventricular hypertrophy,[71] left ventricular mass index,[71] incidence of cardiovascular events,[70] adverse effects associated with hypotensive episodes[57, 58, 70, 71] and fatigue.[70]

Of the five outcome measures that were meta-analysed, mortality was reported in three trials. Two trials reported the hazard ratio at 12 months and, for the trial by Ponce et al.,[58] this was computed by obtaining the probability of death in both the treatment group and the control group and using the formula r=-ln(1-p) to estimate the hazard rate in the two groups. The hazard ratio was then calculated from the estimated hazard rates. The standard error was estimated using the method described by Parmar et al.[72]

The remaining four outcomes were all continuous measures, so mean differences between the treatment and control groups were pooled from the included trials and a

95% confidence interval was calculated to test whether the pooled summary effect showed a significant difference between treatment and control.

Heterogeneity across trials was explored by visual inspection of forest plots and assessed by means of the Chi-squared and I-squared statistics.

There are six trials in the meta-analyses. Five of these trials randomised at the individual level while Ponce et al.[58] randomised centres rather than individual patients. In order to include the trial by Ponce et al. in our meta-analyses, the method described by Fawzi et al[73] was used to inflate the standard error.

A subgroup analysis was performed according to the type of dialysis: haemodialysis versus peritoneal dialysis. Only the Luo trial[60] assessed peritoneal dialysis while the remaining five trials assessed haemodialysis. We were able to conduct subgroup analyses only for the following outcome measures: systolic blood pressure and absolute hydration.

3.2 Results

Performance of multiple frequency bioimpedance devices

A formal evaluation of the accuracy and validation of the multiple frequency bioimpedance devices under assessment was out with the scope of this assessment. However, information on the validation and accuracy of the specified devices was gathered from the available literature. Only information on the validation of the BCM - Body Composition Monitor was found in the current literature.

Wabel et al.[55] reviewed a number of studies on haemodialysis patients comparing the BCM - Body Composition Monitor against standard clinical methods for measuring extracellular and total body volumes, as well as intracellular volume. The authors concluded that there was good agreement between the BCM - Body Composition Monitor and the standard clinical measurements of fluid overload.

Huan-Sheng[74] assessed the relationship between the dry weight determined by clinical evaluation and the 'normally hydrated' weight estimated by the BCM - Body

Composition Monitor from serial follow-up data. The authors used serial measurements of six fluid parameters in the same haemodialysis patients to demonstrate that intra-person precision of the device was at an acceptable level of reliability for clinical use.

No studies have validated the BCM - Body Composition Monitor in people having peritoneal dialysis. The BCM - Body Composition Monitor manufacturer maintains that the method used is valid across both forms of dialysis.[4]

Quantity of evidence available

4106 records were retrieved by the database searches. In addition, 18 conference abstracts were obtained by searching the selected recent conference abstracts, giving a total of 4124 records. After de-duplication, 2592 abstracts were screened for relevance. Of these, 129 were selected for full text assessment from which 15 met our inclusion criteria. All 15 studies involved use of the BCM - Body Composition Monitor and none enrolled paediatric populations. A list of all excluded studies is presented in Appendix 6 together with the main reasons for exclusion.

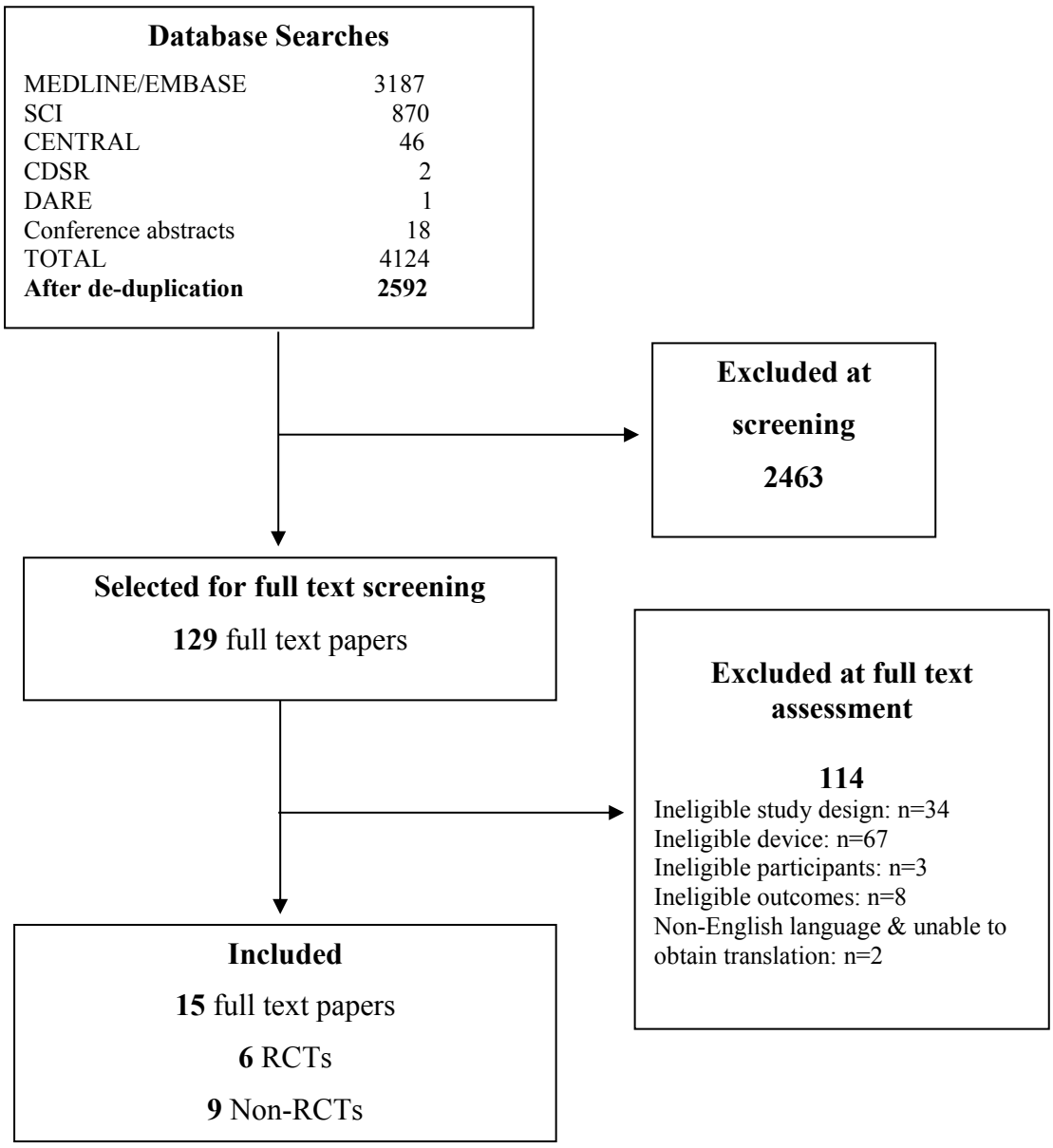

Figure 2 Flow diagram outlining the studies selection process

Characteristics of the included studies

A total of six RCTs and eight non-randomised studies (published in nine papers) were included in the review of clinical effectiveness. Characteristics of included studies are detailed in Appendix 7.

Randomised controlled trials

All six included RCTs were available in full text format. The BCM - Body Composition Monitor was the multiple frequency device used in all six trials. Two

trials were conducted in Romania,[57, 75] one trial in Taiwan,[70] one in Turkey,[71]one in Portugal[58] and the remaining trial did not provide this information.[60] One trial recruited patients from 23 dialysis centres,[58] one trial from two dialysis centres,[71] another trial from six dialysis centres[70]and two trials from a single dialysis centre.[57, 75] In the remaining trial it was unclear whether patients were recruited from a single dialysis centre or from multiple dialysis centres.[60] Five trials enrolled solely patients who were treated with haemodialysis,[57, 58, 70, 71, 75] and one trial enrolled continuous ambulatory peritoneal dialysis patients.[60] All six trials involved dialysis in a hospital setting. The multiple frequency bioimpedance device used for assessment of fluid status by all six trials was the BCM - Body Composition Monitor (Fresenius, Bad Homburg, Germany). Five trials included only adults aged 18 or older[57, 58, 60, 70, 71] while the remaining trial did not specify any age limitation for patients inclusion.[75] The main exclusion criteria reported in the trials, which assessed patients receiving haemodialysis, were: coronary stents or pacemakers;[70, 71, 75] metallic devices in body, such as joint prostheses;[57, 58, 70, 71, 75] limb amputations[57, 70, 71, 75] and pregnancy.[57, 58] The trial, which assessed peritoneal dialysis patients,[60] excluded those who had been on one or two exchanges a day due to economic limitation and those with acute infection and cardiovascular events in the month prior to enrolment.

The length of follow-up of the included trials ranged from 3 months[58] to 2.5 years[57] with half of the trials (i.e. three trials) reporting follow-up of 12 months.[58, 71, 75]In the case of the trial by Luo and colleagues, the authors decided to terminate follow-up at 3 months rather than at 6-months as originally planned, as the emerging differences between the groups and the adverse effect of fluid overload led the decision to extend the follow-up period to be considered unethical.[60]

Three of the six trials had links to Fresenius Medical Care, the company which manufactures the BCM - Body Composition Monitor,[57, 58, 71] albeit two of these trials reported that Fresenius had no involvement in the design or conduct of the trial.[57, 71] One trial did not report its source of funding [75] and two trials were supported by grants from independent sources.[60, 70]

Non-randomised studies

The eight non-randomised studies were reported in nine full-text papers, with the study by O'Lone and colleagues[76] also reported in a secondary study with an additional 51 participants and 21 months longer follow-up period.[77] The BCM - Body Composition Monitor was the multiple frequency device used in all eight studies. None of these studies enrolled paediatric populations. Two studies were conducted in the UK,[76, 78] two in Seoul, South Korea,[46, 79] and one each in Spain,[80] Poland,[81] Romania,[82] and Europe.[26] Three studies were multi-centred[26, 79, 80] and the remaining five studies were conducted in single dialysis centres.[46, 76, 78, 81, 82] Six studies involved patients receiving haemodialysis[26, 46, 79-82] and the remaining two studies involved solely patients treated with peritoneal dialysis.[76, 78]

Length of follow-up in the eight non-randomised studies ranged from 16 weeks[79] to 3.5 years.[26] Four studies reported median follow-ups of 24 months,[46] 23.9 months,[78] 27 months,[76] and 66.2 months.[82] O'Lone and colleagues[76] further specified that patients were enrolled between January 2008 and March 2012 and followed up until September 2012, with follow-up continuing until June 2014. Three studies had no apparent links with Fresenius Medical Care[46, 78, 81] and the other five studies reported either funding from Fresenius Medical Care[79] or some form of connection with the company.[26, 76, 80, 82]

Characteristics of participants

Table 1 summarises the baseline characteristics of the randomised and non-randomised studies included in this assessment.

Table 1 Summary of baseline characteristics of included studies

Characteristics	RCTs (n=6)	NRS (n=8)
Enrolled Randomised Analysed	1202 (n=5) 1074 (n=6) 1039 (n=6)	993 (n=3) N/A 4915 (n=8)[a]
Age: Median (range) of means, years	56.5 (51.7-66.3) (n=6)	61.9 (53.8-68.2)(n=7)
Sex: Median (range) % men	51.9 (46.3-76.2) (n=6)	62 (52.5-64.7) (n=7)
Diabetes: Median (range) % participants	22.4 (9.5-39.2) (n=6)	29.9 (10.4-37) (n=6)
Dialysis vintage: Median (range) of means, months	61.9 (34.2-105.5) (n=3)	44.7 (10.7-66)[b] (n=4)
Dialysis modality: HD (of which HDF) PD	 1037 (n=5) 218 (n=1) 165 (n=1)	 4050 (n=6) 1305 (n=1) 865 (n=2)

Note: RCT randomised controlled trial; NRS non-randomised study; HD haemodialysis; HDF haemodiafiltration; PD peritoneal dialysis. Dialysis vintage refers to the length of time on dialysis. n refers to the number of studies reporting the pertinent data as not all studies reported all data.

[a]Not including the 51 patients reported by Santhakumaran 2016 which were additional to the original O'Lone 2014 study.

[b]Hoppe: converted from 42.8 weeks to 10.7 months (42.8/4); Kim 2012: converted from 5.5 years to 66 months (5.5*12).

Randomised controlled trials

The six RCTs randomised a total of 1074 participants; 540 to bioimpedance measurements and 534 to standard clinical assessment.

Mean age for each intervention group was reported in five of the six RCTs[57, 58, 60, 70, 71] and ranged from 50.9 years[71] to 65.8 years[58] in the bioimpedance intervention group and from 52.5 years[71] to 66.7 years[58] in the standard clinical assessment group. Five RCTs reported the proportion of males and females for each intervention group.[57, 58, 60, 70, 71] Study populations tended to involve approximately equal proportions of men and women, with the exception of the studies by Hur et al. (69% men)[71] and Ponce et al. (76.2% men).[58] Proportion of men ranged from 43.6%[60] to 71.3%[58] in the bioimpedance intervention group and from 48.8%[60] to 81.8%[58] in the standard clinical assessment group. Prevalence of diabetes among participants varied across trials. Of the five trials that reported the proportion of participants with

diabetes,[57, 58, 60, 70, 71] values ranged from 10%[57] to 38.6%[58] in the bioimpedance intervention group and from 9%[57] to 38.6% in the standard clinical assessment group.[58] Mean dialysis vintage was reported in three RCTs [57, 60, 71] and ranged from 35.2 months[60] to 107 months[57] in the bioimpedance group and from 33.2 months to 104 months[57] in the control group.

Non-randomised studies

The eight included non-randomised cohort studies assessed a total of 4915 participants. Six cohort studies reported mean age of participants, which ranged from 53.8 to 68.2 years.[26, 46, 79-82] The two remaining cohort studies reported median ages of participants of 57.9 years[78] and 57 years.[76] Three studies reported mean age for normohydrated and overhydrated groups.[26, 46, 79] Age range was 55.9[79] to 66[26] for the normohydrated groups and 58.4[79] to 65.6[46] for the overhydrated groups, respectively. The proportion of men in the seven studies reporting this information[46, 76, 78-82] ranged from 52.5%[82] to 64.7%[81] and was, in general, higher than reported in the included RCTs. Proportion of participants with diabetes was reported by six of the observational studies[26, 76, 78, 80-82] and ranged from 10.4%[82] to 37% .[78] Mean dialysis vintage was reported by half of the studies and ranged from 10.7 months[81] to 66 months.[79] In the study by Hoppe et al., participants were split into short dialysis vintage (≤24 months) or long dialysis vintage (>24 months), with mean dialysis vintage being 9.3 weeks and 76.2 weeks, respectively.[81] The trial by Kim et al. 2012 reported mean dialysis vintage separately for dehydrated, normohydrated and hyperhydrated participants, which was 6.0 years, 4.1 years and 5.7 years, respectively.[79]

Frequency of BCM measurements

Randomised controlled trials

Frequency of measurements using the BCM - Body Composition Monitor in the RCTs was at least every 3 months. The most frequent use of the device was twice monthly in the bioimpedance intervention group (and every 3 months in the control group).[71] Three-month assessments were reported by Onofriescu et al. 2012 and Onofriescu et al. 2014; monthly assessments by Huan-Sheng et al. and Ponce et al., and 6-week assessments by Luo et al.[57, 58, 60, 70, 75]

Non-randomised studies

Frequency of BCM – Body Composition Monitor assessments in the non-randomised studies varied across studies: one study involved only one assessment within the first week of dialysis;[46] two studies involved three assessments per week;[26, 82] another study involved weekly assessments;[81] two other studies involved monthly assessments;[79, 80]one study involved quarterly assessments;[76] and the remaining study did not report the frequency of the BCM - Body Composition Monitor use.[78]

Standard clinical assessment: RCTs

In general, the type of standard clinical assessment in the included RCTs was not consistently reported across included trials. Only two trials provided details of their control intervention: Onofriescu et al. 2012[75] explained that *"The target dry weight was set according to clinical criteria by the attending physicians from the dialysis unit (i.e., target BP equal to or less than 140/90 mm Hg, absence of edema, and absence of intra-dialytic or inter-dialytic hypotension or other symptoms"*; and Onofriescu et al. 2014[57] reported that *"The target dry weight was set according to clinical criteria by the attending physicians from the dialysis unit; i.e. target BP equal to or less than 140/90 mm Hg, absence of edema, and absence of intra-dialytic or inter-dialytic hypotension or other symptoms."* In the other four trials, details of the assessment in the control group were not reported.[58, 60, 70, 71]Bioimpedance analysis was carried out on both intervention and control groups of all studies at the frequencies reported above (with the difference between the groups being that treated physicians in the control groups were blinded to the results). It was not explicitly stated by any of the studies whether standard clinical assessment was also carried out at these visits and no further information on the frequency of standard clinical assessments was reported.

Risk of bias

Randomised controlled trials

Figure 3 presents the summary of risk-of-bias assessments for all included trials. Risk of bias assessment of individual studies is presented in Figure 4.

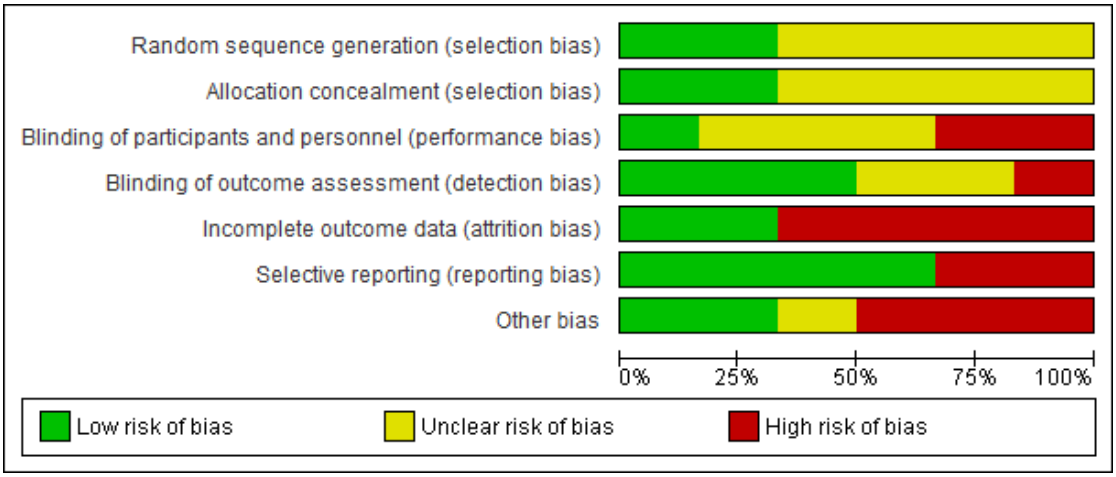

Figure 3 Summary of risk-of-bias assessments for all included trials

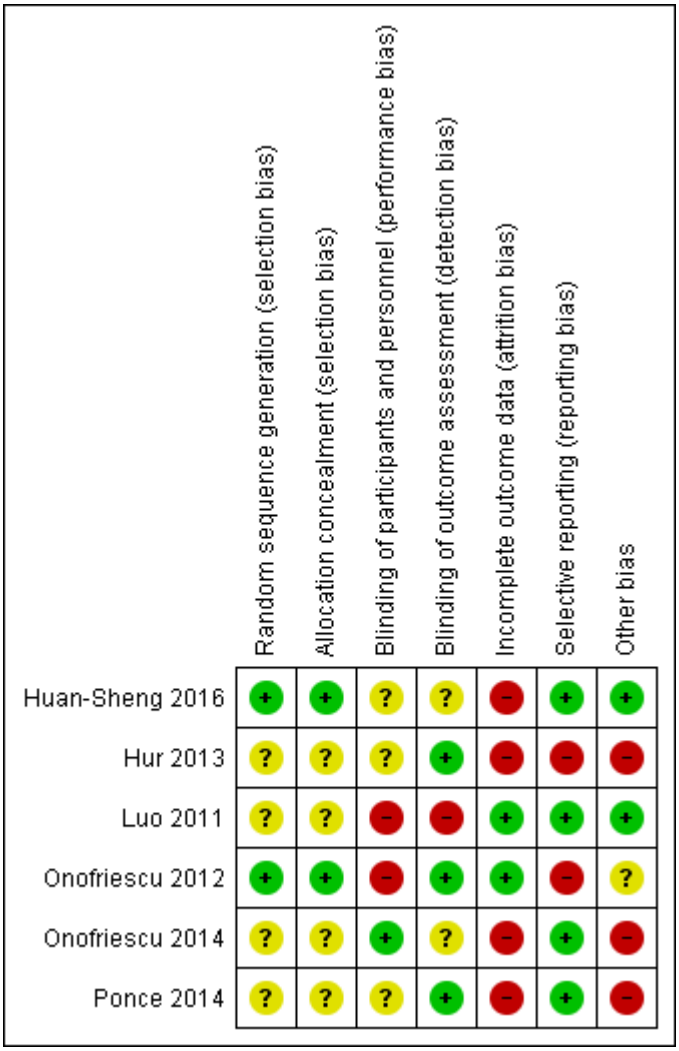

Figure 4 Risk-of-bias assessments of individual studies

According to the pre-specified criteria for the assessment of the overall risk of bias, one of the six RCTs was judged to be at low risk of bias,[75] one at high risk of bias[60] and the remaining four trials did not provide sufficient information on which to make a robust judgement.[57, 58, 70, 71]

Selection bias

Two trials reported sufficient information on which to make a full assessment of selection bias.[70, 75] Full details of allocation concealment were not reported, but the method of generation of sequence (i.e. random generation by computer) implies that the study personnel would be unable to predict the allocation, thus fulfilling the criterion of Low risk. The trial by Ponce et al. involved randomisation of centres, as opposed to randomisation of individuals within centres.[58] No details of the randomisation process were reported. The remaining three trials merely stated that they were randomised trials, but provided no details of how randomisation was achieved.[57, 60, 71]

Performance and detection bias

Only one trial reported that participants were blinded.[57] Two trials reported that participants were not blinded.[60, 75] In the remaining three trials both the intervention group and the control group received BCM – Body Composition Monitor assessments but the measurements were used to assess the intervention group only.[58, 70, 71]

Three trials reported that outcome assessors were blinded.[58, 71, 75] Luo et al. reported that patients, investigators and dialysis staff were not blinded to treatment assignment; the trial was, therefore, judged to be at high risk of bias for the blinding of outcome assessors domain and for overall risk.[60] In the trials by Huan-Sheng et al. and Onofriescu et al., it was unclear whether outcome assessors had been blinded.[57, 70]

Attrition bias

Two trials had either no dropouts[75] or a low number of dropouts[60] and therefore were judged to be at low risk of attrition bias. The remaining four studies were judged to be at high risk of bias due to the high proportions of participants who dropped out.[57, 58, 70, 71] It is worth noting that, in the Ponce et al. trial, 29/101 (28.7%) and 42/88 (47.7%) discontinuations were observed in the intervention and control groups, respectively.[58]

The reasons given for terminating the trial prematurely were the following: '*no valid data available within the time frame, death, transplant or transfer to another clinic'*. Proportions of participants within each of these categories and distribution of dropouts across centres were, however, not given.

Reporting bias

In four of the six included trials, the outcomes reported were in accordance with those specified in the respective methods section.[57, 58, 60, 70] The trial by Hur et al.[71] was judged to be at high risk of reporting bias as some outcome measures, which had not been previously specified, were reported, such as iron dose, RVDd, urine output, triglyceride levels, cholesterol. Onofriescu et al. 2012[75] did not report follow-up haematology, biochemistry or applanation tonometry data, despite stating in the methods section that these measurements were recorded. Reporting bias for this trial was, therefore, classified as high risk of bias.

Other bias

Three RCTs reported links with Fresenius Medical Care (either funding, as honorary speaker, or employment) and were judged to be at high risk of 'other bias'.[57, 58, 71] One trial did not disclose its source of funding[75] and two trials were supported by grants from independent sources.[60, 70] No other sources of bias were apparent in the included trials.

Non-randomised studies

Figure 5 presents a summary of the risk of bias assessments for the included non-randomised cohort studies. The results of individual study level assessments are presented in Appendix 8.

The majority of studies identified important prognostic factors, provided information on non-respondents/dropouts, included a sufficient length of follow-up, used objective outcome measures, considered important outcomes, delivered the intervention in an appropriate setting and by an experienced person, clearly defined the intervention, collected data prospectively, clearly defined the inclusion/exclusion criteria and involved a representative sample. None of the studies involved blinding of participants or study personnel. Two studies enrolled participants who entered the

study at varying points in their disease progression. The study by Hoppe et al.[81] compared short versus long dialysis vintage and the study by O'Lone et al. compared incident and prevalent patients.[76] The majority of studies failed to provide information on the characteristics of participants who withdrew or did not complete follow-up.[26, 46, 76, 78, 79, 82]

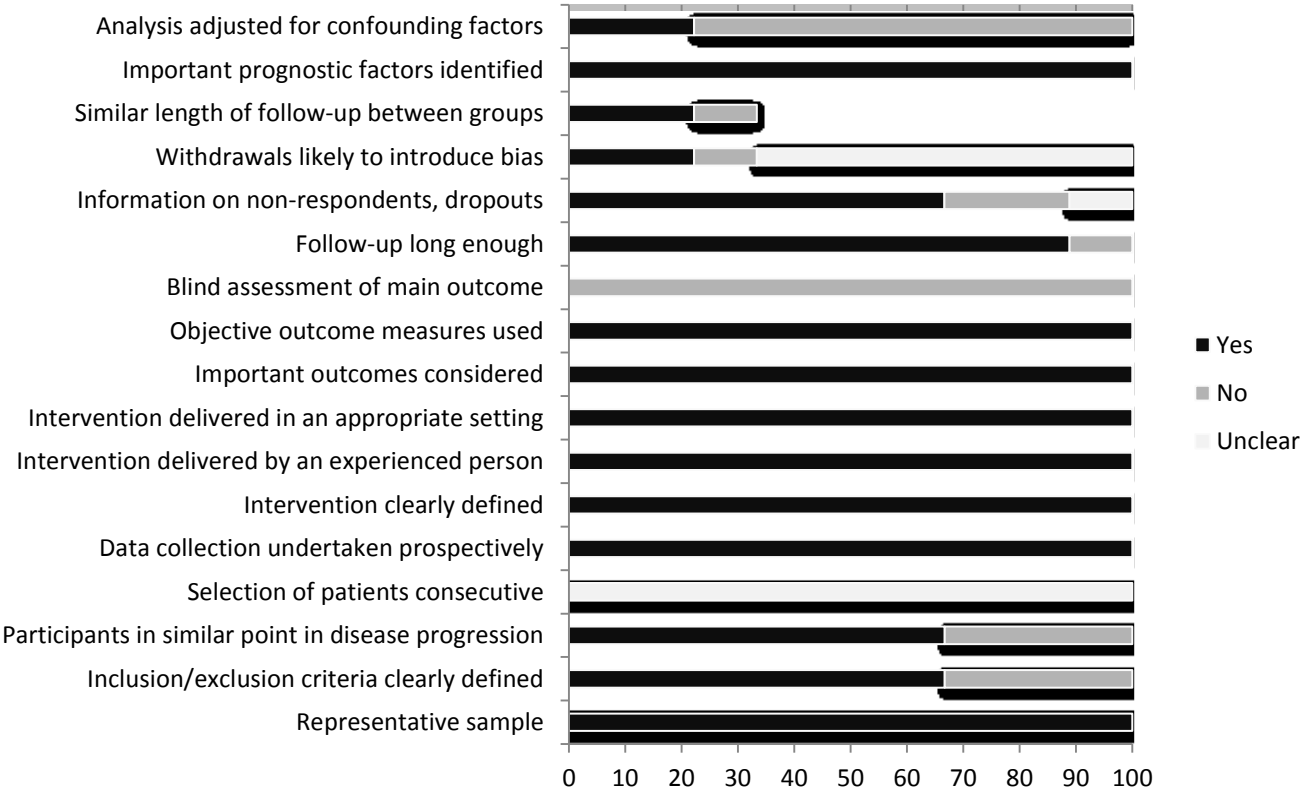

Figure 5 Summary risk of bias for non-randomised cohort studies

3.3 Clinical effectiveness results

Evidence from RCTs: meta-analyses results

Meta-analyses of relevant clinical outcomes were performed, where appropriate, using random-effects models. As the trial by Ponce et al.[58] is a cluster randomised trial, the variance has been inflated by the method used in Fawzi et al.[73] to allow to be included in the meta-analysis. The uninflated summary data for the Ponce et al. trial are presented in Table 2.

Table 2 Uninflated summary data for the Ponce et al. trial[58]

	Treatment			Control		
	Mean	**SD**	**N**	**Mean**	**SD**	**N**
Systolic blood pressure	134.6	27.3	101	136.5	24.7	88
Absolute hydration	2.92	1.47	101	3.36	1.75	88
Relative hydration	15.4	6.36	101	16.26	8.48	88

Full details of the relevant outcome measures extracted from the included RCTs are presented in Appendix 9.

Blood pressure

Six trials reported systolic blood pressure measurements, which were included in a meta-analysis.[57, 58, 60, 70, 71, 75] Figure 6 shows that systolic blood pressure was significantly lower in participants who underwent bioimpedance measurements using the BCM device than in those assessed by standard clinical assessment (mean difference=-3.48, 95%CI=-5.96 to -1.00, p=0.006, I^2=10%).

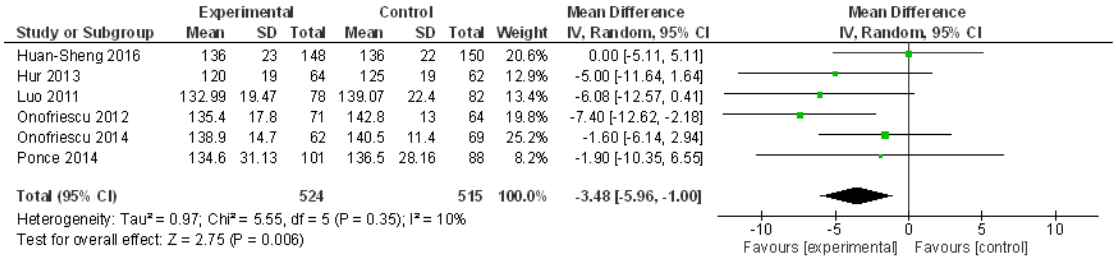

Figure 6 Meta-analysis for systolic blood pressure

Arterial stiffness

Three trials reported arterial stiffness results, which were included in a meta-analysis.[57, 71, 75] Figure 7 shows that arterial stiffness was significantly lower in the bioimpedance group as compared with the standard clinical assessment group (mean difference=-1.53, 95%CI=-3.00 to -0.07, p=0.04, I^2=88%). Statistical heterogeneity between trials was observed.

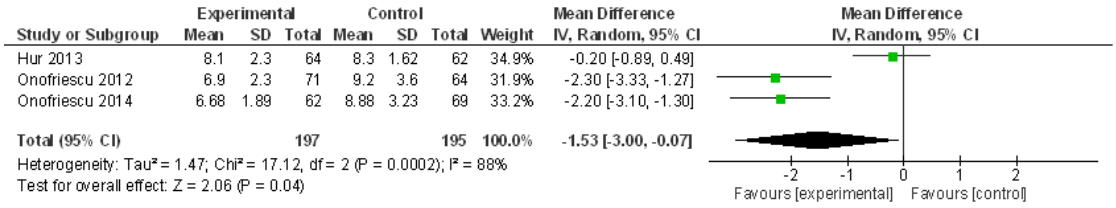

Figure 7 Meta-analysis for arterial stiffness

Mortality

Three of the included trials reported mortality data.[57, 58, 70] As mortality was reported with a hazard ratio, the log hazard ratio and log standard error for the three trials were input manually (Table 3).

Table 3 Log hazard ratio and log standard error for three trials included in meta-analysis of mortality

	Treatment		Control			
	Events	**Total**	**Events**	**Total**	**Weight**	**HR; 95% CI**
Huan-Sheng 2016	6	148	7	150	39.4	0.850,(0.288,2.511)
Onofriescu 2014	1	62	8	69	19.4	0.112,(0.014,0.907)
Ponce 2014	12	101	8	88	41.2	1.327,(0.479,3.680)
Overall	19	311	23	307	100.0	0.689,(0.228,2.084)

A total of 19/311 (6.1%) of participants in the bioimpedance group and 23/307 (7.5%) of participants in the standard clinical assessment group died. Figure 8 shows that compared with standard clinical assessment, the use of the BCM - Body Composition Monitor had no significant effects on mortality (HR=0.69, 95%CI=0.23 to 2.08, p=0.51, I^2=54%). Moderate statistical heterogeneity was evident amongst trials.

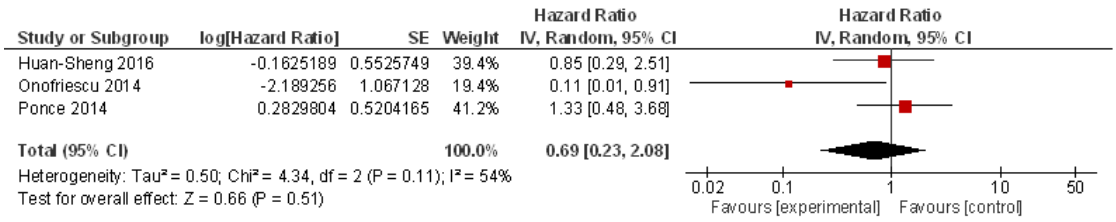

Figure 8 Meta-analysis for mortality

Absolute overhydration

Five trials assessed absolute overhydration,[58, 60, 70, 71, 75] which was defined as the difference between expected extracellular water and actual extracellular water. No data on underhydration were available. Figure 9 shows that absolute overhydration was significantly lower in the BCM - Body Composition Monitor group compared with the standard clinical assessment group (WMD=--0.39, 95%CI -0.62 to -0.15, p=0.001, I^2=36%).

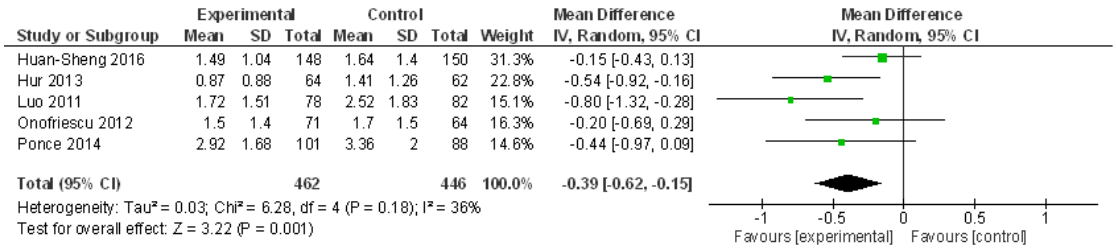

Figure 9 Meta-analysis for absolute overhydration

Relative overhydration

Four trials reported data on relative overhydration[57, 58, 70, 75] which was defined as the ratio of absolute fluid overload to extracellular water. Figure 10 shows that relative overhydration was significantly lower in the BCM - Body Composition Monitor group compared with the standard clinical assessment group (WMD=-1.54, 95%CI -3.01 to -0.07, p=0.04, I^2=39%).

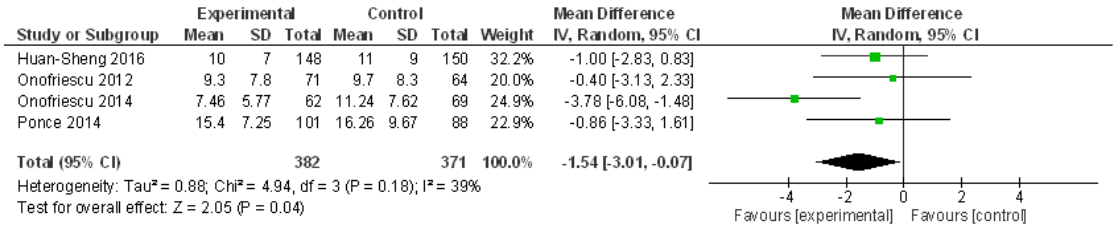

Figure 10 Meta-analysis of relative overhydration

RCT evidence: subgroup and sensitivity analyses

We had initially planned to perform subgroup analyses according to the type of dialysis (haemodialysis or peritoneal dialysis), the type of population (children younger than 5 years), ethnicity groups, and to certain characteristics of the patient population, i.e. people for whom recommended configurations of electrodes cannot be

used, people who cannot assume the required positions for measurements to be made or people at extremes of body composition measurements. However, due to lack of available data, we were able only to perform subgroup analyses of systolic blood pressure and absolute overhydration according to the type of dialysis utilised.

Figure 11 presents the forest plot of the subgroup analysis of systolic blood pressure according to the type of dialysis. As there was only one trial in the PD group, we considered that testing for subgroup effects would have been statistically unsound. We considered the comparison of the overall effect with the HD group effect (similar to a sensitivity analysis) a better, more reliable approach. In this case, there was still a significant effect on blood pressure (WMD=-3.09, 95%CI -5.88 to -0.31, z=2.18, p=0.03).

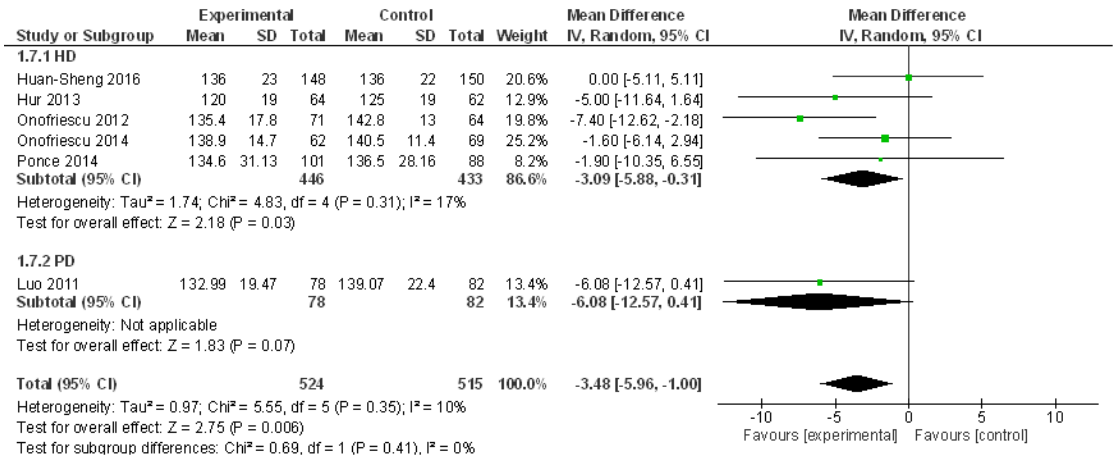

Figure 11 Subgroup analysis for systolic BP according to type of dialysis

Figure 12 presents the subgroup analysis for absolute hydration according to the type of dialysis. As described above, we did not perform a test of subgroup effects. In the case of absolute overhydration, there is a difference between the overall effect compared with the haemodialysis subgroup effect (WMD=-0.29, 95%CI -0.49 to -0.10, z=2.98, p=0.003) but this is not large enough to suggest a significant dialysis effect.

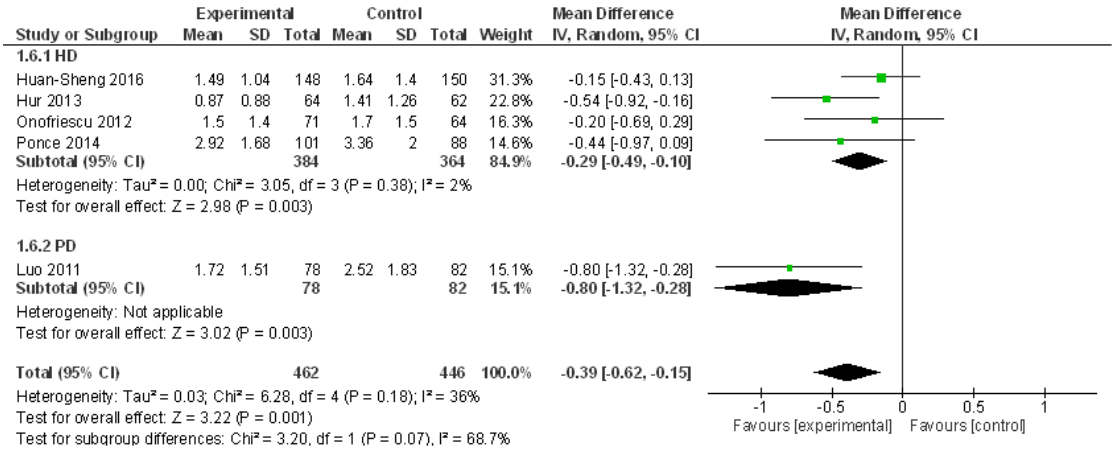

Figure 12 Subgroup analysis for absolute overhydration according to type of dialysis

We were unable to perform the planned sensitivity analyses (i.e. based on low risk of bias studies only or according to the type of multiple frequency bioimpedance device) as only one trial was assessed as being at low risk of bias and only one device (the BCM-Body Composition Monitor) was used in all included trials.

RCT evidence: other outcomes

Intermediate reported outcomes

Hospitalisation

Three trials reported data on hospitalisation.[58, 70, 71] Huan-Sheng et al. 2016 reported 71 events of all-cause hospitalisation, with an incidence of 0.52 (95% CI 0.44 to 0.61) per patient-year, in the bioimpedance group.[70] In the standard clinical assessment group, there were 73 all-cause hospitalisation events, with an incidence of 0.54 (95% CI 0.46 to 0.63). The hazard ratio was 1.19 (95% CI 0.79 to 1.80). Hur et al. 2013 reported 6 participants in the bioimpedance group hospitalised due to new CV events during the study period, with a hospitalisation rate/100-patient-years of 12.5. Four participants were hospitalised in the standard clinical assessment group, with a hospitalisation rate/100-patient-years of 30.9. The difference between the groups was not statistically significant. Ponce et al. 2014 reported that 39.6% of the bioimpedance group and 31.8% of the standard clinical assessment group were hospitalised at least once.[58]

Left ventricular hypertrophy

Hur et al. 2013 reported presence of left ventricular hypertrophy at 12 months in 44% of the bioimpedance group and 50% of the standard clinical assessment group.[71] The difference from baseline, although not statistically significant, decreased in both groups (from 67% and 53%, respectively).

Left ventricular mass index

Hur et al. 2013 reported a significant reduction in LVMI in the bioimpedance group from 131 (SD 36) at baseline to 116 (SD 29) at 12 months ($p<0.001$).[71] In contrast, there was no change in LVMI in the standard clinical assessment group; 121 (SD 35) at baseline and 120 (SD 30) at 12 months, $p=0.9$.

Clinical outcomes

Incidence of cardiovascular events

One study reported a combination of acute fluid overload or CV-related events, which included hospitalisation related to CV or cerebrovascular events and episodes of acute fluid overload. Huan-Sheng et al. 2016[70] reported 14 events in the bioimpedance group, with an incidence rate of 0.10 (95% CI 0.06-0.17) per patient-year, and 28 events in the control group, with an incidence rate of 0.21 (95% CI 0.15-0.29) per patient-year. The overall incidence ratio was 0.50 (95% CI 0.26-0.94) per patient-year, $p=0.03$.

Residual renal function

No trials reported residual renal function but two studies reported urinary volume, which could be considered as a surrogate measure thereof. Hur 2013[71] reported a significant increase in the proportion of anuric patients and a significant decrease in urine output in nonanuric patients at 12 months in the bioimpedance group. In contrast, there was no change in the proportion of anuric patients in the control group and the decrease in urine output in nonanuric patients was not significant at follow-up. Luo 2011 reported non-significant decreases in urine volume in both the BCM - Body Composition Monitor group and the standard clinical assessment group at 12 weeks, albeit the bioimpedance group showed a numerically larger decrease. [60]

Adverse effects associated with hypotensive episodes

The top five intradialytic complications reported by Huan-Sheng et al. 2016 were hypotension, cramping, skin itching, chest tightness and headache.[70] There were significant differences between the bioimpedance group and the standard clinical assessment group for all of these complications, but not in the same direction. In the bioimpedance group, there was significantly more cramping, chest tightness and headaches, but significantly less hypotension and skin itching.

Frequency of intradialytic hypotensive events was reported by Hur et al. 2013;[71] there was no difference between groups at baseline (63.2 in the bioimpedance group and 63.8 events/1000-dialysis-sessions in the standard clinical assessment group, p=0.9) or at 12 months (66.6 and 63.9 events/1000-dialysis-sessions, respectively, p=0.4). Similarly, Onofriescu et al. 2014 reported no difference between groups in hypotension/cramps events/patient-year (p=0.6).[57] Ponce et al. 2014 defined hypotensive events as SBP reduced by at least 30mmHg during dialysis or intradialytically below 90mmHg and reported no significant difference between groups at baseline (39 events in 17 patients in bioimpedance group; 38 events in 12 patients in the standard clinical assessment group) or 12 months (48 events in 20 patients and 41 events in 15 patients, respectively).[58]

No data were available on incidence of oedema or incidence of peritonitis.

Patient-reported outcomes

Fatigue

Only one trial reported details of any specified patient-reported outcomes. Huan-Sheng et al. 2016 reported 4 events of intra-dialytic fatigue in the bioimpedance group and 5 events in the standard clinical assessment group.[70] The difference between groups was not statistically significant (p=0.7).

Other relevant outcomes

Achievement of target weight

Three trials reported achievement of target weight. Huan-Sheng et al. 2016[70] reported that post-dialysis target weight (PDTW) adjustment was performed in 816 months (out of a total of 1658 monthly assessments across the 148 participants in the

intervention group over the 12 months follow-up). Post-dialysis target weight was achieved in 650 of these months (80%). Of the 816 months, clinical signs and symptoms were comparable with the BCM - Body Composition Monitor results in 482 months (59%), of which PDTW was reached in 426 months (88%). The authors further reported that PDTW adjustments based on BCM – Body Composition Monitor results were not supported by firm and clear clinical evidence in up to 41% of occasions. Onofriescu et al. 2014[57] stated that a significantly higher proportion of participants in the bioimpedance group than in the control group maintained dry weight within 1.1kg of the bioimpedance-recommended level. However, there is some uncertainty around the number of participants at each time point and replicating the analysis was not possible. Ponce 2014 reported that at 12 months target weight was generally less overestimated in the BCM - Body Composition Monitor group compared with the standard clinical assessment group (0.67 versus 1.00 kg).[58]

Non-randomised evidence

Table 4 presents the relevant results reported by the eight included non-randomised cohort studies, which were of two main types: in some studies the BCM - Body Composition Monitor was used to classify patients into groups (for example, overhydrated/non-overhydrated) and then outcomes were compared across the groups;[26, 82] in other studies, the BCM - Body Composition Monitor was used as a basis for adjustment of dry weight[46, 76, 79, 80] or to obtain hydration parameters.[78, 81]

Use of antihypertensive medication

Two studies reported the use of antihypertensive medication in specified patient subgroups.[79, 80] Castellano et al. 2014 reported significantly higher consumption of antihypertensive medications per month in the group with average relative overhydration not reduced within 6 months, as compared with those in which average relative overhydration was reduced within 6 months.[80] Kim et al. 2012 reported no significant difference in the consumption of antihypertensive drugs between dehydrated and hyperhydrated patients, although the amount of drugs used at week 16 was significantly lower than that at baseline or week 8 in the hyperhydrated group.[79]

Blood pressure

Four studies reported blood pressure among specified subgroups.[79-82] There were no statistically significant differences between groups in which average overhydration within 6 months was reduced versus not reduced;[80] short versus long dialysis groups;[81] or groups where relative fluid overload was <17.4% versus > 17.4%.[82] Kim et al. 2012 compared the blood pressure of dehydrated and hyperhydrated patients, and found that systolic blood pressure was higher in the hyperhydrated group, albeit the statistical significance of the comparison was not reported.[79]

Left ventricular hypertrophy

One study assessed left ventricular hypertrophy[81] and showed that left ventricle wall (mm) was not significantly different for short versus long dialysis vintage subgroups.

Hospitalisation

Two studies reported data on hospitalisation.[46, 82] Kim et al. 2015 reported a non-significant difference between overhydrated and nonoverhydrated patients in the number of hospital days per event.[46] Onofriescu et al. 2015 reported a significantly higher all-cause hospitalisation rate for patients classified as overhydrated according to a 17.4% cut-off compared to those classified as being not overhydrated. The value of 17.4% was proposed by the authors as a threshold for classifying a patient as overhydrated (i.e. relative fluid overload of at least 17.4 %), as opposed to the value widely accepted in the literature of 15%.[82] In contrast, there was no significant difference in all-cause hospitalisation rates for patients classified as overhydrated according to the traditional 15% threshold as compared with those classified as being not overhydrated.

Hydration status

The majority of studies reported hydration status at follow-up, albeit not in a consistent way. Subgroups in which higher levels of overhydration at follow-up were reported were: the subgroup whose average relative overhydration was not reduced to <15% in 6 months, as compared with the subgroup whose values were reduced to the desired level;[80] the long versus short dialysis vintage subgroup;[81] patients with a cardiac cause of death, as opposed to those with a non-cardiac cause of death;[78] both

absolute fluid overload and relative fluid overload in subgroups with relative fluid overload > 17.4% as compared with subgroups with relative fluid overload < 17.4%.[82]

Some studies reported the effects of hydration status on mortality. Kim et al. 2015 reported a significant effect of overhydration as risk factor for death;[46] O'Lone et al. 2014 reported a significant effect of absolute overhydration on mortality;[76] Onofriescu 2015 reported that patients assessed as being overhydrated were at significantly increased risk for all-cause mortality;[82] Wizemann et al. 2009 reported a significant risk of relative hydration status on mortality.[26]

Cardiovascular events

Three studies reported data on cardiovascular events. A non-significant difference in the incidence of acute myocardial infarction and stroke was observed between short and long dialysis vintage subgroups;[81] no differences were found in the number of cardiovascular events per year between overhydrated and non-overhydrated subgroups;[46] no significant differences in the incidence of coronary heart disease, peripheral vascular disease, heart failure or stroke were detected between the subgroup with relative fluid overload <17.4% and that with relative fluid overload >17.4%.[82]

Mortality

One study reported a significantly higher number of deaths in the long versus short dialysis vintage subgroup.[81]

Table 4 Summary of included non-randomised studies' outcomes

Study outcomes relevant to this review	Study authors' conclusions
Castellano 2014[80] (Spain; cohort study; 6mo follow-up)	
AvROH reduced within 6 months (n=325) vs AvROH not reduced within 6 months **Intermediate outcomes (n=494) [M (SD)]** 1) Time undergoing HD (months): 52.56 (43.69) vs 59.88 (50.51), *p = 0.028* 2) Use of antihypertensive medication (u/month): 37.97 (47.99) vs 50.0 (58.12), *p = 0.001* 3) SBP (mmHg): 136.31 (20.44) vs 137.74 (22.93), *p = NS* DBP (mmHg): 65.78 (11.71) vs 67.25 (13.35), *p = NS* 4) Average relative overhydration %: 18.52 vs 21.59, *p=0.000* **Clinical outcomes:** 1) Age-adjusted Charlson comorbidity index: 5.82 (1.81) vs 5.55(1.90), *p = 0.050*	Reduction in hyperhydration status related to better control of blood pressure and anaemia with fewer AHT and ESA. Maintained hyperhydrated patients, diabetic patients with many comorbidities and young males with longer time on haemodialysis and non-adherence treatment, may benefit from close monitoring of hydration state & individualized dialysis and drug treatments
Hoppe 2015[81] (Poland; cohort study; 30mo follow-up)	
Short (n=119) vs long (n=122) dialysis vintage subgroups **Intermediate outcomes:** 1) SBP (mmHg): 137.0 (17.1) vs 138 (17.4), *p = NS* DBP (mmHg): 82.8 (9.6) vs 83.7 (10.4), *p = NS* 2) Left ventricular hypertrophy: 13.3(1.6) vs 13.8 (2.0), *p = 0.61* 3) Overhydration %: 2.8 (2.1) vs 3.5 (2.4), *p = 0.013* **Clinical measures:** 1) Incidence of cardiovascular events (n): AMI, 7 vs 11, p = NS; stroke, 3 vs 3, *p = NS* 2) Mortality (n): 15 vs 27, *p = 0.045*	Longer dialysis vintage associated with CV dysfunction, overhydration and increased mortality, which may be predicted with OH% and cardiac troponin T
Kim 2012[79] (Korea; interventional cohort study; 16w follow-up)	
Dehydration (n=18) vs Hyperhydration (n=44) subgroups **Intermediate outcomes:** *1)* No. of anti-hypertensive drugs, mean (SD): 1.33 (1.5) vs 4.05 (2.53), *p = NR* 2) SBP (mmHg): 130 (22.3) vs 143 (21.9), *p = NR*	BCM-guided optimisation of body fluid status may lead to improvement of inflammatory markers and anti-atherogenic adipokines as well as

DBP (mmHg): 70.7 (14.9) vs 70.7 (11.2), *p = NR*	haemodynamic parameters in people having haemodialysis
Kim 2015[46] (Korea; cohort study; median 24mo follow-up)	
Overhydrated group (n=160) vs nonoverhydrated group (n=80) **Intermediate outcomes:** 1) Hospital days: mean (SD) days/event: 8.0 (19.4) vs 6.3 (14.7), *p = 0.438* 2) Presence of overhydration as a risk factors of death during entire follow-up: OR= 2.569, CI=95% (1.077-6.126), *p = 0.033* **Clinical outcomes:** 1) Cardiovascular disorder (Events/y): 0.3 (0.9) vs 0.2 (0.5), *p = 0.126*	The ratio of OH/ECW volume measured with BCM is related to the overall survival of end-stage renal disorder patients who have started maintenance haemodialysis
Oei 2016[78] (UK; cohort study; median 23.9mo follow-up)	
Death from cardiac vs non-cardiac causes **Clinical outcomes:** 1) Overhydration level in people who died, L: 2.95 vs 1.35, *p<0.05*	Patients that were overhydrated had higher cTnT, and their deaths were more likely to be cardiac related. Reduction in OH correlated with lowering of cTnT
O'Lone 2014[76] (UK; cohort study; median 27mo follow-up)	
Intermediate outcomes: 1) Effect of OH (per L) on mortality (all participants): HR=1.10, *p=0.025,* CI=95% (1.01 – 1.20) 2) Effect of OH (per L) on mortality (severely overhydrated participants): HR=1.83, *p=0.01*, CI=95% (1.19 – 2.82) OCH/ECW: HR = 2.09, *p = 0.00*, CI=95% (1.36-3.20) **Clinical outcomes:** 1) Peritonitis (n=580; mean 17.1mo follow-up): 289 new episodes (rate of 1 in 34.3 patient months)	Body mass index (BMI) did not influence the hydration parameter OH/ECW, which remained an independent predictor of mortality when BMI and lean tissue index were included in a multivariate model. However, it remains to be determined if correcting the OH status of a patient will lead to improvement in mortality
Onofriescu 2015[82] (Romania; cohort study; median 66.2mo follow-up)	

Relative fluid overload (RFO) <17.4% (n=135) vs RFO>17.4% (N=22) **Intermediate outcomes:** 1) All cause hospitalisations (n=181 vs n = 40, events/100 pt-years): 60.4 vs 77.8, RR: 0.78, CI=95% (0.64 – 0.95) 2) SBP (mmHg): 142.9 (15.6) vs 143.6 (14.2), *p = 0.89* DBP (mmHg): 81.4 (9.9) vs 81.1 (9.3), *p = 0.76* 3) Left ventricular mass index (g/m^2): 147.1 (120.9-178.1) vs 151.8 (119.7 – 184.2), *p = 0.79* 4) Absolute fluid overload (L): 1.3 (1.1) vs 3.6 (0.8), *p<0.001* 5) Relative fluid overload (L): 7.7 (6.4) vs 20.1 (3.1), *p<0.001* **Clinical outcomes:** 1) CV comorbidities, N (%): CAD, 34 (25.2) vs 3 (13.6), *p =0.24*; PVD, 17 (12.6) vs 2 (9.1), *p = 0.64*; Heart failure, 50 (37.0) vs 8 (36.4), *p=0.95*; Stroke, 6 (4.4) vs 1 (4.5), *p = 0.98*	Hydration status is associated with the mortality risk in a HD population, independently of cardiac morphology and function
Wizemann 2009[26] (Europe; cohort study; 3.5y follow-up)	
Clinical outcomes: 1) Mortality risk, Cox adjusted hazard ratios (HR): Age, HR = 1.05, 1/year*; p < 0.001*, CI=90% (1.029-1.066); Systolic blood pressure HR = 0.986 1/mmHg; *p = 0.014*, CI=90% (0.979-0.995); Diabetes, HR = 2.766; p < 0.001, CI=90% (1.879-4.073); Peripheral vascular disease (PVD), HR= 1.683, *p = 0.045,* CI=90% (1.097-2.583); Relative hydration status, HR = 2.102, *p = 0.003,* CI=90% (1.389-3.179)	Hydration state is an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes. It is essential to measure hydration status objectively and quantitatively to obtain a more clearly defined assessment of HD patients' prognosis

3.4 Ongoing trials

Four relevant ongoing trials were identified. Table 5 summarises the main characteristics of the ongoing trials. More detailed study characteristics are presented in Appendix 10.

Table 5 Main characteristics of relevant ongoing trials

Study details	Study aim	Primary outcome(s)
Probing the Dry Weight (DW) by Bioimpedance (BIA): Which is the Gold Standard Between Clinical DW and BIA DW? **NCT02446535**[83] (Italy)	To verify if BIA-based DW (BIA DW) control is truly superior to current volume management in HD patients	The definition for each patient of the gold standard DW when comparing the Clinical and the BIA DW
Fluid Management Guided by Bioimpedance Analysis in Peritoneal Dialysis (PD) Patients **NCT02000128**[84] (China)	To investigate the effect of bioimpedance analysis (BIA) guided fluid management versus experiential way on clinical outcome in peritoneal dialysis patients	All-cause mortality; cardiovascular related mortality
Control Of Fluid Balance Guided by Body Composition Monitoring in Patients on PeritoneAl dialySiS (COMPASS) **NCT01887262**[85] (Korea)	Bioimpedance-guided fluid management in peritoneal dialysis patients may provide better protection of residual renal function over 1 year period, compared with management guided by clinical information alone	Change of glomerular filtration rate from baseline to the 12th month
Bio-impedance spectroscopy to maintain renal output (BISTRO) **ISRCTN11342007**[86] (UK)	NIHR funded open-label multi-centre RCT to test whether taking regular measurements with a bioimpedance device improves outcomes for people > 18 years of age who have recently started haemodialysis treatment for kidney failure CKD stage 5. Target sample size is 516 patients from 30 UK dialysis units. Enrolment due to start 02-01-17.	Time to anuria (loss of urine output), <100ml/day or 200ml in the short inter-dialytic period confirmed by a further collection after 2 weeks to exclude temporary illness

4 Assessment of cost-effectiveness

The aim of the economic evaluation for this assessment was to assess the cost-effectiveness of using multiple frequency bioimpedance technologies versus standard clinical assessment for fluid management in people with chronic kidney disease having dialysis. The bioimpedance technologies considered include the BCM - Body Composition Monitor, MultiScan 5000, BioScan 920-II, BioScan touch i8, and the InBody S10.

The specific objectives were to:

- Review existing economic evaluations of multiple frequency bioimpedance devices for fluid management in people with chronic kidney disease having dialysis.
- Develop a de novo economic model to assess the cost-effectiveness of using the identified multiple frequency bioimpedance devices compared with standard clinical assessment alone, to guide fluid management in people with chronic kidney disease having dialysis - from a UK NHS and personal social services perspective.

4.1 Systematic review of existing cost-effectiveness evidence

Electronic searches were undertaken to identify reports of economic evaluations. The following bibliographic databases were included: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations Embase, NIHR Economic Evaluations Database (NEED, HTA Database and the RePEC database. No date or language restrictions were imposed, Searches were undertaken on 5th July 2016. Details of the search strategies are reproduced in Appendix 1. In addition, recent conference proceedings (2014-2016) including those of the European Renal Association, American Society of Nephrology, the Annual Dialysis Conferences and the International Society for Pharmacoeconomics and Outcomes Research were also screened. Relevant websites of key professional organisations, registries and device manufacturers were checked for additional data and information. The searches identified no full economic evaluations of relevance to the scope of this assessment.

To help inform the design of the de novo economic model, broader searches were carried out to identify existing economic models in the area of CKD/ESRD, and NHS cost data applicable to relevant patient populations and health states included in the model. A separate search was also developed for health state utility data relevant to the health states included in the economic model. Databases searched included MEDLINE, EMBASE, CEA registry and ScHarrHUD. The searches were undertaken on 8th July 2016 and no date or language restrictions were imposed. The search strategies are reproduced in Appendix 1. Discussion of the potential data sources identified by these broader searches are provided under the relevant subheadings below.

4.2 Independent economic assessment

A de novo economic model was developed in TreeAge Pro (TreeAge Software, Williamstown, MA, 2013). The model was designed to assess the cost-effectiveness using multiple frequency bioimpedance testing to help guide fluid management decisions in people with chronic kidney disease having dialysis.

The model structure was informed by the hypothesized benefits of bioimpedance testing, and review of published models in the area of end stage renal disease - with particular emphasis on models previously used to inform NHS policy surrounding the provision of dialysis.[17, 87-90]

The model was populated using data derived from focused reviews of the literature (to inform baseline mortality and hospitalization risks in patients with ESRD), the systematic review of clinical effectiveness (to inform relative treatment effects), and other focused reviews to inform sources of cost and utility data. The model was built and analysed in accordance with the NICE reference case for the evaluation of diagnostic tests and devices.[17, 90]

Methods

Relevant patient population(s)

The model compared the alternative fluid management strategies for a prevalent cohort of people with ESRD on either haemodialysis (HD) or peritoneal dialysis (PD). The base case analysis was conducted using the weighted average of the median age

and sex distribution for the respective prevalent dialysis cohorts as reported in the UK renal registry report;[91] age 67.2 years, 61% male for those on haemodialysis, and 64.2 years, 61% male for those on peritoneal dialysis. Thus the base case was run for a mixed cohort at the average age of 66 years, 61% male, with 87% on HD and 13% on PD. Separate subgroup analyses were also conducted for the PD and HD cohorts, applying the median ages for the respective subgroups. In addition, comorbidity burden is also used in the model in the estimation of baseline hospitalisation risks, and this was estimated from UK registry data.[91, 92] Based on these sources, 63% of patients aged ≥ 65years, and 36% of patients aged < 65 years are modelled to have at least one comorbidity at baseline. The estimated mean number of comorbidities in those with any comorbidity is 1.6 and 2 for the PD and HD cohorts respectively.

Monitoring strategies evaluated

Bioimpedance monitoring strategies, to help adjust target weight and guide fluid management, were compared with standard clinical assessment where target weight is set based on clinical signs and symptoms including: blood pressure, presence of oedema, changes in weight, residual renal function, pre-existing cardiovascular conditions, and patient reported symptoms of overhydration or underydration. For the bioimpedance strategies, it was assumed that all patients would have their hydration status assessed every 3 months (4 times per year), and have their target weight modified in line with the results if necessary. The above monitoring strategy is in line with clinical opinion regarding the necessary frequency of bioimpedance testing in an adult dialysis population, and is also consistent with the approach used in two of the trials included in the systematic review of clinical effectiveness.[57, 75] It is less intensive than the testing strategies applied in the other RCTs included in the clinical effectiveness review, which varied from once per week[93] to once every 6 weeks.[60] It is assumed in the base case cost-effectiveness scenarios that quarterly testing can deliver effects in keeping with those observed across all the included randomised trials. The impact of increased testing frequency is addressed in sensitivity analysis.

The bioimpedance technologies included in the scope for this assessment included the BCM - Body Composition Monitor, MultiScan 5000, BioScan 920-II, BioScan touch i8, and the InBody S10. However, the review of existing literature only uncovered clinical effectiveness evidence relating to the BCM - Body Composition Monitor.

Therefore, the economic modelling focussed on assessing the cost-effectives of bioimpedance testing using the BCM - Body Composition Monitor device. For comparison, we include cost per test estimates using each of the other competitor devices, and assess the impact of applying these costs in sensitivity analysis (assuming equivalent effects).

Framework (method of synthesis)

A semi-Markov model was developed to assess the clinical and cost-effectiveness of using multiple frequency bioimpedance testing compared with standard clinical practice for guiding fluid management decisions in the dialysis cohort. Key states included in the model are "Stable on HD", "Stable on PD", "Post-incident cardiovascular (CV) event - H", "Post-incident CV event - PD", "Post-transplant" "Post-transplant, post CV event", "Dialysis post-transplant", "Dialysis post-transplant, post CV event" and "Death". The model also includes an option to dichotomise the "stable" and "post CV event" dialysis states by baseline relative overhydration (ROH) status: severely overhydrated (>15% ROH) and normohydrated (≤15% ROH) as measured by the BCM. This is to allow mortality and hospitalisation rates for the severely overhydrated portion of the prevalent cohort to be factored upwards, reflecting the observed adjusted association between hydration status and these outcomes.[22, 26, 57, 76]

Modelled transitions between the relative hydration states were then used to drive effects in an alternative scenario analysis (see "Further adjustments to baseline risks" below for further details). States representing underhydration were not included in this alternative model structure due to a dearth of evidence on: 1) the prevalence of underhydration, as measured by the BCM, in UK dialysis cohorts; 2) the impact of underhydration, as measured by the BCM, on the risk of adverse events and/or quality of life; and 3) the effectiveness of bioimpedance guided fluid management on reducing the prevalence of underhydration. If underhydration (as measured by bioimpedance spectroscopy) is associated with adverse outcomes and quality of life, and bioimpedance guided fluid management can reduce the prevalence of this, then this secondary model may fail to capture the associated benefits.

The model simulates mortality, hospitalisation events and transition to transplant over the life-time of the modelled cohorts on a constant three monthly cycle (in keeping with the BCM testing cycle). All cause hospitalisation events are disaggregated across cardiovascular and other causes. It is assumed in the model that hospitalisation for a new incident CV event results in an increased comorbidity burden which increases the risk of subsequent hospitalisations.

Costs of dialysis (by modality), background medication (blood pressure, erythropoietin stimulating agents (ESA), transplant, all-cause hospitalisation and outpatient attendances are included in the baseline model. Health state utility multipliers are applied to the dialysis states, and utility decrements are also incorporated for hospitalisations. These decrements are applied for an acute period for all hospitalisations. For hospitalisations due to cardiovascular events, a long-term utility multiplier is also applied. This reflects the lasting impact that these events can have on health related quality of life. A schematic of the model structure is provided in Figure 13. A simplifying assumption of the model precludes switching between dialysis modes. This is unlikely to have a significant impact on results since an equal baseline mortality rate is applied for patients on dialysis irrespective of modality, and the estimated costs of PD and HD were also found to be similar based on current reference costs (see 'Costs of RRT' below). Furthermore, the clinical effectiveness evidence was insufficient to estimate bioimpedance effects by dialysis modality.

The baseline model is replicated for the strategy of bioimpedance guided fluid management, and correspondingly incorporates the additional cost of quarterly testing on top of standard practice. The bioimpedance model also allows for the incorporation of effects of bioimpedance monitoring on mortality, hospitalisation rates, background management costs (e.g., blood pressure medications) and within state health state utility. The incorporation of these hypothesised benefits, in light of the available supporting evidence, is discussed in detail under the relevant headings below. The model can also capture downstream cost savings and quality of life benefits associated with reduced hospitalisation rates and prolonged survival.

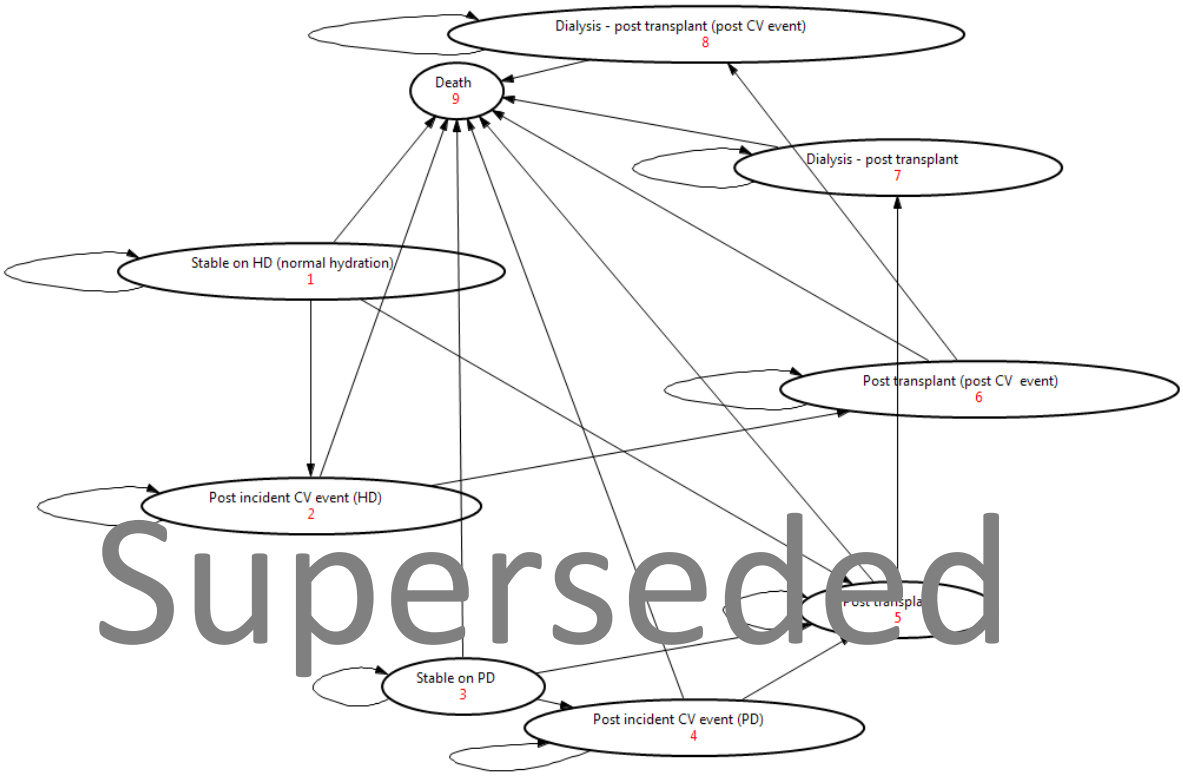

Figure 13 Schematic of the baseline model structure

Modelled baseline risks

The baseline risks of mortality were derived from a number of sources. The UK Renal Registry report was first consulted as a source of population based data. However, this report only provides detailed data on survival (by age) for incident renal replacement therapy (RRT) patients, without censoring for transplantation. This is not suited to the decision model structure (Figure 13), where mortality rates conditioned on remaining on dialysis and conditioned on transitioning to transplant are required. Therefore, the European Renal Association (European Dialysis and Transplant Association - EDTA) annual report was consulted.[94] This report includes adjusted 5-year survival curves with censoring for transplantation in the dialysis survival estimates. The data are reported from day 91, with adjustment based on cox regression for age, gender and primary diagnosis. The survival estimates on different modalities are expressed for a 60 year old cohort, 60% male, with the following distribution for cause of renal disease: diabetes (20%), hypertension (17%), glomerulonephritis (15%), and other cause (48%). This distribution of characteristics is reasonably similar to that of the UK dialysis population, although age is slightly higher in the incident UK cohort at 63 years, and diabetes and hypertension are reported as the primary renal diagnosis in

26% and 6.5 % of incident patients respectively.[91] Whilst it is preferable to reconstruct patient level data from published Kaplan Maier curves for the purpose of extrapolating survival in decision models,[95] the adjusted nature of the reported data precluded estimation of numbers of events and censoring events. Therefore, a simple regression based method was used to fit a Weibull distribution to the summary survival curve data.[96] Given limitations in the evidence base to support differences in survival by mode of dialysis, we based extrapolation on the survival curve for all dialysis modalities combined. The scale and shape parameters from the derived Weibull curves (Table 6) were incorporated in the model and used to extrapolate mortality risks out to ten years. The scale parameter (λ) was further adjusted to reflect the starting age of the modelled cohort (67 years), using a published hazard ratio for mortality (beyond 91 days) associated with a ten year increase in age:[91]

$$\lambda_{adjusted} = \lambda * HR_{ACM}^{(start\_age-60)}$$

Where HR_{ACM} is the hazard ratio for all-cause mortality associated with a 10 year increase in age, and "start_age" is the starting age of the modelled dialysis cohort.

For those transitioning to renal transplant, survival data were derived from a combination of sources (Table 6). In the first year following transplant, survival probabilities by age groups were taken from the ERA-EDTA Registry annual report. [94] The reported one year survival probabilities differ by donor type (deceased/living) and were weighted accordingly. Beyond one year, we used published 10-year Kaplan Maier survival data from a UK population based study of transplant recipients.[97] The individual patient data were reconstructed for 2,887 subjects aged 60-69 years following the approach described by Hoyle et al[95], using reported numbers at risk and steps in the published Kaplan Maier curve. Parametric survival models were then fitted using R, and the best fitting model selected based on the Bayesian information criterion. This was a Weibull model. The scale parameter of the derived Weibull curve is adjusted in the model for the recipient's age at time of transplant using the hazard ratios for age reported by Karim et al.[97] All the parameters used to model survival are presented in Table 6.

To minimise uncertainty associated with the use of parametric curves to extrapolate survival beyond ten years, we applied an alternative approach to model mortality in the longer-term. Mortality rates on RRT were estimated by applying reported relative risks of mortality in the RRT population compared to the UK general population[91] to age/sex adjusted general population mortality rates from UK life tables. For those remaining in a post-transplant state beyond ten years following transplant, an adjusted relative risk[98] was applied to the modelled annual mortality rate of age matched patients on dialysis. Tonelli et al. conducted a systematic review of observational studies reporting an adjusted hazard ratio for all-cause mortality with renal transplant versus dialysis.[98] Whilst a formal meta-analysis of this data was not conducted due to diversity across the included observational studies, the central estimate (0.42) of the reported range (0.16 to 0.76) across 23 included studies was applied in base case model. The reported range was treated as a confidence interval for purposes of assigning a lognormal distribution to this parameter.

Table 6 Clinical parameters used to model mortality, renal transplant and graft failure

	Value (95% CI)	Parameter distribution	Source
Clinical parameter			
Mortality on dialysis (to 10 years)			
Weibull scale parameter (60 year old cohort)	0.114		ERA-EDTA Registry annual report 2013[94]
Weibull shape parameter	1.035		ERA-EDTA Registry annual report [94]
Hazard ratio (10 year age increase on RRT)	1.65 (1.56-1.75)	Lognormal	UK Renal Registry Report[91]
Mortality year 1 post-transplant (deceased donor)			ERA-EDTA Registry annual report 2013[94]
Rate per patient year (0-19)	0.018 (0.006-0.029)	Lognormal	
Rate per patient year (20-44)	0.019 (0.016-0.022)	Lognormal	
Rate per patient year (45-64)	0.044 (0.040-0.048)	Lognormal	
Rate per patient year (65-74)	0.104 (0.090-0.120)	Lognormal	
Mortality year 1 post-transplant (living donor)			ERA-EDTA Registry annual report 2013[94]
Rate per patient year (0-19)	0.007 (0.004-0.010)	Lognormal	
Rate per patient year (20-44)	0.007 (0.004-0.010)	Lognormal	
Rate per patient year (45-64)	0.02 (0.014-0.026)	Lognormal	
Rate per patient year (65-74)	0.053 (0.028-0.079)	Lognormal	
Mortality post-transplant 1-10 years			Karim et al. 2014[97]

	Value (95% CI)	Parameter distribution	Source
Weibull scale parameter (65 year old cohort)	0.05	logscale multinormal	
Weibull shape parameter	1.027	logscale multinormal	
Hazard ratio (10 year increase in transplant recipient age)	1.766 (1.540-2.028)	Lognormal	Karim et al. 2014[97]
Hazard ratio for all-cause mortality with transplant versus dialysis (applied beyond ten years post-transplant)	0.42 (0.16-0.76)	Lognormal	Tonelli et al. 2011[98]
Proportion of prevalent dialysis population waitlisted for transplant			Annual report on Kidney Transplantation 2014;[99] UKRRR, 2015[91]
<65 years	0.346 (0.338-0.354)	Beta	
65-75 years	0.135 (0.128-0.142)	Beta	
>75 years	0		
Probability of transplant (3 monthly) among those waitlisted	0.057 (0.055-0.058)	Beta	Annual report on Kidney Transplantation 2014[99]
Probability of graft failure (3 monthly)			Annual report on Kidney Transplantation 2014[99]
Deceased donors	0.0075 (0.007-0.0081)	Beta	
Living donors	0.0047 (0.004-0.005)	Beta	
Proportion of transplants from deceased donors (age 60-70)	0.723 (0.706-0.40)	Beta	Karim et al. 2014[97]; Varies by age of recipient

Three monthly probabilities of renal transplantation for those on dialysis were derived from the percentage of dialysis patients waitlisted for transplant (<65 and ≥65 years),[91] combined with the median duration of time to transplant (1,082 days).[99] The graft failure rate for those receiving a transplant was derived from the five year graft survival rates reported for grafts from living and deceased donors.[99]

All cause inpatient hospitalisation was modelled using the first part of a published two-part cost model developed by Li et al.[92] Li et al. used a dataset for a cohort of patients on the UK renal registry who started dialysis or received a kidney transplant in England between the 1 April 2003 and 31 December 2006. The data on these patients was linked to health episode statistics (HES) data for inpatient hospital activity (excluding activity for maintenance dialysis or transplant surgery) up to 6 years following initiation of dialysis or transplant. Each hospital event was costed using the appropriate Health Care Resource Group (HRG) Payment by Results (PbR) tariff for the admission. The data were then analysed using a two part model; Logistic regression was used to predict the probability of a patient incurring any inpatient

hospital costs in a given year on RRT (up to year 6), and a general linear model was used to predict total inpatient costs in those who had at least one hospital episode in a given year. The models were adjusted for age, gender, years on dialysis, mode of dialysis, comorbidities, transplant, and year of death (to account for increased hospital resource use in the year of death and year preceding death). The published two-part models for dialysis and transplant patients are replicated in Tables 7 and 8 below.

These models were incorporated in our decision model to predict the annual probability of hospitalisation each year based on the characteristics of the modelled cohort, and then to apply the associated inpatient hospitalisation costs. To keep the approach manageable in the context of a Markov cohort model, the odds ratios and cost coefficients associated with comorbidities were collapsed into a single weighted average for any one comorbidity, based on the reported frequency of each individual comorbidity. We then estimated the risk of hospitalisation at the cohort level by computing the weighted average of the risk for males and females, with and without comorbidities. The expected number of comorbidities among those in the cohort with any comorbidity was derived from the UK Renal Registry report, and the weighted average odds of hospitalisation associated with any one comorbidity was raised to this power in the calculation of hospitalisation risk in this segment of the cohort.

To fit the 3 month Markov cycle, the annual probabilities of hospital admission were converted to 3 monthly probabilities assuming a constant inpatient hospitalisation rate over the year. Furthermore, the underlying rate was disaggregated into CV and other cause hospitalisation rates. To inform this process, we conducted a focused search of the literature for data on cause of hospitalisation in ESRD patients on dialysis. A number of studies were identified suggesting that CV hospitalisation rates account for ~20% of all hospitalisations in dialysis cohorts.[100-102] The preferred source of evidence reported that CV events made up 17.6% of the annual inpatient event rate in a cohort of 1,226 UK haemodialysis patients included in the Dialysis Outcomes and Practice Patterns Study (DOPPS).[102] This value was applied in the base case. We then further disaggregated expected CV hospitalisation events across types of CV events, in line with the reported relative frequency of CV event histories in the dialysis population (Table 7). Whilst this is an uncertain assumption, we could not identify any better UK population based data by which to model the relative frequency of

different types of CV event in the dialysis population. A further limitation of the models used to predict annual hospitalisation risk, is the fact that it requires extrapolation beyond the period of follow-up in the datasets used to develop it (i.e. beyond 6 years). We therefore had to assume that estimated probabilities of hospitalisation at 6 years on dialysis are generalisable across future years on dialysis.

Table 7 Odds of annual inpatient hospitalisation and associated costs for dialysis patients - Reproduced from Springer European Journal of Health Economics, "Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation", volume 17, 2016, pages 663 and 665, Li B, Cairns J, Fotheringham J, Ravanan R, Group AS (© Springer-Verlag Berlin Heidelberg 2015).[92] With permission of Springer.

	Dialysis inpatient		**Mean annual costs (£) for dialysis patients (GLM)**	
	Odds ratio	95% CI	Coefficient (£)	95% CI
Constant	2.34	(2.18, 2.51)	7782	(7423, 8140)
Age group				
<50 years	Reference		Reference	
50-64 years	0.98	(0.91, 1.05)	-170	(-489, 149)
65-75 years	0.91	(0.85, 0.97)	-181	(-513, 151)
>75 years	0.87	(0.81, 0.94)	-444	(-806, -83)
Sex				
Male	Reference		Reference	
Female	1.10	(1.05, 1.16)	208	(-23, 439)
Years on dialysis				
1	Reference		Reference	
2	0.59	(0.56, 0.62)	-1189	(-1487, -891)
3	0.5	(0.47, 0.52)	-1434	(-1729, -1140)
4	0.58	(0.54, 0.62)	-1848	(-2166, -1530)
5	0.61	(0.56, 0.67)	-1709	(-2099, -1319)
6	0.65	(0.57, 0.74)	-2270	(-2774, -1767)
Dialysis modality				
Haemodialysis	Reference		Reference	
Peritoneal dialysis	0.83	(0.79, 0.88)	-612	(-838, -385)
Comorbidities				
Myocardial infarction (17%)	1.22	(1.14, 1.31)	390	(96, 683)
Congestive heart failure (17%)	1.11	(1.04, 1.19)	321	(58, 584)
Peripheral vascular disease (16%)	1.33	(1.24, 1.42)	721	(423, 1019)
Cerebrovascular disease (11%)	1.15	(1.07, 1.24)	506	(174, 383)
Pulmonary (15%)	1.26	(1.17, 1.35)	412	(128, 696)
Liver (1%)	-	-	1682	(-161, 3524)
Diabetes (34%)	1.27	(1.21, 1.34)	1191	(929, 1453)
Cancer (8%)	1.22	(1.11, 1.33)	-	-
Hypertension (62%)	1.09	(1.04, 1.14)	-	-
Transplant	1.11	(1.02, 1.21)	-1863	(-1863, -1585)
Recovered renal function	0.82	(0.69, 0.96)	1293	(513, 2073)
Death	1.94	(1.81, 2.07)	2403	(2152, 2654)
Death first half following year	2.61	(2.34, 2.92)	4415	(3926, 4904)

Table 8 Odds of annual inpatient hospitalisation and associated costs following renal transplant - Reproduced from Springer European Journal of Health Economics, "Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation", volume 17, 2016, pages 664 and 666, Li B, Cairns J, Fotheringham J, Ravanan R, Group AS (© Springer-Verlag Berlin Heidelberg 2015).[92] With permission of Springer.

	Transplant inpatient		**Mean annual costs (£) for transplant patients (GLM)**	
	Odds ratio	95% CI	Coefficient (£)	95% CI
Constant	1.89	(1.65, 2.16)	4735	(4331, 5138)
Age group				
<35 years	Reference		Reference	
36-45 years	0.81	(0.72, 0.92)	-318	(-664, 29)
46-55 years	0.73	(0.64, 0.82)	-310	(-676, 56)
>55 years	0.76	(0.67, 0.87)	-91	(-487, 306)
Sex				
Male	Reference		Reference	
Female	1.35	(1.22, 1.49)	190	(-76, 455)
Years following transplant				
1	Reference		Reference	
2	0.21	(0.19, 0.23)	-1576	(-1881, -1271)
3	0.18	(0.16, 0.2)	-1919	(-2228, -1611)
4	0.19	(0.17, 0.22)	-2138	(-2485, -1790)
5	0.19	(0.16, 0.23)	-2061	(-2502, -1620)
6	0.18	(0.14, 0.22)	-2654	(-3212, -2096)
Transplant type				
Deceased donor	Reference		Reference	
Living donor	0.82	(0.75, 0.9)	-223	(-486, 39)
Comorbidities				
Myocardial infarction (8%)	1.47	(1.24, 1.73)	641	(145, 1138)
Congestive heart failure (6%)	1.48	(1.22, 1.73)	1248	(646, 1851)
Peripheral vascular disease (11%)	1.87	(1.62, 2.16)	1222	(729, 1715)
Cerebrovascular disease (6%)	1.38	(1.16, 1.65)	898	(271, 1524)
Pulmonary (13%)	1.24	(1.09, 1.4)	264	(-87, 616)
Liver (1%)	2.18	(1.37, 3.47)	2093	(30, 4155)
Diabetes (26%)	1.62	(1.46, 1.8)	1046	(734, 1395)
Cancer (4%)	1.62	(1.31, 2.01)	485	(2, 969)
Hypertension (74%)	1.33	(1.21, 1.46)	324	(56, 592)
Graft failure	-	-	2438	(1723, 3152)
Death	1.62	(1.14, 2.31)	4924	(3726, 6123)
Death first half following year	4.55	(2.47, 8.39)	5725	(3350, 8100)

Further adjustments to baseline risks

To allow for modelled scenarios where effects are mediated through associations between hydration status and outcomes, the model was structured to enable mortality and hospitalisation rates to be adjusted upwards for proportions of the dialysis cohorts estimated to be severely overhydrated (ROH > 15%). Modelled reductions in severe overhydration were then used to drive effects in scenarios using this version of the model.

The expected prevalence of severe overhydration (ROH > 15%) was based on studies taking BCM measures at clinic visits (not necessarily first thing in the morning) for the PD cohort, and pre-dialysis for the HD cohort. The ROH > 15% threshold was selected because as noted in the clinical effectiveness section, it has been associated with increased rates of mortality and hospitalisation in observational studies.[26, 46, 76, 82] Time averaged volume overload (TAVO) may give a more accurate estimate of the average exposure to fluid overload, but this measure has not been linked with mortality in observational studies. Limited data were identified regarding the prevalence of ROH >15% in UK dialysis cohorts. One observational study of 529 PD patients from a single UK centre[76] reported that ~31% of patients had ROH > 10%. A multicentre European study, which included 734 patients from centres in Belgium, France, Romania, the UK (167 patients from 2 centres), and Switzerland, reported that 25.2% of the cohort were severely overhydrated (ROH > 15%).[103] There were less published data available on the prevalence of severe OH in the UK HD population. However, a further multicentre European study matched PD patients from France, Romania, and the UK with HD patients from the corresponding countries.[104] This study showed that pre-dialysis ROH in HD patients was similar to the ROH in PD patients – although the TAVO in HD patients was lower in comparison to the ROH value of PD patients. Based on this available data, the baseline prevalence of ROH > 15% was set at 25% for both the HD and the PD cohorts.

The mortality rate for the severely overhydrated portion of the HD cohort was increased using an adjusted hazard ratio (95% CI) of 1.87 (1.12-3.13) reported by Onofriescu et al.[82] The all cause hospitalisation rate was also inflated upwards using an adjusted hazard ratio of 1.19 (0.99-1.41) reported by Onofriescu et al, 2015.[82] For the corresponding segment of the PD cohort, all-cause mortality was adjusted

upwards using the hazard ratio (95% CI) of 1.83 (1.19-2.82) reported by O'Lone et al.[76] No data were identified reporting the increased risk of all cause hospitalisation in severely overhydrated PD patients, and so the same value as used for HD patients was applied. It is plausible that any mortality/morbidity benefits associated with bioimpedance testing are also partly attributable to the avoidance on underhydration. However, no studies were identified linking underhydration, as measured using bioimpedance spectroscopy, to mortality and adverse events. Therefore, an underhyration state was not included in the model. As mentioned above, this could potentially underestimate the benefits if bioimpedance guided fluid management can simultaneously reduce the proportion of patients that are seriously over and underhydrated. Conversely, if the use of bioimpedance testing to guide fluid management decreases the proportion of patients that are overhydrated at the expense of increasing the proportion that are undehydrated, this model could potentially overestimate the benefits.

Incorporation of relative treatment effects

Alternative approaches to modelling effects of bioimpedance guided fluid management on the baseline event rates were considered. Given the limitations in the existing evidence base for the clinical effectiveness of bioimpedance testing, combined with further limitations in the evidence base to inform certain baseline events, the modelled cost-effectiveness scenarios are subject to significant degree of uncertainty.

With the availability of some trial evidence for the technology, the application of direct evidence for effects on final health outcomes was considered the preferred approach for modelling benefits. However, given the limitations in the trial evidence base, this was only possible for all-cause mortality. Of the three available BCM trials that included all cause hospitalisation rates,[58, 70, 71] these showed inconsistent and insignificant effects on this outcome. Therefore we did not incorporate an effect on the overall hospitalisation rate in scenarios applying direct estimates of effects. Alternative approaches were explored in further scenario analyses to model plausible effects on CV and non-CV hospitalisation rates.

Since a number of the trials reported effects on surrogate endpoints, including left ventricular mass index (LVMI) and pulse wave velocity (PWV), we conducted a focussed literature search to identify appropriate published sources of evidence to link changes in these surrogates to final health outcomes in the relevant patient population. A hierarchical approach was adopted to identify suitable sources if evidence, with priority given in descending order to the following types of evidence:

1. Evidence linking intervention induced changes in available surrogate outcomes to changes in the risk of final health outcomes
2. Evidence linking non-intervention induced longitudinal changes in surrogate outcomes to changes in the risk of final health outcomes
3. Evidence from large UK or European cohort studies assessing the prognostic value of baseline measures of the surrogate measures for final health outcomes.

One recently conducted systematic review considered the value of LVMI as treatment target in the area of ESRD, and concluded that there was no clear and consistent association between intervention induced LVM change and all-cause or CV related mortality.[105] Furthermore, since only one of the BCM - Body Composition Monitor trials included this as an outcome, LVMI was considered no further. The search of available evidence did not identify any existing data showing a clear link between intervention induced changes in PWV and final health outcomes in ESRD, but a large European observational study was identified.[106] This study assessed the prognostic value of baseline PWV on all-cause mortality and non-fatal CV events in a cohort of 1,084 patients recruited from 47 European dialysis centres over a period of 2 years. It highlighted the importance of simultaneously considering abdominal aortic calcification (AAC) when assessing the prognostic value of PWV. Based on a multivariate cox regression, both variables were found to be significant predictors of mortality and non-fatal CV events, but the effect of PWV was ameliorated at higher levels of aortic calcification (incorporated as tertiles) as a result of a significant negative interaction. The relevant hazard ratios from the published cox regression are shown in Table 9. Based on these estimates, and assuming the UK dialysis cohort is similarly distributed across the aortic calcification tertiles, we estimated an average effect on all-cause mortality and non-fatal CV events of a unit change in PWV, accounting for the interaction. This yielded a hazard ratio of 0.942 (0.879-1.009) per

unit reduction in PWV. We then explored the impact of scaling this effect to the magnitude of the pooled mean reduction in PWV (1.53 m/s) across the included BCM trials (Figure 7), and applying it to the modelled proportion of all cause hospitalisation events estimated to be attributable to CV events (assumes 1.53 m/s reduction in PWV is generalizable to the UK dialysis cohort). We also explored the impact of applying it to the all-cause mortality rate in the model. This analysis should be treated with caution, as it relies on cross sectional associative evidence from an observational study to inform possible effects of bioimpedance monitoring. Furthermore, the negative interaction between increasing abdominal aortic calcification (AAC) tertiles and the effect of baseline PWV on mortality and CV hospitalisation, suggests that the relative effect of reductions in PWV may be greater in lower risk groups (with lower AAC scores). On the other hand, evidence for an interaction in the prognostic value of baseline measures of these two variables, does not necessarily mean that the AAC score would modify the effect of an intervention induced reduction in PWV. Therefore, this model could potentially over or underestimate the likely effects of the estimated reduction in pulse wave velocity on final health outcomes. Better evidence on the effects of intervention induced reductions in PWV are required to inform this issue.

Table 9 Effect of a unit change in PWV on mortality and non-fatal CV events

Variable	Hazard ratio	95% CI	Source
PWV (m/s)	1.154	1.085-1.228	Verbeke et al., 2011[106]
PWV x AAC lower tertile	1		Verbeke et al., 2011[106]
PWV x AAC middle tertile	0.895	0.828-0.968	Verbeke et al., 2011[106]
PWV x AAC upper tertile	0.865	0.808-0.925	Verbeke et al., 2011[106]
Inferred average effect per unit reduction in PWV across AAC tertiles =1/(((1.154x1)+(1.154x0.895)+(1.154x0.865))/3)	0.942	0.879-1.009	Assessment Group calculation
Inferred average effect for a 1.533 reduction in PWV 0.942^1.533	0.9123	0.821-1.014	Assessment Group calculation

AAC, abdominal aortic calcification.

As an alternative approach to indirectly estimate possible effects of bioimpedance guided fluid management on mortality and CV hospitalisation, we considered linking the estimated pooled reduction in systolic blood pressure (3.48 mmHg, Figure 11) to effects on CV events and mortality using a meta-analysis on the effects of blood pressure lowering medications in dialysis patients. Heerspink and colleagues[107] estimated pooled relative risks of 0.71 (0.55-0.92) for CV events and 0.8 (0.66-0.96) for all all-cause mortality across 8 trials; corresponding to a mean reduction in systolic blood pressure (SBP) of 4.5 mmHg. Assuming a log-linear relationship between SBP reduction and the relative risk of events, these effects can be rescaled to the mean reduction in SBP across included BCM trials (3.44 mmHg):

RR for CV events for a 3.44 mmHg reduction in SBP
= exp(ln(0.71)(3.44/3.5))*
= 0.770

RR for ACM for a 3.44 mmHg reduction in SBP
= exp(ln(0.80)(3.44/3.5))*
=0.843

These effects are substantially larger than the estimated effects using PWV above, and suggest a potentially larger effect on CV events than on all-cause mortality. However, it is uncertain whether the effects of reductions in SBP induced by blood pressure medication can be generalized to reductions in SBP induced by the management of fluid status; i.e. some blood pressure medications are thought to have effects on CV events that are independent of their blood pressure lowering effects.[108] Furthermore, there is a complex relationship between fluid management and blood pressure,[109] which makes it difficult to generalise. Nevertheless, the effect of bioimpedance guided fluid management on SBP in combination with the effect on PWV, is suggestive of a plausible beneficial effect on both CV events and mortality. We, therefore, explored the impact of applying larger and differential relative effects on these outcomes in further scenario analyses.

Finally, we also explored the impact of using associations between overhydration and all-cause mortality and hospitalisation rates to drive effects in the model. For this

analysis, we used data from Huan-Sheng et al.,[74] to estimate the proportion of patients who could be shifted from the overhydrated to the normally hydrated states in the bioimpedance and standard care arms of the model. This analysis assumes that for everyone who is moved from the overhydrated (RFO >15%) to the normally hydrated state, the increased risks associated with overhydration are completely reversed. This is an optimistic assumption, as again cross-sectional associations between baseline measures and final outcomes are being used to drive the effects of bioimpedance guided fluid management in the model. The increased risk associated with baseline overhydration may not be fully reversible for those that can be returned to normal hydration status (≤15%).

A further problem with this approach is the lack of reporting in the randomised controlled trials on the effect of bioimpedance guided fluid management on the proportion of patients with pre-dialysis ROH > 15% at baseline and follow-up. Onofriescu and colleagues[82] did report proportions of patients within, and >1.1 kg above and below the BCM guided target weight, and this study suggested no real change in the average percentage of patients > 1.1 kg above target weight across follow-up. Yet, the study did demonstrate a significant effect on PWV and mortality, leading the authors to speculate that the mechanism for effect may be as much due to the avoidance of chronic underhydration as overhydration. Huan-Sheng et al. reported a significantly larger reduction in mean OH (litres) in patients with ROH >15% at baseline.[70] We used this data to approximate percentage reductions in ROH >15% (absolute OH > 2.5 litres) over follow-up by: 1) assuming normal distributions for absolute OH at follow-up up; and 2) subtracting mean reported reductions in OH (litres) from simulated gamma distributions of baseline OH above 2.5 litres. This yielded plausible percentage reductions in ROH>15% of 28% to 38% with bioimpedance guided management relative to control. These were applied in model scenarios utilising the change in ROH status to drive effects on all-cause mortality and all-cause hospitalization.

Further hypothesised benefits of bioimpedance guided fluid management that were not incorporated in the main analyses included changes in quality of life (independent of effects on hospitalisation and CV events), maintenance of residual renal function, and effects on dialysis requirements (number and duration of sessions).

None of the identified BCM – Body Composition Monitor trials reported on health related quality of life, and only one included any patient reported outcomes.[74] One observational study was identified that reported an association between hydration status and quality of life in Korean PD patients as measured by the Kidney Disease Quality of Life-Short Form (KDQOL-SF). This showed that reductions in absolute OH (per litre) between baseline and 12 months were associated with improvements in the physical component score (1.81; 0.78-2.84), mental component score (0.92; 0.2-1.65), and the kidney disease component score (0.9; 0.36-144) as measured by the instrument. These analyses were adjusted for various potential confounders including age, sex, dialysis vintage, haemoglobin, baseline OH, and comorbidities (as measured by the Charleston Index). Whilst this study suggests that use of the BCM - Body Composition Monitor could lead to improvements in heath related quality of life (independent of effects on adverse events), it is not clear how generalizable the reported changes are to the UK population. In addition, it is not possible to map from changes in the reported aggregate component scores of the KDQOL-SF to changes in health state utility values. Furthermore, our model already captures QALY gains associated with prevention of hospitalisation events and increasing comorbidity, and so including a constant utility increment associated with the use of bioimpedance testing could lead to double counting of QALY gains. Nevertheless, the impact of including a 2% and 5% improvement in health state utility as a result of improved inter-dialytic symptoms was assessed in a further scenario analysis.

The omission of residual renal function as an explicitly modelled state, and its knock-on effects on dialysis requirements and outcomes as potential benefits, is justified by a current lack of supporting evidence. The only BCM trial that assessed proxies for residual renal function in HD patients reported a significant increase in the proportion of anuric patients and a significant decrease in urine output in nonanuric patients at 12 months in the bioimpedance group.[71] In the only other bioimpedance trial to report renal output, PD patients randomised to bioimpedance guided fluid management showed a slightly greater reduction in mean urine volume at 12 weeks, although not statistically significant.[82] There is a recognised risk that aggressively pursuing lower target weights using a high ultrafiltration rate may in fact lead to increased morbidity/mortality as a result of hypoperfusion-induced ischaemic injury and

accelerated loss of residual renal function.[110, 111] Conversely, identifying patients that are severely underhydrated and adjusting their target weight upwards may help to preserve residual renal function. This question is currently being evaluated in two ongoing randomised controlled trials, one in PD patients[112] and one in HD patients based in the UK (Table 5).[86] If bioimpedance testing can preserve residual renal function in non-anuric patients, then our model may underestimate the average benefits in the population as a whole. Conversely, if its use leads to decisions that accelerate the loss of residual renal function, this is a dis-benefit which could have knock on effects on dialysis costs and adverse outcomes.

Related to the above issue, there is also a lack of evidence on the effects of bioimpedance monitoring on the number and the duration of dialysis sessions required to achieve the prescribed target weight. A potential cost-saving could be achieved through a requirement for fewer dialysis sessions in some incident patients, if it is found to be effective in preserving residual renal function. As discussed above, this question remains currently unanswered. Conversely, the use on bioimpedance spectroscopy could result indirectly in increased dialysis costs through identification of patients that are severely overhydrated and require longer or additional dialysis sessions to achieve their new target weight without exceeding safe ultrafiltration rates and volumes.[110] Our cost-effectiveness model assumes that any effects of bioimpedance guided fluid management on dialysis requirements are cost neutral.

Resource use estimation

The base case cost-effectiveness model incorporates health service costs associated with maintenance dialysis, blood pressure medication and erythropoietin stimulating agents (on dialysis), all cause inpatient hospitalisation, renal transplantation (including work-up, surgery and follow-up), post transplantation immunosuppression and outpatient visits.

Costs of RRT

It has previously been noted that dialysis treatment in CKD results in high costs to the health service, and that this can undermine the cost-effectiveness of technologies that prolong survival on dialysis. In some circumstances, a technology that prolongs survival on dialysis may not be cost-effective at zero price. This has led to

inconsistency across economic evaluations in the area of ESRD with respect to whether dialysis costs are included. Some have argued that they should not be included for interventions that aim to extend survival without impacting the need for dialysis.[113] A further argument for their exclusion is that a decision has already been made to fund dialysis on broader ethical/equity considerations that are not reflected in cost-effectiveness of dialysis itself. It may then seem unfair to include dialysis costs were they act as an insurmountable barrier to demonstrating the cost-effectiveness of other technologies that prolong survival on dialysis. The alternative argument is that dialysis costs do represent a real opportunity cost associated with ongoing treatment for ESRD, and so should be included in the analysis. The NICE DSU have produced a report on assessing technology's that are not cost-effective at zero price, and suggest that all NHS and PSS costs that differ between the technology being appraised and the comparator technologies should be included within the ICER, as this provides the ICER that reflects the real opportunity cost of recommending the technology being appraised.[114] However, the report does also note that a case could have been made in a previous technology appraisal of cinacalcet[115] for treating secondary hyperparathyroidism (SHPT) in ESRD, to exclude dialysis costs on grounds that they are unrelated to the treatment of SHPT (the condition of interest in the appraisal). A similar argument was adopted in the modelling assessing the cost-effectiveness of alternative phosphate binders for people with stage 4 and 5 CKD with hyperphosphatemia.[90] In this example, the costs associated with dialysis were argued to be unaffected and unrelated to the choice of phosphate binder, with the target condition being hyperphosphatemia.

Considering the above, it is difficult to argue that dialysis costs are unrelated to a technology being used to guide fluid management decision in dialysis patients, and in theory the use of the technology could impact on dialysis costs in survivors, as well as prolong survival on dialysis. Therefore, dialysis costs are included in our base case cost-effectiveness scenarios. However, it is a plausible argument that the cost-effectives of dialysis reflected in our model, does not capture its broader value to society relating to ethical and equity issues. Therefore, we also explore the impact of excluding dialysis costs.

Dialysis costs were taken from the current NHS reference costs.[116] For HD costs, we took the weighted average of the reference costs (per HD session) for the HRG codes LD01A to LD10A (at base and away from base), weighted by the relative proportion of overall activity reported against each code. This was multiplied by 3 sessions per week, and then by 52 to estimate the average annual cost of maintenance HD. For PD, we applied the weighted average of the reference costs (per day) for HRG codes LD11A to LD13A. These costs were multiplied by 365 to estimate total annual maintenance PD costs.

Transplantation costs were also taken from the reference costs, applying the average costs for HRG codes LA01A, LA02A and LA03A (elective inpatient). We also included costs for follow-up post transplantation. For year one this was derived from Treharne and colleagues.[89] To this we added the costs of immunosuppressant in year one, based on an initiation regimen in the first two weeks and a maintenance regimen thereafter. For the initiation period we costed Basilixinate (day 0 and day 4), Prednisolone (60 mg per day), Mycophenolate Mofetil (1g twice per day), and Tacrolimus (5 mg twice daily). For the maintenance period we costed Prednisolone (7.5 mg per day), Mycophenolate Mofetil (1g twice per day), and Tacrolimus (5 mg twice daily). Beyond year one post-transplant, we applied maintenance immunosuppression costs and added average outpatient costs observed in the transplant cohort (see "Outpatient costs" below). The maintenance dialysis and transplantation costs are provided in Table 10.

Table 10 Maintenance dialysis and transplantation costs

	Cost	Lower quartile	Upper quartile	Parameter distribution	Source
HD per session	154	130	169	Gamma	NHS reference costs, 2015[116]
PD per day	69	50	69	Gamma	NHS reference costs, 2015[116]
Transplant	14915	11720	17797	Gamma	NHS reference costs, 2015[116]
Follow-up post-transplant (year 1)*	£11,204				Treharne 2014[89]
Immunosuppressant costs (year 1)	£10,622				NICE GID-TAG348[117]; expert opinion, BNF[118]
Annual immunosuppressant costs (beyond year 1)	£9,054				

*Excluding immunosuppressant drugs

Costs of unplanned inpatient hospitalisations

Annual inpatient hospital costs for patients on maintenance dialysis and post-transplant were estimated using the two-part model developed by Li et al. 2016,[92] as described above (see "Modelled baseline risks" and Tables 7 and 8 above). The second part of this model predicts annual inpatient costs conditional on experiencing any hospitalisation event(s) within a given year. Estimates are based on age, sex, years on dialysis (or years following transplant), dialysis modality, and the comorbidity status of the modelled cohort. The model also accounts for increased costs in the year of death and the year preceding deaths that occur in the first half of the following year. This reflects the increasing level of morbidity experienced by patients towards the end of life.

To generate estimates of the cost incurred per hospitalisation event rather than costs per year, the predicted annual cost is divided by the expected number of events per patient year in our model. The expected event rate is derived from the estimated annual probability of experiencing any hospital inpatient event, assuming a constant event rate across the year. This results in a cost per hospitalisation event that varies by the underlying characteristics of the modelled cohort, but comes to ~£4,500 per event for patients on HD and £4,300 per event for patients on PD. These estimates are substantially higher than costs per hospitalisation event that have been applied in previous models in the area of ESRD.[17, 89, 90] However, these previous models generally applied averages of aggregate reference costs. The estimates derived from the data reported by Li et al, are based on a large dataset of actual hospital episodes costed according to admission code and adjusting for length of stay. Thus, the estimates derived from Li are applied in the base case analysis. Alternative estimates are applied in sensitivity analysis. Further, since the above approach makes a simplifying structural assumption of one hospitalisation event per quarter, it will actually slightly underestimate annual inpatient hospital costs as predicted by the published two part model of Li et al.[92] Therefore, we also applied a structural sensitivity analysis where the annual probability of hospitalisation and the conditional annual costs were only applied in the first cycle of whole years. This had very little impact on the ICER.

A further limitation of the inpatient cost models reported Li et al.,[92] are that they predict average costs across all causes of admission. Thus, our base case model assumes that both CV and other cause hospitalisation events incur the same cost on average. A further uncertainty relates to the fact that some inpatient costs will be unrelated to ESRD. However, as Li et al noted in their paper, it is difficult to judge whether individual admissions are related or unrelated, since ESRD is associated with increased risks of hospitalisation across many major causes. The inclusion of all-cause hospitalisation as an outcome in a number of the bioimpedance trials further justifies inclusion of all cause hospitalisation events in the baseline model.

Outpatient costs

Total outpatient costs for dialysis and transplant patients were also included in the base case model. These were taken simply as the observed annual outpatient costs on dialysis and transplant as reported by Li et al., 2016;[92] £1202 per year for dialysis patients, and £2,388 per year for transplant patients. These were divided by 4 and applied per quarterly cycle in the model.

Costs of background medications for dialysis patients

Unit costs and the proportion of patients on blood pressure medicine have been applied to provide the total cost of blood pressure medicine (Table 11). The percentage of patients on different types of blood pressure medicine was taken from the baseline data of a randomised controlled trial,[119] which recruited dialysis patients form 3 UK dialysis centres - Stoke-on-Trent, Leeds and Sheffield. For the different classes of drugs, prices for specific drug names commonly prescribed under each class (informed by the AGs clinical advisor) were taken from the British National Formulary (BNF).[118] Drugs were costed at the recommended dose as described in the BNF.

We further considered the potential impact of incorporating an effect of bioimpedance testing on the use/cost of blood pressure medication. Only two of the existing BCM – Body Composition Monitor trials reported on this outcome. [57, 60] Luo et al reported no significant changes in the dose of blood pressure medication in either the control or BCM – Body Composition Monitor groups of their trial. Onofriescu et al. reported that there was no statistically significant change from baseline to end of study in the

percentage of patients taking BP medication in the control group of their trial, but they did report a significant within group reduction in the BCM - Body Composition Monitor arm (from 66% to 55%). No formal comparison was reported for this outcome. However, as an exploratory analysis, we assess the impact of assuming a 10% reduction in blood pressure medication use in the bioimpedance arm of our model. To estimate the associated cost reduction, we assumed 68.4% of the cohort would be on at least one blood pressure medication,[120] at an average cost of £129.81 (£88.76/0.684) per year. The average cost reduction associated with an absolute 10% reduction in proportion of patients on any BP medication was then estimated: (0.684x£129.81)-(0.584*£129.81) = £12.98.

Table 11 Estimated average costs of blood pressure medications

	Unit cost (per year)	Proportion of patients on class	Total Average Cost	Source[118, 119]
ACE inhibitor	£33.33	0.211	£7.03	Tan et al. 2016, BNF
ARBs	£98.19	0.156	£15.29	Tan et al. 2016, BNF
Calcium-channel blockers	£258.95	0.219	£56.75	Tan et al. 2016, BNF
Diuretics	£10.82	0.487	£5.26	Tan et al. 2016, BNF
Beta-blockers	£17.14	0.248	£4.25	Tan et al. 2016, BNF
Alpha-blockers	£13.69	0.172	£0.17	Tan et al. 2016, BNF
Total average cost per year			£88.76	

The unit costs, units per week and proportion of patients on erythropoiesis stimulating agents (ESA) were applied to provide an estimate of the total annual cost for ESAs for dialysis patients (Table 12). The proportion of patients receiving an ESA was taken from the UK Renal Registry report;[91] i.e. 87%, of those on haemodialysis dialysis and 68% of those on peritoneal dialysis. The median dose for the corresponding population on HD and PD was 7400 international units (IU) per week and 4500 IU per week respectively. Based on opinion obtained from the AGs clinical advisor, the unit cost per IU was derived as the average of the unit costs for NeoRecormon and Aranesp as reported in the BNF (£0.00718 per IU). Thus, the total annual cost of ESA was estimated to be £2,403.69 (=0.87*7400*52*0.00718) for people on HD and £1,142 (=0.68*4500*52*0.00718) for people on PD (Table 12).

Table 12 Cost of erythropoietin stimulating agent for patients on dialysis

	HD	PD	
Proportion on ESA	87%	68%	UK renal registry report, 2015[91]
Dose (IU) per week	7400	4500	UK renal registry report, 2015[91]
Unit cost per IU	0.00718	0.00718	BNF (average price per IU for NeoRecormon and Aranesp)[118]
Cost per year	£2,403.69	£1,142	

Costs of bioimpedance testing/monitoring

The costs of the devices, provided by the companies (Table 13), were annuitized over five years using an annual depreciation rate of 3.5%. The cost of the BCM - Body Composition Monitor was applied in the base case analysis because of a lack of clinical effectiveness evidence for the alternative devices. For comparison, we also estimated the costs per patient year and cost per test for the alternative devices, with identical assumptions about numbers of tests and staff time requirements per patient. Estimated costs of BCM – Body Composition Monitor equipment maintenance was provided at two levels: £250 for an annual maintenance contract; and £600 for annual maintenance including parts and labour. We included the higher level maintenance contract in the base case scenarios but also assessed the impact of removing the maintenance costs in sensitivity analysis.

Table 13 Costs of the bioimpedance devices

	Cost	Expected service life	EAC*	Quarterly cost	Maintenance cost	Maintenance cost (including parts and labour)
BCM – Body Composition Monitor	£5,750	5	£1,273.52	£318.38	£250	£600
MultiScan 5000	£7,600	5	£1,683.26	£420.81	£70[+]	
BioScan 920-II	£4,950	5	£1,096.33	£274.08	£333[++]	
InBody S10	£8,100	5	£1,794.00	£448.50		

*Equivalent annual cost; [+]Assumes a replacement set of leads annually; [++]Assumes replacement or repair of cables every two years and an annual calibration check.

The unit costs of staff involved in bioimpedance testing were taken from the Unit costs of Health and Social Care (Table 14).[121] These were applied to estimates of staff time required to conduct and interpret tests. They were also used to place a cost on staff time invested in training in the use of bioimpedance testing. The Company responsible for the BCM - Body Composition Monitor device indicated that it takes 5-10 minutes on average to conduct a test (Information from Company). In the base case analysis, the time to perform the measurement was assumed to be 7 minutes. The Company responsible for the BCM - Body Composition Monitor device indicated that they provide free training on its use, taking half-a-day to attend. In the base case analysis, the training was assumed to take 3.5 hours.

Table 14 Staff unit costs

Staff Unit costs	Cost per patient contact hour	Cost per contracted hour	Cost per patient contact (7min)	Source
Grade 6 hospital nurse	£109.00	£45.00	£12.72	PSSRU, 2015[121]
Consultant medical	£139.65	£105.00	£16.29	PSSRU, 2015; PSSRU, 2010[121]
Clinical support worker*	£52.47	£21.19	£6.12	PSSRU, 2014[121]
Registrar group (40 hour week)**	£65.17	£49.00	£7.60	PSSRU, 2015[121]
Hospital dietician	£45	£34.00	£5.28	PSSRU, 2010; PSSRU, 2015[121]

*The technicians are costed at the same band as clinical support workers. **The cost per hour of patient contact is not available for the registrar group, therefore, the same ratio for a hospital consultant was assumed.

To gain a better understanding of the number of bioimpedance devices required to cover quarterly testing of the dialysis population, a brief questionnaire (Appendix 11)

was sent to the specialist members of the appraisal committee. Six different members responded, although three were from a single large centre covering adults and children. Therefore, we had information on testing practices from three centres covering adults, and two centres covering children (one exclusively).

The questionnaire included questions about centre size (number of HD and PD patients), number of satellite units, current practice with respect to fluid management decisions, and current practice regarding the use of bioimpedance testing. Questions were also included about the estimated level of resource that would be required to conduct quarterly testing of all HD and PD patients that the individual's centre was responsible for. Respondents from two of the centres described a situation where the majority of their patients were already being monitored using bioimpedance testing at least every three months. For the third centre, it was noted that bioimpedance testing was not currently performed systematically, but was rather used for selected patients. Consequently, only the anticipated resource use required for quarterly bioimpedence testing was used for this centre.

Details of relevant resources and costs required for quarterly testing, based on the responses from the three adult centres, are summarised in Table 15. Total equipment costs were estimated by multiplying the equivalent annual cost per device by the estimated number of devices required for quarterly monitoring of all the centres dialysis patients. This was then divided by the total number of patients to estimate the cost of equipment per patient per year, and then further divided by 4 to estimate the equipment costs per test performed. For example, Centre A reported 15 bioimpedance devices to cover a total of 585 patients ((£1273.52 x 15)/585 = £32.65). The maintenance costs also depend on the reported number of devices required by the centre to cover quarterly testing of their dialysis population. The total estimated annual maintenance cost, with and without parts and labour, was allocated across patients using the same approach as for equivalent annual costs of equipment. The larger centre latterly reported that they did not take out a maintenance contract on their machines, and so we also explored the impact of removing these completely.

Staff costs associated with the time required to conduct each test, were estimated based on 7 minutes of direct patient contact with a band 6 nurse (7 x (£109/60) =

£12.72). This was further multiplied by four to estimate the staff costs per patient per year (£12.72*4 = £51). The added consultant time required to interpret the findings of each bioimpedance test was assumed to be 5 minutes in the base case (5 x (105/60) = £8.75). Total training costs for each centre were estimated based on the number of different grades of staff trained, multiplied by their costs per contract hour and the number of hours of training attended. This total initial investment was spread over five years, and the equivalent annual cost was divided through by the number of patients in the centre to give a cost per patient per year. For example, for centre A the total training costs were estimated to be £11,171. Annuitized over 5 years this comes to £2,474, and 4.23 per patient per year (=2,474/585).

Table 15 Resource use and costs of bioimpedance testing

	Centre		
Resource use	**A**	**B**	**C**
Patients/equipment			
Number of HD patients	529	788	456
Number of PD patients	56	154	82
Total Dialysis Patients	585	942	538
Assumed number of tests per year	4	4	4
Estimated number of devices required	15	5	6
Estimated equipment cost per patient year	£32.65	£6.76	£14.20
Estimated equipment cost per patient test (assuming 4 tests per year)	£8.16	£1.69	£3.55
Estimated maintenance cost per patient	£6.41	£1.33	£2.79
Estimated maintenance cost per patient (including parts and labour)	£15.38	£3.18	£6.69
Total staff cost*	£12.72	£12.72	£12.72
Total staff cost per year (assuming 4 tests per year at 7 minutes of band 6 nurse time)	£51	£51	£51
Total cost of interpreting results of test (assuming 4 tests per year at five minutes of consultant time)	£9	£9	£9
Staff for training (number)			
Consultant nephrologists		2	
Trainee nephrologists		8	
Nurses	60	32	8
Technicians			
Dieticians	2	2	5
Others	20		
Total training cost (assumes 3.5 hr commitment)	£11,171.16	£7,385.00	£1,855.00
Assumed average useful life of training (years)	5	5	5
Total EAC of training	£2,474.20	£1,635.64	£410.85
EAC of total training (per patient)	£4.23	£1.74	£0.76

*Assume nurse (band 6) performs the measurement using the BCM - Body Composition Monitor.

Finally, to estimate the total annual cost of adding bioimpedance testing to standard practice, the total cost of consumables (electrodes and patient cards), also based on quarterly testing (Table 16), was added to the estimated device, maintenance, staff time, and training costs. The total estimated cost per patient year for each adult centre, and the average cost per patient across centres, is reported in Table 17 for each device. For the base case cost-effectiveness analysis, we applied the average cost per patient per year using the BCM based on the higher maintenance costs (£101.41) and applied a distribution incorporating the lower and upper 95% confidence limits of £85 to £125. Given uncertainty regarding the ongoing maintenance costs for each device, Table 17 also presents estimated costs per patient year for each device excluding all maintenance costs. The costs are very similar cross the different devices. In addition to the estimates presented in Table 17, based on responses from dialysis units, we also estimated a cost per patient year based on responses from two paediatric units. As a result of substantially lower throughput, these were significantly higher; £149-£349 based on 4 tests per year and £243 - £451 based on 12 tests per year. However, these may be overestimated in situations where devices can be shared between adults and children.

Table 16 Cost of device consumables

Consumables	BCM – Body Composition Monitor	Multiscan 5000	Inbody S10	BioScan 920-II
Electrodes (per test)	£3.00	£1.10	Reusable	£0.65
Electrodes (per year) assuming 4 tests annually	£12.00	£4.40	Reusable	£2.60
Patient cards (per card) 20 readings	£6.28	N/A	N/A	N/A
Patient cards (per year) assuming 4 tests annually	£1.26	N/A	N/A	N/A
Results sheets (per year) assuming 4 tests annually	NA	NA	£2.08	NA
Total	£13.26	£4.40	£2.08	£2.60

Table 17 Estimated annual cost per patient per year for quarterly testing using the BCM - Body Composition Monitor and alternative devices

Annual cost per patient	A	B	C	Average across centres
BCM – Including maintenance contract without parts and labour	£116	£83	£91	£96.50
BCM – Including maintenance cost with parts and labour	£125	£85	£95	£101.41
Multiscan 5000	£114	£75	£85	£91.22
Inbody S10	£119	£74	£86	£93.03
Bioscan	£103	£72	£79	£84.51
BCM – excluding any maintenance costs	£110	£81	£88	£92.99
Multiscan 5000 – excluding any maintenance costs	£112	£75	£84	£89.88
Inbody S10 – excluding any maintenance costs	£114	£73	£83	£90.36
Bioscan – excluding any maintenance costs	£95	£70	£75	£79.85

Health measurement and valuation

Health state utility values for patients on dialysis and post-transplant were identified from a focused review of the literature. We first identify two systematic reviews of utility data in the context of ESRD incorporating studies relevant to the NICE reference case (reporting EQ-5D data for UK patients).[122, 123] We focused our searches on identifying any more recent studies published following December 2010 (the end date of the search conducted for the most recent systematic review). This identified no further studies reporting EQ-5D values specifically for UK patients. The systematic review conducted by Wyld et al included a random effects meta-regression to predict utility based on several factors: treatment (transplant, dialysis, pre-treatment, conservative management), and utility elicitation method. This model predicted an EQ-5D utility value for patients on dialysis of 0.64, and an EQ-5D utility for transplant patients of 0.75. However, a limitation of this study was that some of the EQ-5D scores were measured from mapping algorithms, and the age to which the mean utility estimates applied was not reported. The earlier systematic review by Liem et al restricted a meta-analysis to those studies using the EQ-5D index directly for each modality of RRT, and reported the pooled mean age and sex distribution for

the corresponding pooled EQ-5D values.[122] These are reported in Table 18. The age and sex matched EQ-5D UK population norms were calculated using an equation published by Ara and Brazier[124] and used to derive age/sex adjusted utility multipliers from the raw pooled estimates.[125] The alternative utility values derived from Wyld et al[123]. were applied in a sensitivity analysis, assuming the same age and sex distributions, as reported by Liem et al.[122] for purposes of adjustment.

A significant proportion of inpatient hospitalisations are associated to cardiovascular events in the dialysis population, as assumed in the model. It is reasonable to assume that such events will be associated with short term and lasting disutility. This is the assumption that is used in cardiovascular event models in non-dialysis populations, and the best recognised source of English EQ-5D data for different CV event histories is the Health Survey for England, as reported by Ara and Brazier.[124] Therefore, these data were used to estimate age adjusted utility multipliers during the first and subsequent years following different types of CV event. A weighted average of these multipliers for the first and subsequent years was then calculated (based on relative frequency of CV event histories in the dialysis population) and applied to the portion of the cohort modelled to experience an incident CV event. For example, a 60 year old cohort stable on HD would be assigned a utility value of 0.56, whilst a 60 year old HD cohort with an incident CV event within a year would be assigned a utility of 0.466 (=0.56*0.832), and a 60 year old cohort over a year since an incident CV event would be assigned a utility value of 0.521 (=0.56*0.931).

Finally, hospitalisations for any other reason were also assumed to incur an acute utility decrement. These were taken from the modelling used to inform the NICE guideline on peritoneal dialysis.[17] In the modelling for CG125, a 6% reduction was applied to for any dialysis complication. The same 6% reduction is applied in our model for the second half of the 3 month cycle in which complications occur.

Table 18 Utility estimates and age adjusted utility multipliers applied in the model

Model State	HSUV	SE	Age of cohort	Prop male	Age related population norm	Age adjusted multiplier for use in model	Adjusted SE	Source
Stable HD	0.560	0.033	60.400	0.580	0.826	0.678	0.040	Liem et al. 2008; Ara and Brazier, 2010[122, 124]
Stable PD	0.580	0.043	57.900	0.550	0.836	0.694	0.052	Liem et al. 2008; Ara and Brazier, 2012[122, 124]
Stable post-transplant	0.810	0.046	51.400	0.600	0.863	0.939	0.053	Liem et al. 2008; Ara and Brazier, 2013[122, 124]
MI within 12 months	0.721	0.045	65.4	0.500	0.803	0.898	0.056	HSE data - Ara and Brazier 2010[124]
MI history	0.742	0.02	65.1	0.500	0.804	0.923	0.025	HSE data - Ara and Brazier 2010[124]
Angina within 12 months	0.615	0.019	68.8	0.500	0.787	0.782	0.024	HSE data - Ara and Brazier 2010[124]
Angina history	0.775	0.015	68.0	0.500	0.790	0.981	0.019	HSE data - Ara and Brazier 2010[124]
Stroke with 12 months	0.626	0.038	67.9	0.500	0.791	0.792	0.048	HSE data - Ara and Brazier 2010[124]
Stroke history	0.668	0.018	66.8	0.500	0.796	0.839	0.023	HSE data - Ara and Brazier 2010[124]
Any new CV event (within 12 months)						0.832	0.042	Weighted average of parameters above
New CV event history						0.931	0.022	Weighted average of parameters above

Time horizon and discounting of costs and benefits

The modelling was analysed over the lifetime of patients; 30 years for a 66 year old cohort in the base case analysis. The time horizon was extended in years for scenario analyses involving younger cohorts. All future costs and benefits were discounted at a rate of 3.5% per annum.

Analysis

The results of the model are presented in terms of a cost-utility analysis over the lifetime of the simulated cohorts. The bioimpedance guided fluid management strategy is compared incrementally to standard care, to estimate its incremental costs and quality adjusted life year gained (QALY). This is expressed as the incremental cost-effectiveness ratio. The net benefit framework is used to identify the optimal fluid management strategy at different threshold ratios of willingness to pay per QALY. To characterise the joint uncertainty surrounding point estimates of incremental costs and effects, probabilistic sensitivity analyses was undertaken. The results of these analyses are presented in the form of cost-effectiveness acceptability curves (CEACs). Further deterministic sensitivity analyses was used to address other forms of uncertainty.

The primary analysis was conducted for a mixed cohort of patients on haemodialysis or peritoneal dialysis. Subgroup analyses were conducted to explore any differences in cost-effectiveness by mode of dialysis and, where data allowed, by characteristics of the patient population. The impact of applying different assumptions with respect to testing frequency and throughput was also explored through scenario analyses. Scenario analyses were also used to explore the impact on cost-effectiveness of other sources of uncertainty.

Cost-effectiveness results

The model was first set up assess the cost-effectiveness of bioimpedance guided fluid management versus standard care for a mixed cohort of HD (87%) and PD (13%) patients.

The key assumptions of the base model are as follows:

- The starting age of the cohort is 66 years

- Survival on HD and PD is equivalent, and patients do not switch between dialysis modes
- Survival to ten years on dialysis is based on parametric extrapolation of 5 year survival curves, reported for patient in the European renal registry.[94]
- Survival beyond ten years is estimated by applying published, age-specific, relative risks of death on RRT compared to general population norms.[91]
- Fixed proportions of the cohort are waitlisted for transplant, and wait a median of ~3 years conditional on survival.[99] No transplants occur beyond the age of 75.
- Following graft failure, transplant patients incur costs of dialysis; i.e. no further transplants are modelled.
- Probabilities of all-cause inpatient hospitalisation are estimated by age band, time on RRT, RRT modality, sex, and comorbidity status, using a published regression based on linked UK renal registry - health episode statistics data.[92]
- It is assumed that 17.6% of all inpatient hospitalisations are due to cardiovascular events.
- Health state utility decrements are applied in the acute period for all hospitalisation events, and ongoing health state utility decrements are also applied post CV hospitalisation.[102]
- First incident CV hospitalisations increase the comorbidity burden on the cohort by 1, resulting in an increased risk of hospitalisation in subsequent cycles.
- Costs of dialysis, treatment for anaemia (EPA), blood pressure medication, all inpatient hospitalisations, all outpatient attendances, renal transplant, all post-transplant hospitalisation and outpatient attendance, and immunosuppression post-transplant are included in the base model.
- Costs of CV hospitalisation are assumed equal to the average cost across all hospitalisations in dialysis patients (i.e. CV events account for 17.6% of all hospitalisation costs)
- The incremental cost of monitoring patients using bioimpedance testing is added in the bioimpedance arm of the model (assuming 4 tests per year).
- Effects of bioimpedance monitoring acting on all-cause mortality are applied for 10-years in the model.

- Effects of bioimpedance monitoring acting on CV or all-cause hospitalisation are applied over the lifetime of the cohort.
- Costs and QALYs are discounted a rate of 3.5% per annum.

The following set of results are based on several alternative base case scenarios with respect to possible effects of bioimpedance guided fluid management on mortality, hospitalisation rates, and blood pressure medication use. There is significant uncertainty surrounding the clinical effectiveness of bioimpedance monitoring, as highlighted in the clinical effectiveness chapter. Therefore, the point estimates of incremental cost-effectiveness should be treated with caution.

The main clinical effectiveness scenarios explored are described below and summarised in Table 19:

1. Only the pooled hazard ratio (0.689 (0.228-2.084)) for the effect of bioimpedance testing on mortality is applied to the base model. It should be noted that this pooled effect from the meta-analysis (Figure 8) is not statistically significant, but directionally favours bioimpedance guided fluid management. Given uncertainty regarding long term effects, this effect is applied over ten years in the model (up to cycle 40).
2. A plausible effect of bioimpedance testing on non-fatal CV events is added to the effect on mortality in scenario 1. The applied hazard ratio (0.9123 (0.8208-1.014)) was derived as described above using published observational data on prognostic value of PWV on the risk of CV events and mortality (Table 9), combined with the pooled mean reduction in PWV (Figure 7) observed across the bioimpedance trials included in our systematic review. This scenario is heavily caveated by the reliance on the observation prognostic study model the effect.
3. This scenario applies the same effect, derived through the pooled reduction in PWV, to both mortality and non-fatal CV events in the model; i.e. a hazard ratio of 0.9213 is applied to both all-cause mortality and the CV hospitalisation rate. This scenario comes with same caveats as scenario 2.
4. Scenario 4 replicates scenario 3, but adds a possible effect of bioimpedance guided fluid management on blood pressure medication use. As described

under “Costs of background medications for dialysis patients”, a possible cost reduction of £12.98 per year was derived from existing trial evidence. Note, however, that this was only observed/reported in one of the RCTs, [57] and was not based on a formal adjusted comparison.

5. Scenario 5 uses reported observational associations between baseline hydration status (as measured by the BCM - Body Composition Monitor), and mortality and all-cause hospitalisation. The effect of bioimpedance testing is modelled through a plausible reduction in the proportion of the cohort (25%) that is severely overhydrated (ROH > 15%).[74] Using data reported by Huan-Sheng et al.,[70] it was estimated that the proportion of severely overhydrated patients could be reduced proportionally by 28-38% with bioimpedance guided fluid management relative to control. This scenario applies a 28% proportional reduction in severe OH in the bioimpedance arm of the model.
6. Scenario 6 replicates scenario 5, but applies a 38% proportional reduction in severe OH in the bioimpedance arm of the model.

Table 19 Summary of effect estimates applied for bioimpedance guided fluid management in the main scenarios

Scenario	Relative effect on all-cause mortality; HR	Relative effect on non-fatal CV hospitalisation; HR	Effect on blood pressure medication costs (mean reduction); £	Proportional reduction in severe overhydration (ROH > 15%)
Scenario 1	0.689 (0.228-2.084)	1	0	NA
Scenario 2	0.689 (0.228-2.084)	0.912 (0.821-1.014)	0	NA
Scenario 3	0.912 (0.821-1.014)	0.912 (0.821-1.014)	0	NA
Scenario 4	0.912 (0.821-1.014)	0.912 (0.821-1.014)	-12.98	NA
Scenario 5*	NA	NA	NA	0.28
Scenario 6*	NA	NA	NA	0.38

Table 20 presents the model based cost-effectiveness findings for the main clinical effectiveness scenarios 1 to 6 (described above). Across the scenarios, bioimpedance guided fluid management comes out as the more costly strategy, resulting in increased costs to the health service between £4,518 and £35,676. These increased costs are accompanied by QALY gains under the alternative effectiveness scenarios between 0.07 and 0.58. The incremental cost-effectiveness ratios for bioimpedance testing range from £58,723 to £66,007 per QALY gained. It should be noted that the increased costs associated with bioimpedance guided fluid management are primarily driven by the high dialysis costs during life years gained. The cost of bioimpedance testing is modest, adding on average £101 per patient year.

As discussed in the methods section, others have argued for the exclusion of dialysis costs in the assessment of technologies that aim to extend survival of dialysis patients without influencing the need for dialysis, as they can act as an insurmountable hurdle to demonstrating cost-effectiveness. The results for effectiveness scenarios 1 to 6 with dialysis costs excluded are therefore provided for comparison in Table 21. It can be noted that this results in a large reduction in the ICERs for bioimpedance testing; now ranging between £15,215 and £21,201 per QALY gained. Note, however, that these point estimates are based on uncertain effects incorporated as deterministic point estimates.

Table 20 Deterministic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (including dialysis costs)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. Applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£158,104		2.7014			-£104,077
BCM	£193,780	£35,676	3.272	0.5706	£62,524	-£128,341
2. Applying the point estimate for the pooled effect of BCM on mortality, and a linked effect on non-fatal CV events through the pooled reduction in PWV						
Standard care	£158,104		2.7014			-£104,077
BCM	£193,386	£35,282	3.2812	0.5798	£60,850	-£127,762
3. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV						
Standard care	£158,104		2.7014			-£104,077
BCM	£166,997	£8,893	2.8517	0.1504	£59,146	-£109,962
4. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV, and a 10% reduction in BP medications use						
Standard care	£158,104		2.7014			-£104,077
BCM	£166,933	£8,829	2.8517	0.1504	£58,723	-£109,899
5. Modelling effects of bioimpedance testing through associations between severe OH and mortality and all cause-hospitalisation (assumes a 28% reduction in severe OH)						
Standard care	£162,039		2.77			-£162,039

BCM	£166,557	£4,518	2.84	0.07	£66,007	-£166,557
6. Modelling effects of bioimpedance guided fluid management through associations between severe OH and mortality and all cause-hospitalisation (assumes a 38% reduction in severe OH)						
Standard care	£162,039		2.77			-£162,039
BCM	£167,999	£5,959	2.86	0.09	£64,151	-£167,999

Table 21 Deterministic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (excluding dialysis costs)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. Applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£46,214		2.7014			£7,813
BCM	£55,555	£9,341	3.272	0.5706	£16,370	£9,884
2. Applying the point estimate for the pooled effect of BCM on mortality, and a linked effect on non-fatal CV events through the pooled reduction in PWV						
Standard care	£46,214		2.7014			£7,813
BCM	£55,161	£8,947	3.2812	0.5798	£15,430	£10,463
3. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV						
Standard care	£46,214		2.7014			£7,813
BCM	£48,565	£2,351	2.8517	0.1504	£15,638	£8,469

4. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV, and a 10% reduction in BP medications use						
Standard care	£46,214		2.7014			£7,813
BCM	£48,502	£2,288	2.8517	0.1504	£15,215	£8,533
5. Modelling effects of bioimpedance testing through associations between severe OH and mortality and all cause-hospitalisation (assumes a 28% reduction in severe OH)						
Standard care	£47,046		2.77			-£47,046
BCM	£48,497	£1,451	2.84	0.07	£21,201	-£48,497
6. Modelling effects of bioimpedance guided fluid management through associations between severe OH and mortality and all cause-hospitalisation (assumes a 38% reduction in severe OH)						
Standard care	£47,046		2.77			-£47,046
BCM	£48,843	£1,797	2.86	0.09	£19,345	-£48,843

Markov Traces

Figures 14 and 15 below show the Markov traces for the standard care arm and the bioimpedance arm under clinical effectiveness scenario 3. In the standard care arm, the ten year mortality for the 66 year old cohort is 78.8%. This is consistent with the observed 10 year mortality in UK RRT patients surviving beyond 90 days (~68% in 56-64 year-olds and ~88% in 65-74 year-olds).[91] Assuming a constant effect of bioimpedance guided fluid management on mortality, over ten years, the ten year mortality in the bioimpedance arm comes to 76%. Over the lifetime of the modelled cohort, the gain in undiscounted life expectancy is 0.37 years (6.37 versus 6.0). The modelled life-time cumulative incidence of any CV hospitalisation event is 46.8% in the bioimpedance arm of the model, and 47.1% in the standard care arm. 7.9 % of patients in the bioimpedance arm receive a transplant during their lifetime, whilst the corresponding figure is 7.6% in the standard care arm.

Table 22 provides a breakdown of the cumulative costs for the standard care and bioimpedance arms respectively – under clinical effectiveness scenario 3. The costs are higher across all categories in the bioimpedance arm, due to the slight increase in survival. However, it can be noted that it is the additional dialysis costs in extra years that makes up 74% of the total incremental cost of the bioimpedance guided strategy. This same pattern is consistent across all the main clinical effectiveness scenarios (1-6). The actual increase in lifetime costs due to bioimpedance testing is small (£479 per patient in effectiveness scenario 3).

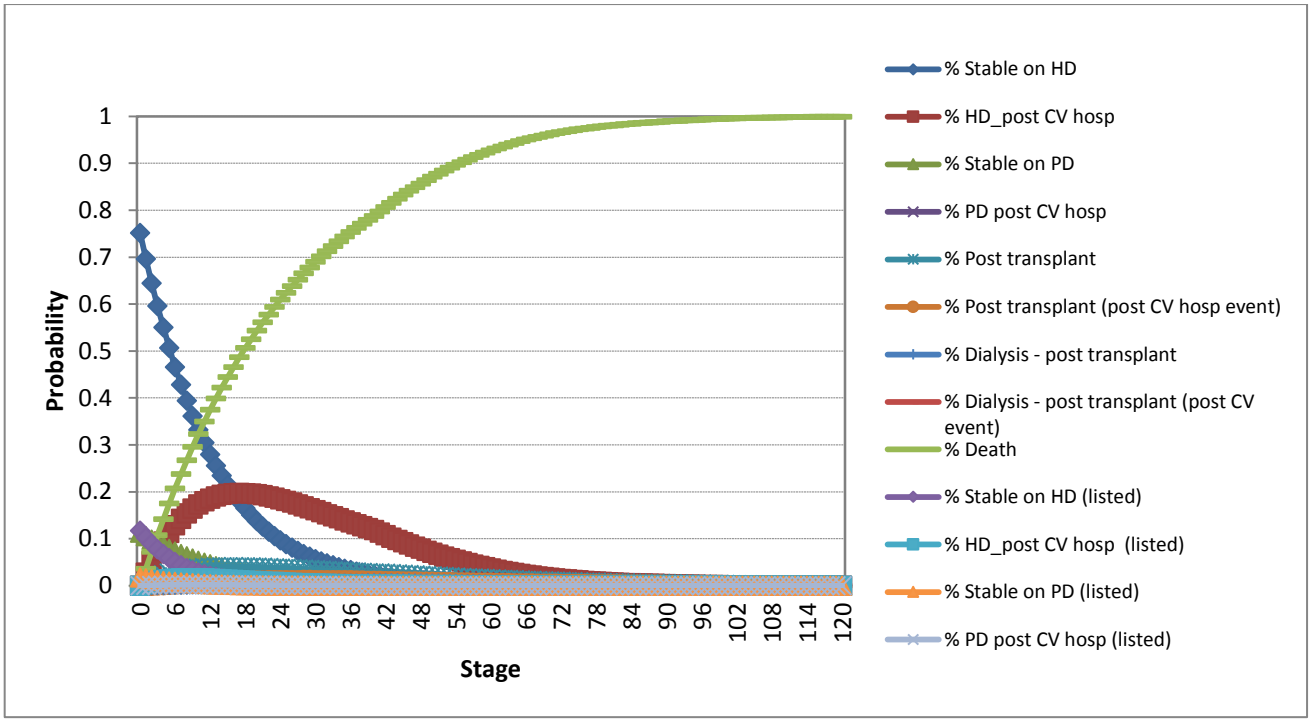

Figure 14 Markov cohort trace, Standard care (1 stage equals three months)

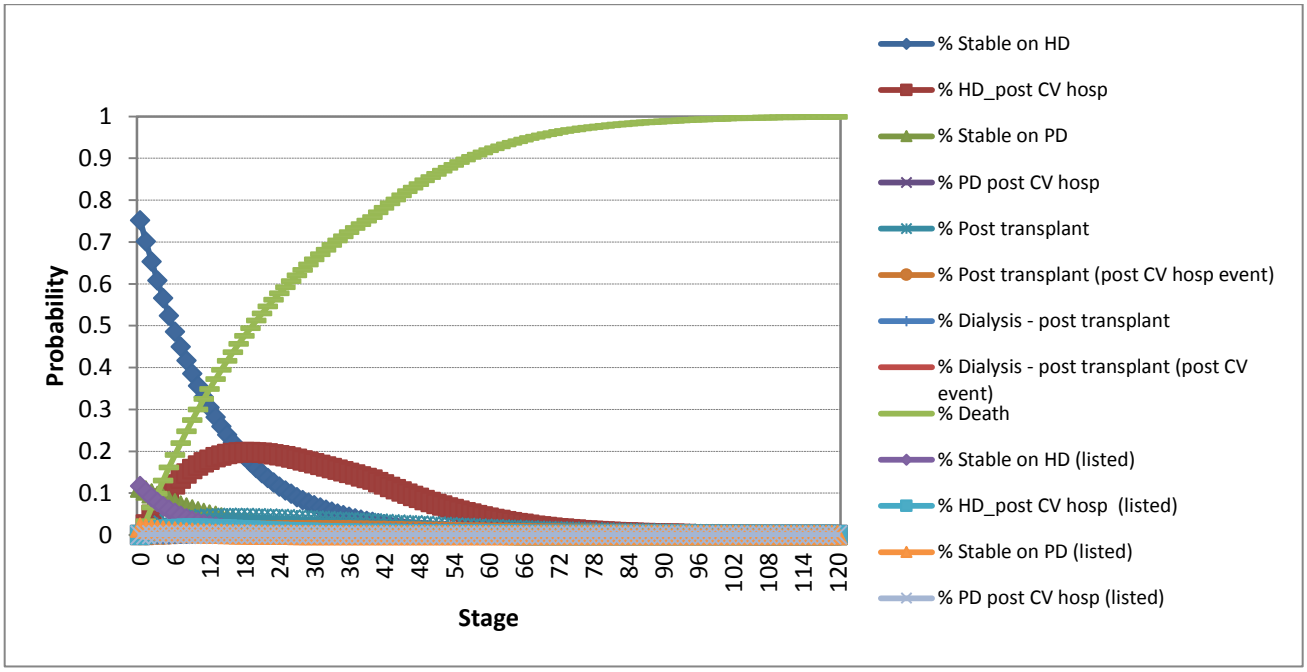

Figure 15 Markov cohort trace, BCM - Body Composition Monitor, under clinical effectiveness scenario 3 (1 stage equals three months)

Table 22 Breakdown of cumulative costs by categories

	Standard Care	Body Composition Monitor-BCM	Difference BCM versus standard care
Cumulative in-patient hospital costs	£21,775	£22,404	£629
Cumulative dialysis costs	£111,890	118,432	£6,542
Cumulative medication costs	£10,792	£11,423	£631
Cumulative outpatient costs	£6,076	£6,431	£355
Cumulative acute transplant cost	£1,066	£1,101	£35
Cumulative post-transplant follow-up costs	£6,505	£6,709	£204
Bioimpedance testing costs	N/A	£497	£479
Cumulative cost	£158,104	£166,997	£8,893

Deterministic sensitivity analysis

Figures 16 and 17 illustrate the effects of one way sensitivity analysis on key model input parameters, with dialysis costs included (Figure 16) and excluded (Figure 17). These reference ICER for both these tornado diagrams reflects clinical effectiveness scenario 3; i.e. a hazard ratio of 0.912, inferred through the pooled reduction in pulse wave velocity, applied to both all-cause mortality and CV hospitalisation.

When dialysis costs are included, the ICER for bioimpedance guided fluid management in most sensitive to changes in the hazard ratio for the effect on all-cause mortality. The most favourable ICER occurs when the hazard ratio on all-cause mortality is equal to one, as this equalises survival and eliminates the excess dialysis costs incurred in added years.

When dialysis costs are excluded, the ICER remains most sensitive to the hazard ratio on all-cause mortality, but the most favourable ICER occurs for the largest effect (i.e. 0.879). Results are also moderately sensitive to the utility multiplier for haemodialysis, the cost of haemodialysis, and the hazard ratio for CV hospitalisation. However, when dialysis costs are included, the ICER remains well above £30,000 when these parameters are varied within their ranges. Conversely, the ICERs all

remain below £30,000 when the parameters are varied individually within their ranges (referent to clinical effectiveness scenario 3) with dialysis costs excluded.

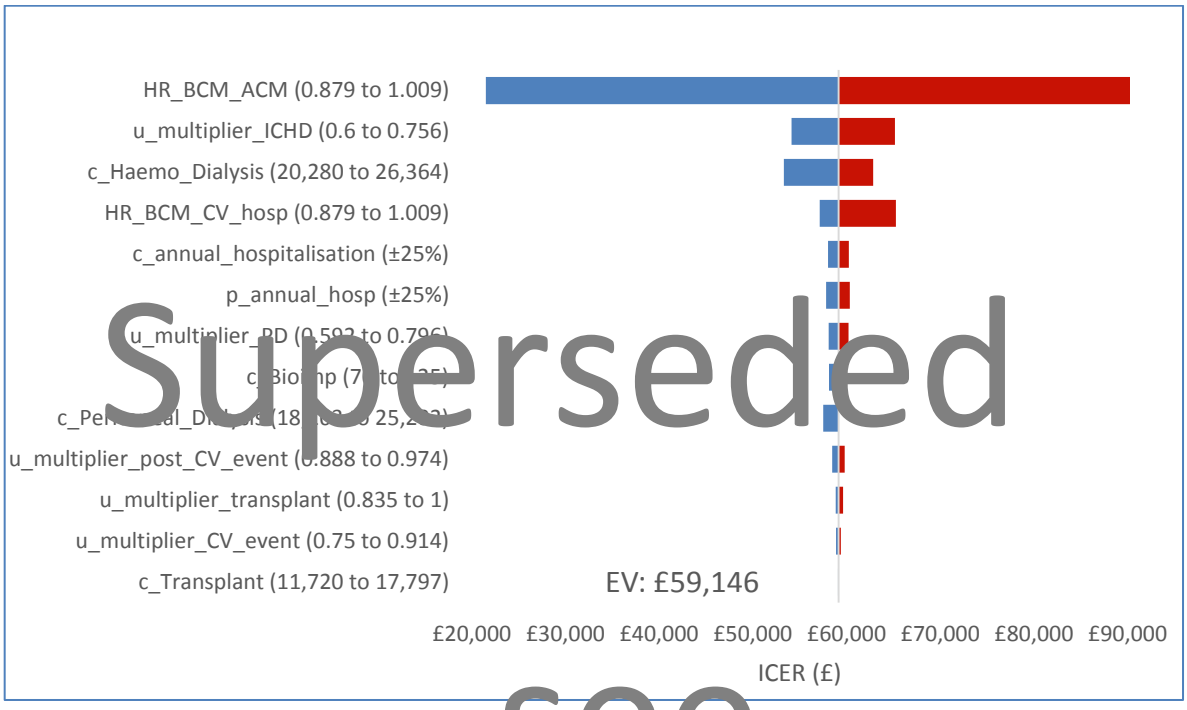

Figure 16 One-way sensitivity analysis: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs)

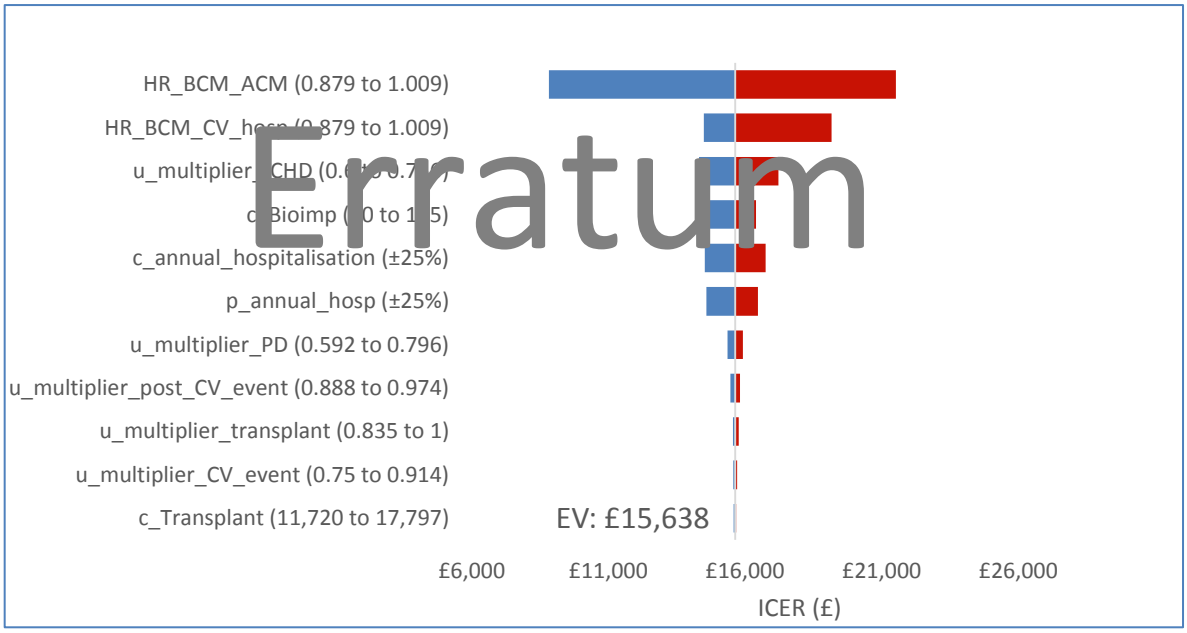

Figure 17 One-way sensitivity analysis: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs)

Scenarios analyses

Table 23 below presents the results of further scenario analyses, referent to clinical effectiveness scenario 3. Unless otherwise stated, these additional scenarios exclude dialysis costs to better illustrate sensitivity (around the cost-effectiveness threshold) should the exclusion of dialysis costs be considered appropriate for the purpose of decision making. Under most of the scenarios with dialysis costs excluded, the ICER for bioimpedance monitoring remains below £30,000, and is most often below £20,000.

Under only a few scenarios does the ICER for bioimpedance monitoring fall close to or below £30,000 when dialysis costs are included: When the effect on mortality is set to zero (i.e. a hazard ratio of 1 is applied to all-cause mortality) and an effect on non-fatal CV hospitalisation is maintained (Scenario 17); when assuming bioimpedance testing results in a 5% or 10% reduction in dialysis costs (Scenarios 15 and 16) over the lifetime of patients; and when it is assumed that bioimpedance guided fluid management results in a 5% increase in health state utility, maintained over the lifetime of all dialysis patients (Scenario 13). However, there is very little data available to justify these possible scenarios.

Table 23 Scenario analyses referent to base clinical effectiveness scenario 3 (all analyses exclude dialysis costs unless stated otherwise)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
Base case scenario 3: applying linked effects on mortality and non-fatal CV events, estimated through the pooled reduction in PWV (HR of 0.912 applied to both all-cause mortality and CV hospitalisation)						
Standard care	£46,214		2.701			£7,813
Bioimpedance guided	£48,565	£2,351	2.852	0.150	£15,638	£8,469
1. Applying an increased cost of monitoring in adults by increasing the number of tests per patient to 12 annually						
Standard care	£46,214		2.701			£7,813
BCM	£49,194	£2,980	2.852	0.150	£19,820	£7,840
2. Applying the estimated costs of bioimpedance monitoring in paediatric centres with lower throughput (assuming 4 tests annually)*						
Standard care	£46,214		2.701			£7,813
BCM	£49,271	£3,057	2.852	0.150	£20,331	£7,764
3. Applying the estimated costs of bioimpedance monitoring in paediatric centres with lower throughput (assuming 12 tests annually)*						
Standard care	£46,214		2.701			£7,813
BCM	£49,770	£3,556	2.852	0.150	£23,649	£7,265
4. Applying the cost of BioScan for bioimpedance monitoring						
Standard care	£46,214		2.701			£7,813
BioScan	£48,483	£2,268	2.852	0.150	£15,087	£8,552
5. Applying the cost of Inbody S10 for bioimpedance monitoring						
Standard care	£46,214		2.701			£7,813

Inbody S10	£48,511	£2,297	2.852	0.150	£15,277	£8,523
6. Applying the cost of MultiScan 5000 for bioimpedance monitoring						
Standard care	£46,214		2.701			£7,813
MultiScan 5000	£48,515	£2,301	2.852	0.150	£15,306	£8,519
7. Applying the lowest estimated annual bioimpedance monitoring from Table 15 (£70)						
Standard care	£46,214		2.701			£7,813
BCM	£48,411	£2,197	2.852	0.150	£14,613	£8,623
8. Applying the highest estimated annual bioimpedance monitoring cost from 15 (£125)						
Standard care	£46,214		2.701			£7,813
BCM	£48,681	£2,467	2.852	0.150	£16,407	£8,354
9. Applying an alternative lower cost per CV hospitalization event (£1386 per CV event)						
Standard care	£44,116		2.701			£9,912
BCM	£46,539	£2,423	2.852	0.150	£16,116	£10,496
10. Applying alternative age adjusted utility multipliers for dialysis and post-transplant[123]						
Standard care	£46,214		2.980			£13,384
BCM	£48,565	£2,351	3.148	0.168	£13,979	£14,396
11. Assume bioimpedance guided management results in a 2% improvement in the health state utility over the lifetime of dialysis patients (including dialysis costs)						
Standard care	£158,104		2.701			-£104,077
BCM	£166,997	£8,893	2.901	0.1999	£44,478	-£108,971
12. Assume bioimpedance guided management results in a 2% improvement in the health state utility over the lifetime of dialysis patients (excluding dialysis costs)						
Standard care	£46,214		2.701			£7,813

BCM	£48,565	£2,351	2.901	0.1999	£11,760	£9,461
13. Assume bioimpedance guided management results in a 5% improvement in the health state utility over the lifetime of dialysis patients (including dialysis costs)						
Standard care	£158,104		2.701			-£104,077
BCM	£166,997	£8,893	2.976	0.274	£32,419	-£107,483
14. Assume bioimpedance guided management results in a 5% improvement in the health state utility over the lifetime of dialysis patients (excluding dialysis costs)						
Standard care	£46,214		2.701			£7,813
BCM	£48,565	£2,351	2.976	0.274	£8,571	£10,948
15. Assume bioimpedance guided management results in a 10% reduction in dialysis costs over the lifetime of patients						
BCM	£155,154		2.852			-£98,119
Standard care	£158,104	£2,950	2.701	-0.150	Dominated	-£104,077
16. Assume bioimpedance guided management results in a 5% reduction in dialysis costs over the lifetime of patients						
Standard care	£158,104		2.701			-£104,077
BCM	£161,076	£2,971	2.852	0.150	£19,761	-£104,041
17. Applying only an effect on non-fatal CV events (HR= 0.912), excluding any effect on mortality (including dialysis costs)						
Standard care	£158,104		2.701			-£104,077
BCM	£158,259	£154	2.709	0.0072	£21,519	-£104,088
18. Applying a smaller effect on mortality and non-fatal CV events (HR = 0.95 for both)						
Standard care	£46,214		2.701			£7,813
BCM	£47,737	£1,523	2.785	0.084	£18,137	£7,970
19. Applying a larger effect of bioimpedance monitoring on both CV events and mortality (0.803); consistent with the cross sectional main effect of a unit change in PWV reported by Verbeke et al[106].						

Standard care	£46,214		2.701			£7,813
BCM	£51,142	£4,928	3.060	0.359	£13,729	£10,064
20. Applying differential effects on mortality (HR = 0.95) and non-fatal CV events (HR = 0.803) – including dialysis costs						
Standard care	£158,104		2.701			-£104,077
BCM	£162,730	£4,625	2.798	0.097	£47,672	-£106,762
21. Applying differential effects on mortality (HR = 0.95) and non-fatal CV events (HR = 0.803) – excluding dialysis costs						
Standard care	£46,214		2.701			£7,813
BCM	£47,186	£972	2.798	0.097	£10,014	£8,782
22. Excluding all non-CV causes of hospitalisation form the analysis – including dialysis costs						
Standard care	£144,931		2.714			-£90,655
BCM	£153,059	£8,128	2.865	0.151	£53,786	-£95,761
23. Applying no effects of bioimpedance monitoring beyond 3 years; HR for all-cause mortality and CV hospitalisation = 0.912 up to three years						
Standard care	£46,214		2.7014			£7,813
BCM	£47,752	£1,538	2.7853	0.0839	£18,329	£7,953
24. Applying no effects of bioimpedance monitoring beyond 3 years; HR for all-cause mortality and CV hospitalisation = 0.95 up to three years						
Standard care	£46,214		2.7014			£46,214
BCM	£47,288	£1,074	2.7488	0.0474	£22,647	£47,288

*Note, these scenarios are not conducted for child cohorts, they just reflect higher estimated costs of bioimpdence testing based on the level of throughput observed in paediatric dialysis centres.

Subgroup analysis

Table 24 presents the results considering key subgroups of the dialysis population.

Separate analyses were considered by comorbidity status (none; at least one), dialysis modality (haemodialysis, peritoneal dialysis), starting age of the cohort (55 years), and transplant listing (yes/no). For comparability, all of these analyses were conducted with clinical effectiveness scenario 3 (HR = 0.912 for the effect of bioimpedance monitoring on mortality and CV hospitalisation). Finally, we also conducted a subgroup analysis using the overhydration states in the model (clinical effectiveness scenarios 6), with the effect of bioimpedance testing modelled through a plausible proportional reduction in severe overhydration (ROH > 15%) – reducing the risk of all-cause mortality and CV hospitalisation. This analysis focusses on the subgroup that are identified as being severely overhydrated at baseline, and assumes a 38% reduction over follow-up (Table 24, scenarios 8 and 9).

These analyses didn't reveal any large differences in cost-effectiveness by subgroups. The ICER is a bit higher in the subgroup waitlisted for transplant, as they spend less time on dialysis and so benefit less from the modelled reduction in all-cause mortality and CV hospitalisation conferred by bioimpedance guided fluid management. In the scenario focussing on the severely overhydrated subgroup, the ICER is ~£5000 lower than in the corresponding base case for that clinical effectiveness scenario, but when dialysis costs are included the ICER remains well above accepted thresholds (£59,318) – as it does for all the subgroups (results not shown).

Table 24 Subgroup analysis (using clinical effectiveness scenario 3 unless otherwise stated)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. People on dialysis who have comorbidities and higher hospitalisation rate*						
Standard care	£47,011		2.6974			£6,937
BCM	£49,389	£2,378	2.8476	0.1502	£15,828	£7,564
2. People on dialysis with no comorbidities and lower hospitalisation rate*						
Standard care	£43,102		2.7166			£11,230
BCM	£45,349	£2,247	2.8673	0.1507	£14,905	£11,998
3. People on haemodialysis (start age: 67; years on dialysis: 3)						
Standard care	£45,821		2.5803			£5,785
BCM	£48,192	£2,371	2.7272	0.1469	£16,138	£6,353
4. People on peritoneal dialysis (start age: 64; years on dialysis: 2)						
Standard care	£53,033		3.3993			£14,954
BCM	£55,212	£2,179	3.5541	0.1547	£14,085	£15,869
5. Mixed haemodialysis/peritoneal dialysis cohort aged 55						
Standard care	£79,985		4.7225			£14,466
BCM	£82,614	£2,629	4.888	0.1655	£15,891	£15,146
6. Patients listed for a transplant*						
Standard care	£87,221		4.1846			-£3,530
BCM	£89,974	£2,753	4.3201	0.1355	£20,315	-£3,572

7. Patients not listed for transplant*						
Standard care	£39,807		2.4696			£9,586
BCM	£42,095	£2,288	2.6223	0.1527	£14,989	£10,351
8. Chronically overhydrated patients only, at increased risk of mortality and all-cause hospitalisation; using modelling structure and assumptions of clinical effectiveness scenario 6 (38% reduction of chronic overhydration with bioimpedance monitoring relative to standard practice) – dialysis costs included						
Standard care	£157,985		2.7			-£157,985
BCM	£179,576	£21,591	3.06	0.36	£59,701	-£179,576
9. Chronically overhydrated patients only, at increased risk of mortality and all-cause hospitalisation; using modelling structure and assumptions of clinical effectiveness scenario 6 (38% reduction of chronic overhydration with bioimpedance monitoring relative to standard practice) – dialysis costs excluded						
Standard care	£46,095		2.7			-£46,095
BCM	£51,306	£5,211	3.06	0.36	£14,409	-£51,306

*Note, the model is not designed to adjust for different mortality rates in these subgroups.

Probabilistic cost-effectiveness results

For comparison with the deterministic results in Table 20 and 21, Tables 25 and 26 present the results for clinical effectiveness scenarios 1, 3 and 4 based on 1000 probabilistic iterations of the model, with dialysis costs included (Table 25) and excluded (Table 26). The point estimates of the ICERs are very similar to the deterministic ICERs. The final column in Tables 25 and 26 indicate the probability of standard practice and bioimpedance testing being the preferred strategy given a willingness to pay of £20,000 per QALY gained. With dialysis costs included, the probability of bioimpedance testing being cost-effective is ~25% under scenario 1 and less than 6% in scenarios 3 and 4.

With the dialysis costs excluded, the probability of bioimpedance testing being cost-effective at a threshold of £20,000 increases substantially; to ~70-73% for across effectiveness scenarios 1, 3, and 4 (Table 26). There remains a high degree of uncertainty inherent in the approach required to link effects of bioimpedance monitoring on arterial stiffness (PWV), to effects on mortality and non-fatal CV events, which is not fully captured in the probabilistic model. Thus the probability of cost-effectiveness in scenarios 3 and 4 may give a somewhat unrealistic impression of precision.

For further comparison, the incremental cost-effectiveness scatter-plots for bioimpedance testing versus standard practice, and the corresponding cost effectiveness acceptability curves, are presented in Figures 18-21 below, for scenarios 1 and 3 (including dialysis costs). The corresponding figures with dialysis costs excluded are presented in Figures 22-25.

Table 25 Probabilistic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (including dialysis costs)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	Probability cost-effective at £20,000 threshold
1. Clinical effectiveness scenario 1; applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£157,313		2.692			0.752
BCM	£190,130	£32,817	3.217	0.525	£62,563	0.248
2. Clinical effectiveness scenario 3; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9123 on both CV events and mortality)						
Standard care	£158,197		2.686			0.944
BCM	£166,875	£8,678	2.832	0.147	£59,198	0.056
3. Clinical effectiveness scenario 4; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9123 on both CV events and mortality), and a 10% reduction in BP medications use						
Standard care	£157,254		2.699			0.960
BCM	£166,246	£8,992	2.855	0.156	£57,652	0.040

Table 26 Probabilistic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (excluding dialysis costs)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	Probability cost-effective at £20,000 threshold
1. Clinical effectiveness scenario 1; applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£45,975		2.691			0.313
BCM	£54,786	£8,811	3.238	0.547	£16,100	0.687
2. Clinical effectiveness scenario 3; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9123 on both CV events and mortality)						
Standard care	£45,937		2.699			0.299
BCM	£48,222	£2,285	2.847	0.148	£15,430	0.701
3. Clinical effectiveness scenario 4; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9123 on both CV events and mortality), and a 10% reduction in BP medications use						
Standard care	£46,172		2.695			0.271
BCM	£48,443	£2,271	2.846	0.151	£15,038	0.729

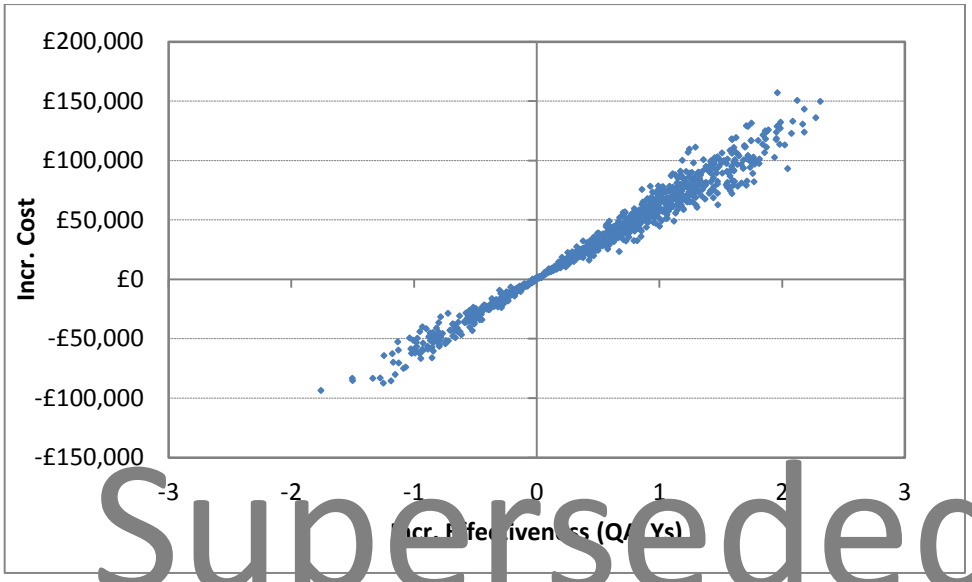

Figure 18 Incremental cost-effectiveness scatter plot: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 1 – including dialysis costs)

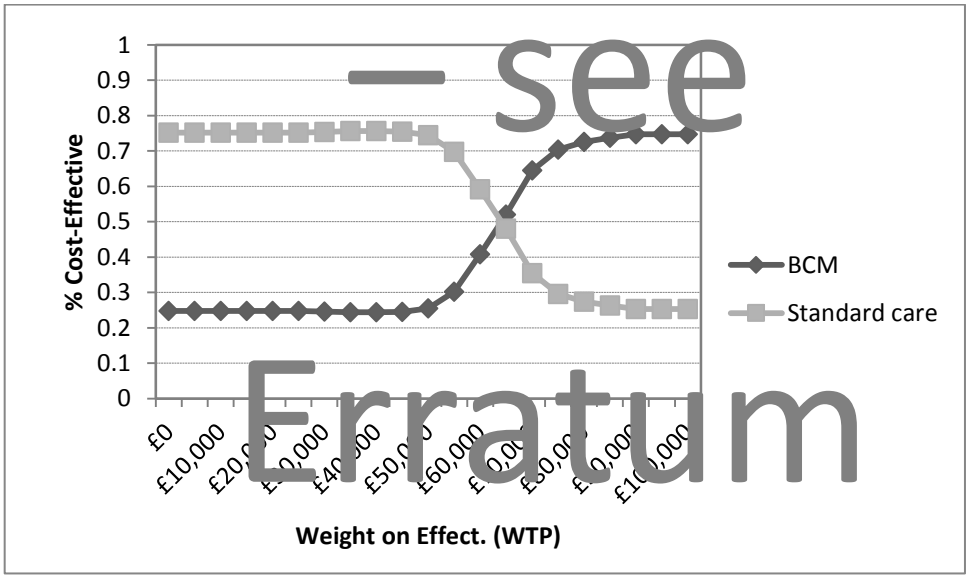

Figure 19 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 1 – including dialysis costs)

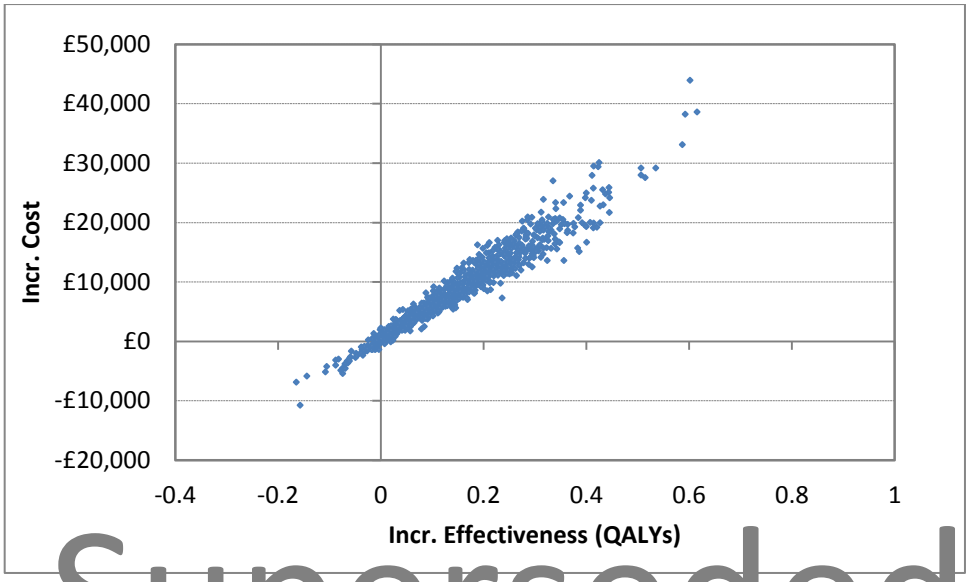

Figure 20 Incremental cost-effectiveness scatter plot: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs)

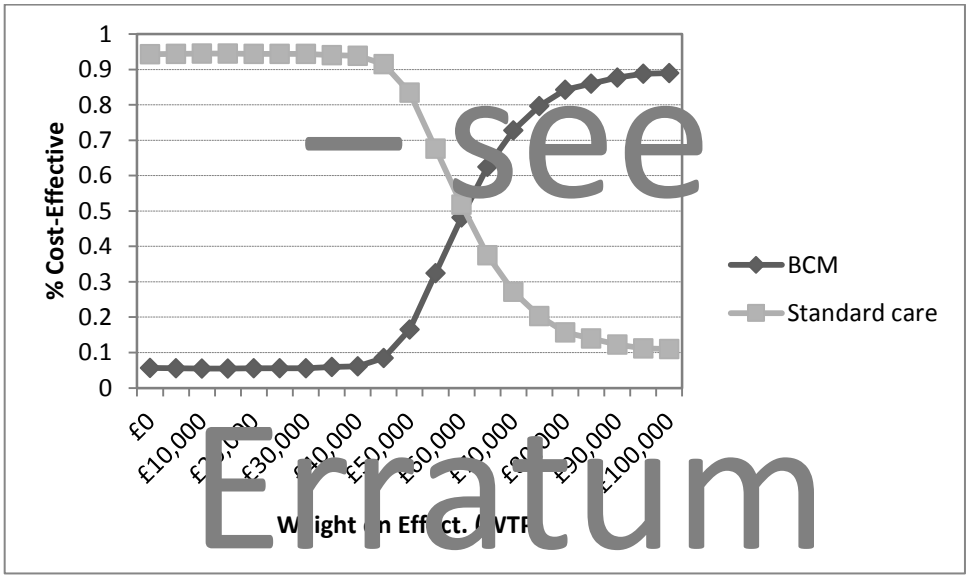

Figure 21 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs)

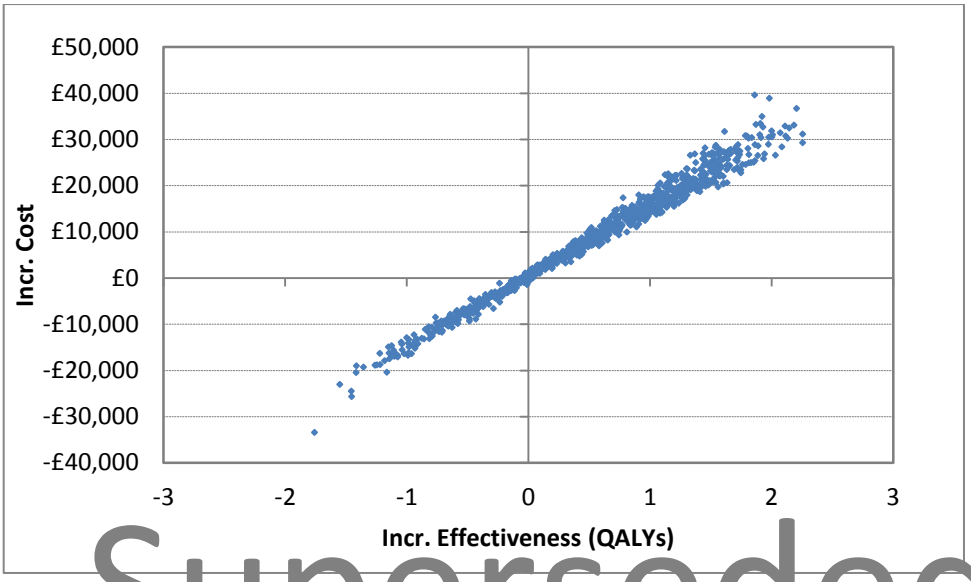

Figure 22 Incremental cost-effectiveness scatter plot BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 1 – excluding dialysis costs)

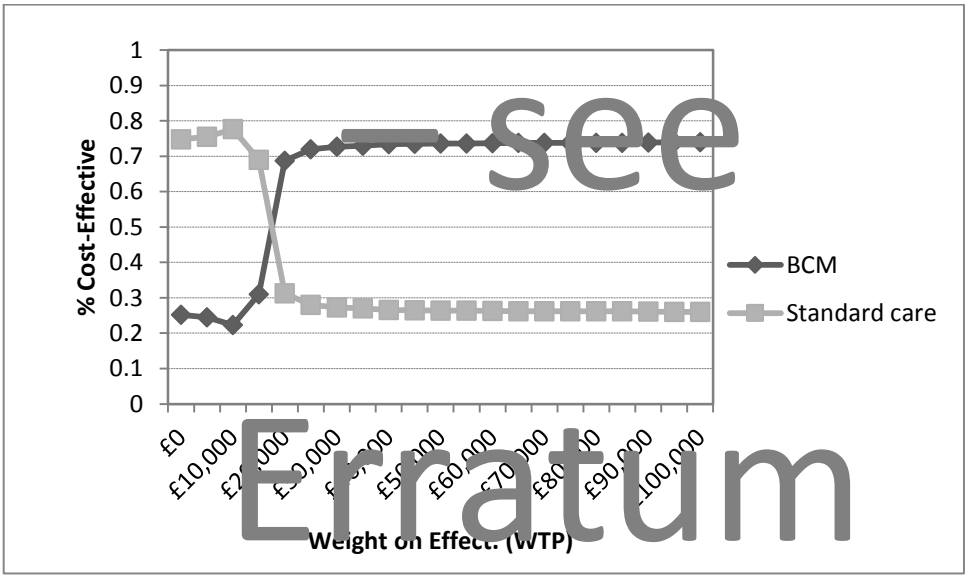

Figure 23 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 1 – excluding dialysis costs)

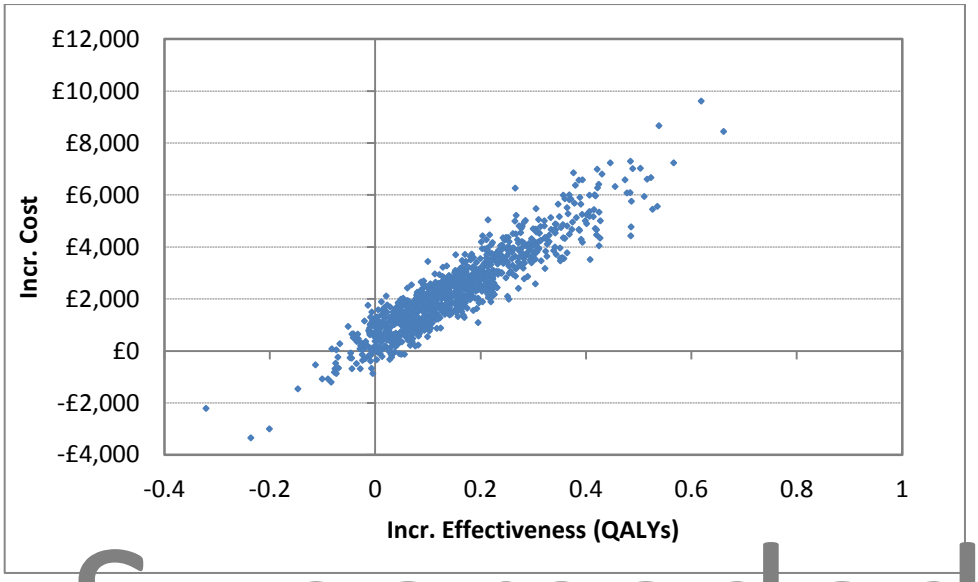

Figure 24 Incremental cost-effectiveness scatter plot: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs)

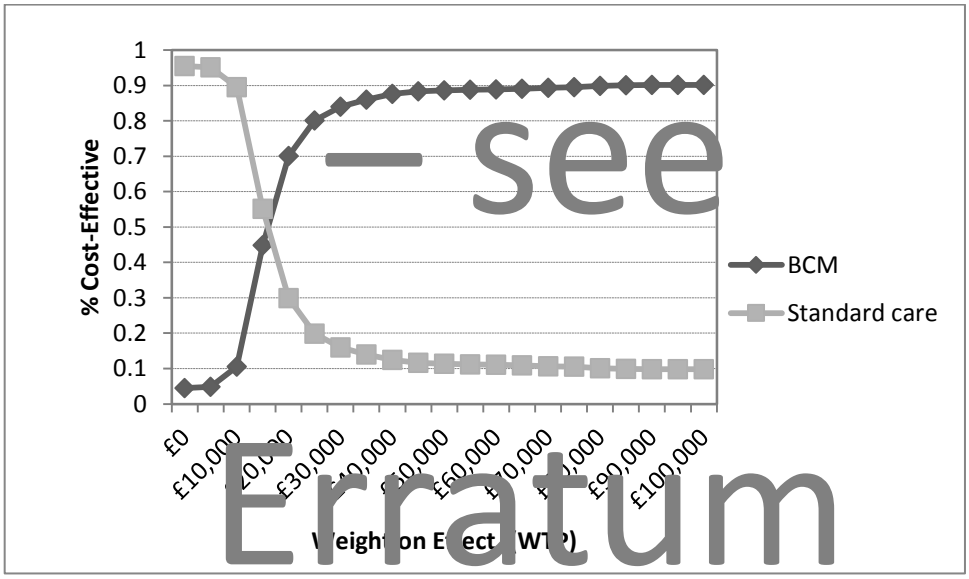

Figure 25 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs)

4.3 Interpretation of the cost-effectiveness results

The cost-effectiveness results above are based on limited evidence for the effects of bioimpedance guided fluid management on mainly surrogate endpoints (PWV, hydrations status). There is very limited high quality evidence available by which to link intervention induced changes in these surrogate endpoints to changes in health outcomes. Therefore, the indirect/linked modelling scenarios rely on observational associations to estimate possible effects of bioimpedance guided fluid management on final health outcomes. As a consequence, the results of the cost-effectiveness modelling are somewhat speculative and subject to considerable uncertainty, which is not fully reflected in the probabilistic sensitivity analysis.

Nevertheless, the results reveal some useful insights. Given the high costs of dialysis, it is unlikely that bioimpedance guided management will be cost-effective against accepted thresholds (£20-£30,000 per QALY gained) if it reduces mortality with these costs included in the model. Table 22 indicates that dialysis costs in additional years make up 74% of the incremental cost of bioimpedance guided management under clinical effectiveness scenario 3 (a modest and equal effect on both mortality and CV hospitalisation). Further scenario analyses suggest that the effect on mortality would have to be accompanied by a 5% reduction in dialysis costs over the lifetime of patients for the ICER to drop below £20,000 under clinical effectiveness scenario 3. Alternatively, with an accompanying 5% improvement in quality of life over the lifetime of patients, the ICER drops close to £30,000. With greater effects on mortality (and dialysis costs included), the magnitude of these accompanying effects would also have to increase to offset the greater increases in dialysis costs in extra years. Bioimpedance guided fluid management also becomes potentially cost-effective with dialysis costs included when no effect on mortality is assumed but an effect on the CV hospitalisation rate is retained. This all but eliminates the incremental cost associated with the bioimpedance guided strategy (reducing it to £150), but also greatly reduces the QALY gain which comes primarily from increased survival in the base case clinical effectiveness scenarios. The plausibility of these additional scenarios is uncertain given the available clinical evidence.

It can also be noted from the modelled scenarios that when dialysis costs are excluded from the model, the effects of bioimpedance guided management do not need to be

large for the ICER to remain below £20,000. The added cost of testing patients quarterly with bioimpedance spectroscopy is small (conservatively estimated to be ~£100 per patient year), and so relatively small effects on mortality and/or non-fatal CV events will compensate for this when dialysis costs in additional years are not included.

5 Discussion

5.1 Clinical effectiveness

This assessment is based on six RCTs (analysing 1039 participants) and eight non-randomised studies (analysing 4915 participants) evaluating the use of the BCM - Body Composition Monitor for fluid management in people with CKD having dialysis. None of the studies involved paediatric populations or the other multiple frequency bioimpedance devices specified in the protocol. Results of the assessment indicate that:

- Of the six RCTs, one was assessed as being at Low risk of bias, one at High risk of bias, and the remaining four trials at Unclear risk of bias.
- Five RCTs enrolled patients having haemodialysis and one RCT enrolled patients having peritoneal dialysis.
- All six RCTs were conducted in countries other than the UK and all involved adult populations.
- Use of the BCM - Body Composition Monitor significantly reduced systolic blood pressure (mean difference -3.48, 95%CI -5.96 to -1.00, p=0.006) and arterial stiffness (mean difference -1.53, 95%CI -3.00 to -0.07, p=0.04), as compared to standard clinical assessment.
- Absolute overhydration and relative overhydration were significantly lower in the BCM - Body Composition Monitor group compared with the standard clinical assessment group (WMD=--0.39, 95%CI -0.62 to -0.15, p=0.001, I^2=36% and WMD=-1.54, 95%CI -3.01 to -0.07, p=0.04, I^2=39, respectively).
- Compared with standard clinical methods, the use of the BCM - Body Composition Monitor had no significant effects on mortality (HR 0.69, 95%CI 0.23 to 2.08, p=0.51).
- There was a difference in absolute hydration at follow-up between patients having haemodialysis and patients having peritoneal dialysis, but the difference was not large enough to suggest a significant effect of type of dialysis.
- No evidence was found regarding use of the other devices specified for this assessment in the relevant clinical population.

- CV events and hospitalisation were reported by few studies and not in a consistent way.
- Patient-reported outcomes were lacking in the included studies.

Comparison with other reviews

We have reinforced and extended the findings of the CADTH review[49] by conducting meta-analyses of both intermediate outcomes (systolic blood pressure, arterial stiffness and absolute and relative fluid overload) and a clinical outcome (mortality). Notably, our assessment also included one study involving people having peritoneal dialysis.

Cost effectiveness

A cost-effectiveness Markov model was developed to simulate the progression of the prevalent dialysis cohort through a set of mutually exclusive health states capturing mortality, CV and other causes of hospitalisation, and transplantation (for those listed). The model included costs to the health service of providing dialysis treatment, inpatient and outpatient hospital costs, transplant costs, post-transplant follow-up and immunosuppressant costs, and costs of dialysis following transplant graft failure. Health state utility multipliers were identified and incorporated for the dialysis and post-transplant states, allowing cumulative QALYs to be estimated. Further proportional reductions in health state utility were modelled in the short-term for all hospitalisation events and in the long-term following incident CV hospitalisation events.

The added costs and plausible effects of bioimpedance guided fluid management were added to the baseline model, and the cumulative costs and QALYs were simulated over the lifetime of the cohorts under standard care and the bioimpedance guided strategy. The base case effectiveness scenarios modelled proportional reductions in all-cause mortality and CV or all-cause hospitalisation with the bioimpedance guided strategy. Given the limited direct evidence from the clinical effectiveness review, these effects were generally estimated by linking effects on surrogate endpoints (arterial stiffness (PWV), hydration status) to effects on the final outcomes using secondary published sources.

The costs and effects of the bioimpedance guided strategy were compared incrementally to standard care under several plausible clinical effectiveness scenarios.

Key findings from the analyses are as follows:

- Under all the main effectiveness scenarios, the ICER for bioimpedance guided fluid management remained well above accepted thresholds for cost-effectiveness when dialysis costs were included in the model.
- This is due to the high costs of dialysis in the added years under the bioimpedance strategy.
- For bioimpedance guided management to appear cost-effective with dialysis costs included (assuming an effect on mortality), it would also have to provide a significant reduction in dialysis costs across the lifetime of patients, or a constant percentage improvement in the health state utility of patients receiving dialysis.
- The ICER for bioimpedance guided management also dropped below £30,000 when no effect on mortality was included in the model, but a proportional reduction in non-fatal CV hospitalisation events was retained.
- There is little evidence to justify the modelled scenarios under which bioimpedance guided fluid management becomes cost-effective (against standard thresholds) when dialysis costs are included in the model.
- When dialysis costs are excluded from the model, the effects of bioimpedance guided management do not need to be great for the ICER remain below £20,000.
- The added monitoring costs associated with the strategy are small (conservatively estimated to be ~£100 per patient year), and so relatively small effects on mortality and/or non-fatal CV events justify the added costs. That said, the costs in added years remain quite substantial given the high background rates of other cause hospitalisation.

5.2 Strength and limitations of the assessment

This assessment has been conducted according to current standards and recommendations and the methods were specified a priori in a research protocol. Comprehensive literature searches of the major electronic databases were conducted,

all potentially eligible studies were assessed for inclusion in the review and methodological quality of all included studies was assessed using the recommended risk-of-bias tools. Despite these efforts, it is still possible that some relevant evidence may have been missed, albeit any omissions are likely to be minimal.

The economic model was able to draw on UK and European registry data to inform baseline mortality, all cause hospitalisation rates, and the likelihood of progression to transplant. Systematic searches were undertaken to identify suitable sources for other parameters in the model, such as the health state utility weights, and costs of RRT were based on standard NHS sources. A short survey of centres with expertise in using bioimpedance testing was carried out to get an accurate picture of the likely incremental cost of adopting it as an adjunct to standard clinical practice. There are limitations relating to the availability of evidence to inform clinical effects of bioimpedance testing in the model, and several simplifying assumptions had to be made in light of the data available to inform baseline probabilities.

The following limitations also need to be acknowledged:

- We were able to include only studies involving the BCM - Body Composition Monitor due to a lack published evidence of the effectiveness of the other specified bioimpedance devices. As the generalisability of the effects of bioimpedance devices has yet to be determined, we cannot generalise our findings across the devices beyond the BCM – Body Composition Monitor.
- The longest follow-up in the included RCTs was 2.5 years and the long-term effectiveness of the BCM - Body Composition Monitor in this population is yet to be established.
- Overall risk of bias was Unclear or High in the majority of included trials, with only one trial assessed as Low risk of bias.
- Units of measurement of some reported outcomes (e.g. hospitalisation) varied across trials and hampered the possibility of synthesising data.
- Some clinically relevant outcomes (e.g., incidence of cardiovascular events, residual renal function, achievement of target weight) were lacking or not consistently reported.

- We were unable to conduct the planned subgroup analyses but were able to make some comparisons of the outcomes of people having haemodialysis and those having peritoneal dialysis.
- The majority of RCTs excluded patients with amputations, cardiac pacemakers and defibrillators. These exclusions further limit the generalisability of current findings.
- Frequency of assessment using the BCM - Body Composition Monitor varied across trials and the optimal frequency of assessment is yet to be determined
- With respect to the economic model, baseline risks of CV hospitalisation had to be estimated as a set proportion of all-cause hospitalisation.
- Plausible effects in the cost-effectiveness model had to be informed by linking effects on surrogate end points to effects on final health outcomes.
- To keep the model manageable and in-keeping with the available data, some simplifying assumptions had to be made
    - Mortality and hospitalisation rates could not be linked to certain explanatory variables and event histories in the model, limiting our ability to explore heterogeneity in cost-effectiveness.
    - It was difficult to capture the long-term health state utility impact of recurrent hospitalisation events, partly due to constraints of the Markov modelling approach, and partly due to a lack of available data to inform the cost and utility impact of recurrent events.
- With many differences between adults and paediatric dialysis patients, and a complete lack of evidence for the effectiveness of bioimpedance guided fluid management in children, we were not able to assess cost-effectiveness in children. As well as requiring data on clinical effectiveness in children, a different baseline cost-effectiveness model would also be required, including different mortality and hospitalisation rates, different costs and utilities, and greater structural complexity to allow for extrapolation over a much longer time horizon; e.g. allowing for multiple transplants over the lifetime of the cohort.
- We were able to obtain a reasonable estimate of what it would cost to monitor children with bioimpedance spectroscopy based on lower throughput in paediatric centres and the need for more frequent testing. Whilst the estimated

cost is substantially higher than in adults, the cost-effectiveness findings in adults were not found to be sensitive to increases in the monitoring cost to this level.

5.3 Uncertainties

- Current evidence focuses exclusively on the use of BCM - Body Composition Monitor and not on other multiple frequency bioimpedance devices.
- The identified RCTs were all conducted outside the UK and the applicability of the results to the UK population is uncertain, with the greatest uncertainty relating to the comparability of the standard clinical assessments in these trials.
- Included studies focused exclusively on adult populations. Therefore, our findings are not generalisable to paediatric populations.
- The main uncertainty in the cost-effectiveness modelling relates to the plausibility of the modelled effects, which were extrapolated from effects on surrogate endpoints (hydration status, arterial stiffness and blood pressure) using other external sources of evidence. Critically, there were no ideal sources of evidence to link intervention induced changes in the relevant surrogates to effects on mortality and hospitalisation rates. Therefore, possible effects were informed by reference to cross-sectional prognostic studies, leading to uncertainty in the robustness of the cost-effectiveness findings.

6 References

1. *Chronic kidney disease*: NHS Choices; 2016. http://www.nhs.uk/conditions/Kidney-disease-chronic/Pages/Introduction.aspx [Accessed November 2016]

2. *Choosing the treatment that's right for you*. Guy's and St Thomas' NHS Foundation Trust and King's College Hospital Foundation Trust: mykidney; 2016. http://www.mykidney.org/TreatmentOptions/Your-Options-1-3.aspx [Accessed November 2016]

3. *Dialysis*: NHS Choices; 2015. URL: http://www.nhs.uk/conditions/Dialysis/Pages/Introduction.aspx [Accessed November 2016]

4. *The BCM - Body Composition Monitor for managing fluid in people having dialysis. NICE advice MIB41*. London: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/advice/mib41 [Accessed November 2016]

5. *Chronic kidney disease in adults: assessment and management. NICE guidelines CG182*. London: National Institute for Health and Care Excellence; 2015. URL:https://www.nice.org.uk/guidance/cg182 [Accessed November 2016]

6. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;**139:**137-47.

7. Ley, Liu JJ, Wong DSM, Tan SHC, Tavintharan S, Sum CF, et al. Association of Circulating Irisin with Renal Function and Body Composition in Type 2 Diabetes Mellitus. *Annals of the Academy of Medicine Singapore Conference: Singapore Health and Biomedical Congress, SHBC* 2013;**42**.

8. Stevens LA, Levey AS. Current Status and Future Perspectives for CKD Testing. *Am J Kidney Dis* 2009;**53:**S17-S26.

9. Vassalotti JA, Stevens LA, Levey AS. Testing for Chronic Kidney Disease: A Position Statement From the National Kidney Foundation. *Am J Kidney Dis* 2007;**50:**169-80.

10. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985;**33:**278-85.

11. Parmar MS. Chronic renal disease. *BMJ* 2002;**325:**85-90.

12. Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;**379:**165-80.

13. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National

Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2007;**18:**2205-13.

14. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: A cohort study. *Lancet* 2010;**376:**2096-103.

15. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al. CKD and Risk of Hospitalization and Death With Pneumonia. *Am J Kidney Dis* 2009;**54:**24-32.

16. Wilhelm-Leen ER, Hall YN, Tamura MK, Chertow GM. Frailty and Chronic Kidney Disease: The Third National Health and Nutrition Evaluation Survey. *Am J Med* 2009;**122:**664-71.e2.

17. *Chronic kidney disease (stage 5): peritoneal dialysis. NICE guidelines CG125*. London: National Institute for Health and Care Excellence; 2011. URL: https://www.nice.org.uk/guidance/cg125 [Accessed November 2016]

18. *Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure. NICE technology appraisal guidance TA48*. London: National Institute for Health and Care Excellence; 2002. URL: https://www.nice.org.uk/guidance/ta48 [Accessed November 2016]

19. Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: An overview. *J Am Soc Nephrol* 1999;**10:**392-403.

20. MacNeill SJ, Casula A, Shaw C, Castledine C. UK Renal Registry 18th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2014: National and Centre-specific Analyses. *Nephron* 2016;**132** Suppl 1**:**41-68.

21. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. *Hypertension* 2010;**56:**512-7.

22. Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V. Importance of normohydration for the long-term survival of haemodialysis patients. *Nephrol Dial Transplant* 2012;**27:**2404-10.

23. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. *Kidney Int* 2014;**86:**489-96.

24. Kim JS, Yang JW, Chai MH, Lee JY, Park H, Kim Y, et al. Copeptin in Hemodialysis Patients with Left Ventricular Dysfunction. *Yonsei Med J* 2015;**56:**976-80.

25. Paniagua R, Ventura MDJ, Avila-Diaz M, Hinojosa-Heredia H, Mendez-Duran A, Cueto-Manzano A, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant* 2010;**25:**551-7.

26. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009;**24:**1574-9.

27. Aguiar PV, Santos O, Teixeira L, Silva F, Azevedo P, Vidinha J, et al. Overhydration prevalence in peritoneal dialysis - A 2 year longitudinal analysis. *Nefrologia* 2015;**35:**189-96.

28. Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. *Ped Nephrol* 2010;**25:**329-34.

29. Oei EL, Fan SL. Practical aspects of volume control in chronic kidney disease using whole body bioimpedance. *Blood Purif* 2015;**39:**32-6.

30. Ozkahya M, Ok E, Cirit M, Aydin S, Akcicek F, Basci A, et al. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998;**13:**1489-93.

31. Ozkahya M, Ok E, Toz H, Asci G, Duman S, Basci A, et al. Long-term survival rates in haemodialysis patients treated with strict volume control. *Nephrol Dial Transplant* 2006;**21:**3506-13.

32. Tsai YC, Chiu YW, Tsai JC, Kuo HT, Hung CC, Hwang SJ, et al. Association of fluid overload with cardiovascular morbidity and all-cause mortality in stages 4 and 5 CKD. *CJASN* 2015;**10:**39-46.

33. Jansen MA. *Renal function, adequacy parameters and patient outcomes in pre-dialysis and dialysis patients*: University of Amsterdam; 2007. URL: http://dare.uva.nl/record/1/385529 [Accessed November 2016]

34. Dasgupta I, Farrington K, Davies SJ, Davenport A, Mitra S. UK National Survey of Practice Patterns of Fluid Volume Management in Haemodialysis Patients: A Need for Evidence. *Blood Purif* 2016;**41:**324-31.

35. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol* 2015;**26:**724-34.

36. Stefansson BV, Brunelli SM, Cabrera C, Rosenbaum D, Anum E, Ramakrishnan K, et al. Intradialytic hypotension and risk of cardiovascular disease.*: CJASN* 2014;**9:**2124-32.

37. Zhou YL, Liu J, Sun F, Ma LJ, Han B, Shen Y, et al. Calf bioimpedance ratio improves dry weight assessment and blood pressure control in hemodialysis patients. *Am J Nephrol* 2010;**32:**109-16.

38. Termorshuizen F, Dekker FW, Van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative Contribution of Residual Renal Function and Different Measures of Adequacy to Survival in Hemodialysis Patients: An analysis of the Netherlands

Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 2004;**15:**1061-70.

39. Vilar E, Farrington K. Emerging Importance of Residual Renal Function in End-Stage Renal Failure. *Semin Dial* 2011;**24:**487-94.

40. Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. *Nephron* 2016;**132** Suppl 1**:**111-44.

41. *Hospital Episode Statistics. Hospital Outpatient Activity 2014-15*: Health and Social Care Infomation Centre; 2015. URL: http://www.hscic.gov.uk/article/2021/Website-Search?productid=19879&q=title%3a+%22hospital+outpatient+activity%22&sort=Most+recent&size=10&page=1&area=both#top [Accessed November 2016]

42. Henderson LW. Symptomatic hypotension during hemodialysis. *Kidney Int* 1980;**17:**571-6.

43. Wystrychowski G, Levin NW. Dry weight: sine qua non of adequate dialysis. *Adv Chron Kidney Dis* 2007;**14:**e10-6.

44. Spiegel DM, Bashir K, Fisch B. Bioimpedance resistance ratios for the evaluation of dry weight in hemodialysis. *Clin Nephrol* 2000;**53:**108-14.

45. Jaffrin MY, Morel H. Body fluid volumes measurements by impedance: A review of bioimpedance spectroscopy (BIS) and bioimpedance analysis (BIA) methods. *Med Eng Physic* 2008;**30:**1257-69.

46. Kim YJ, Jeon HJ, Kim YH, Jeon J, Ham YR, Chung S, et al. Overhydration measured by bioimpedance analysis and the survival of patients on maintenance hemodialysis: a single-center study. *Kidney Res Clin Pract* 2015;**34:**212-8.

47. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. *Clin Nutr* 2004;**23:**1226-43.

48. Abbas SR, Zhu F, Levin NW. Bioimpedance can solve problems of fluid overload. *J Renal Nutr* 2015;**25:**234-7.

49. *Bioimpedance Devices for the Assessment of Body Fluid Volume for Patients Undergoing Dialysis: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update*: Canadian Agency for Drugs and Technologies in Health; 2015. URL: www.cadth.ca/sites/default/files/pdf/htis/aug-2015/RC0695-Bioimpedance%20Final.pdf [Accessed November 2016]

50. Zhu F, Kuhlmann MK, Kaysen GA, Sarkar S, Kaitwatcharachai C, Khilnani R, et al. Segment-specific resistivity improves body fluid volume estimates from

bioimpedance spectroscopy in hemodialysis patients. *J Appl Physiol* 2006;**100:**717-24.

51. Nescolarde L, Garcia-Gonzlez MA, Rosell-Ferrer J, Doate T, Querfeld U. Thoracic versus whole body bioimpedance measurements: The relation to hydration status and hypertension in peritoneal dialysis patients. *Physiol Measure* 2006;**27:**961-71.

52. *BCM - Body Composition Monitor*. Bad Homburg, Germany: Fresenius Medical Care; 2016. URL: http://www.bcm-fresenius.com/ [Accessed November 2016]

53. Chamney PW, Wabel P, Moissl UM, Muller MJ, Bosy-Westphal A, Korth O, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr* 2007;**85:**80-9.

54. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Measure* 2006;**27:**921-33.

55. Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009;**27:**75-80.

56. Zaloszyc A, Fischbach M, Schaefer B, Uhlmann L, Salomon R, Krid S, et al. Body composition monitoring-derived urea distribution volume in children on chronic hemodialysis. *Ped Nephrol* 2016;**31:**991-9.

57. Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, Kanbay M, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2014;**64:**111-8.

58. Ponce P, Pham J, Gligoric-Fuerer O, Kreuzberg U. Fluid management in haemodialysis: Conventional versus Body Composition Monitoring (BCM) supported management of overhydrated patients. *Port J Nephrol Hypert* 2014;**28:**238-48.

59. Di Gioia C, Gallar P, Cobo G, Garcia F, Oliet A, Rodrigues A, et al. Body Composition Changes in Hemodialysis Patients: Implications for Prognosis. *Enliven: Nephrol Renal Stud* 2014;**1:**001.

60. Luo YJ, Lu XH, Woods F, Wang T. Volume control in peritoneal dialysis patients guided by bioimpedance spectroscopy assessment. *Blood Purif* 2011;**31:**296-302.

61. *Multiscan 5000 Bioelectrical Impedance Spectroscopy*. Isle of Man: Bodystat; 2016. URL:http://www.bodystat.com/products/multiscan [Accessed November 2016]

62. *Bioscan 920-II*. Rayleigh, Essex: Maltron International Ltd; 2016. URL: http://maltronint.com/products/bioscan920-2.php [Accessed November 2016]

63. *Assessment of fluid status using Body Composition Monitoring (BCM) Implementation Pack*: NHS Technology Adoption Centre; 2011. http://webarchive.nationalarchives.gov.uk/20130701143131/http://www.ntac.nhs.uk/Publications/Assessment_of_fluid_status_using_Body_Composition_Monitoring_(BCM)_Implementation_Pack.aspx [Accessed November 2016]

64. *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care [document on the Internet]*. University of York 2009. URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm [Accessed November 2016]

65. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [document on the Internet]* 2011. Available from: URL: http://www.cochrane-handbook.org/ [Accessed November 2016]

66. *NICE Diagnostic Assessment Programme manual* London: National Institute for Health and Care Excellence; 2011. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf [Accessed November 2016]

67. Allinovi M, Saleem MA, Burgess O, Armstrong C, Hayes W. Finding covert fluid: methods for detecting volume overload in children on dialysis. *Ped Nephrol* 2016;**10:**10.

68. Canpolat N, Caliskan S, Sever L, Tasdemir M, Ekmekci OB, Pehlivan G, et al. Malnutrition and its association with inflammation and vascular disease in children on maintenance dialysis. *Ped Nephrol* 2013;**28:**2149-56.

69. Zaloszyc A, Schaefer B, Schaefer F, Krid S, Salomon R, Niaudet P, et al. Hydration measurement by bioimpedance spectroscopy and blood pressure management in children on hemodialysis. *Ped Nephrol* 2013;**28:**2169-77.

70. Huan-Sheng C, Yeong-Chang C, Ming-Hsing H, Fan-Lieh T, Chu-Cheng L, Tsai-Kun W, et al. Application of bioimpedance spectroscopy in Asian dialysis patients (ABISAD-III): a randomized controlled trial for clinical outcomes. *Int Urol Nephrol* 2016;**12:**12.

71. Hur E, Usta M, Toz H, Asci G, Wabel P, Kahvecioglu S, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis* 2013;**61:**957-65.

72 Parmar MS, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.

73. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: A meta-analysis. *JAMA* 1993;**269:**898-903.

74. Chen HS, Lee KC, Cheng CT, Hou CC, Liou HH, Lin CJ, et al. Application of Bioimpedance Spectroscopy in Asian Dialysis Patients (ABISAD): Serial follow-up and dry weight evaluation. *Clin Kidney J* 2013;**6:**29-34.

75. Onofriescu M, Mardare NG, Segall L, Voroneanu L, Cusai C, Hogas S, et al. Randomized trial of bioelectrical impedance analysis versus clinical criteria for guiding ultrafiltration in hemodialysis patients: effects on blood pressure, hydration status, and arterial stiffness. *Int Urol Nephrol* 2012;**44:**583-91

76. O'Lone EL, Visser A, Finney H, Fan SL. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. *Nephrol Dial Transplant* 2014;**29:**1430-7

77. Santhakumaran T, Samad N, Fan SL. Hydration status measured by BCM: A potential modifiable risk factor for peritonitis in patients on peritoneal dialysis. *Nephrology* 2016;**21:**404-9

78. Oei E, Paudel K, Visser A, Finney H, Fan SL. Is overhydration in peritoneal dialysis patients associated with cardiac mortality that might be reversible? *World J Nephrol* 2016;**5:**448-54.

79. Kim S, Sung J, Jung ES, Park HC, Lee H, Chin HJ, et al. Hemodynamic and biochemical benefits of the objective measurement of fluid status in hemodialysis patients. *Tohoku J Exp Med* 2012;**228:**125-33.

80. Castellano S, Palomares I, Molina M, Perez-Garcia R, Aljama P, Ramos R, et al. Clinical, analytical and bioimpedance characteristics of persistently overhydrated haemodialysis patients. *Nefrologia* 2014;**34:**716-23

81. Hoppe K, Schwermer K, Klysz P, Radziszewska D, Sawatiuk P, Baum E, et al. Cardiac Troponin T and Hydration Status as Prognostic Markers in Hemodialysis Patients. *Blood Purif* 2015;**40:**139-45.

82. Onofriescu M, Siriopol D, Voroneanu L, Hogas S, Nistor I, Apetrii M, et al. Overhydration, cardiac function and survival in hemodialysis patients. *PLoS ONE* 2015;**10** (8)

83 *Probing the Dry Weight (DW) by Bioimpedance (BIA): Which is the Gold Standard Between Clinical DW and BIA DW (REST) NCT02446535*: ClinicalTrials.gov; 2015. https://clinicaltrials.gov/ct2/show/NCT02446535?term=NCT02446535&rank=1 [Accessed November 2016]

84 *Fluid Management Guided by Bioimpedance Analysis in Peritoneal Dialysis(PD) Patients.* U.S. National Institutes of Health: Clinical Trials.gov; 2016. https://clinicaltrials.gov/ct2/show/NCT02000128?term=NCT02000128&rank=1 [Accessed November 2016]

85. *Control Of Fluid Balance Guided by Body Composition Monitoring in Patients on PeritoneAl dialySiS (COMPASS)*: Clinical trials.gov; 2014.

https://clinicaltrials.gov/ct2/show/NCT01887262?term=NCT01887262&rank=1 [Accessed November 2016]

86. *Bio-Impedance Spectroscopy To maintain Renal Output: a randomised controlled trial* World Health Organisation: International Clinical TRials Registry Platform; 2016. http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN11342007 [Accessed November 2016]

87. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant* 2012;**27:**iii73-iii80.

88. Kirby L, Vale L. Dialysis for end-stage renal disease. Determining a cost-effective approach. *Int J Technol Assess Health Care* 2001;**17:**181-9.

89. Treharne C, Liu FX, Arici M, Crowe L, Farooqui U. Peritoneal dialysis and in-centre haemodialysis: a cost-utility analysis from a UK payer perspective. *Appl Health Econ Health Policy* 2014;**12:**409-20.

90. *Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia Clinical Guidance CG157*. London: National Institute for Health and Care Excellence; 2014. https://www.nice.org.uk/guidance/cg157 [Accessed November 2016]

91. Caskey F, Castledine C, Dawnay A, Farrington K, Fogarty D, Fraser S, et al. *UK Renal Registry 18th Annual Report of the Renal Association*. Bristol: Renal Association; 2015. https://www.renalreg.org/reports/2015-eighteenth-annual-report/ [Accessed November 2016]

92. Li B, Cairns J, Fotheringham J, Ravanan R, Group AS. Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation. *Eur J Health Econ* 2015;**17:**659-68.

93. Moissl U, Arias-Guillen M, Wabel P, Fontsere N, Carrera M, Campistol JM, et al. Bioimpedance-guided fluid management in hemodialysis patients. *Clinical: CJASN* 2013;**8:**1575-82.

94. *ERA-EDTA Registry Annual Report 2013*. Amsterdam: ERA-EDTA, Academic Medical Center, Department of Medical Informations; 2015. https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2013.pdf [Accessed November 2016]

95. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol* 2011;**11:**139.

96. Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. *Eur J Cancer* 2006;**42:**2867-75.

97. Karim A, Farrugia D, Cheshire J, Mahboob S, Begaj I, Ray D, et al. Recipient age and risk for mortality after kidney transplantation in England. *Transplantation* 2014;**97:**832-8.

98. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011;**11:**2093-109.

99. *Annual report on kidney transplantation. Report for 2013/2014*: NHS Blood and Transplant; 2014. http://www.odt.nhs.uk/pdf/organ_specific_report_kidney_2014.pdf [Accessed November 2016]

100. Lafrance JP, Rahme E, Iqbal S, Elftouh N, Laurin LP, Vallee M. Trends in infection-related hospital admissions and impact of length of time on dialysis among patients on long-term dialysis: a retrospective cohort study. *CMAJ open* 2014;**2:**E109-14.

101 Quinn RR, Ravani P, Zhang X, Garg AX, Blake PG, Austin PC, et al. Impact of modality choice on rates of hospitalization in patients eligible for both peritoneal dialysis and hemodialysis. *Periton Dial Int* 2014;**34:**41-8.

102 Rayner HC, Pisoni RL, Bommer J, Canaud B, Hecking E, Locatelli F, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004;**19:**108-20.

103. Van Biesen W, Williams JD, Covic AC, Fan S, Claes K, Lichodziejewska-Niemierko M, et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. *PLoS ONE* 2011;**6:**e17148.

104. van Biesen W, Claes K, Covic A, Fan S, Lichodziejewska-Niemierko M, Schoder V, et al. A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. *Nephrol Dial Transplant* 2013;**28:**2620-8.

105. Badve SV, Palmer SC, Strippoli GF, Roberts MA, Teixeira-Pinto A, Boudville N, et al. The Validity of Left Ventricular Mass as a Surrogate End Point for All-Cause and Cardiovascular Mortality Outcomes in People With CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis* 2016;**68:**554-63.

106. Verbeke F, Van Biesen W, Honkanen E, Wikstrom B, Jensen PB, Krzesinski JM, et al. Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. *CJASN* 2011;**6:**153-9.

107. Heerspink HJL, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009;**373:**1009-15.

108. Agodoa L, Anderson C, Asseibergs F, Baigent C, Black H, Brenner B, et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertension* 2007;**25:**951-8.

109. Wabel P, Moissl U, Chamney P, Jirka T, Machek P, Ponce P, et al. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrol Dial Transplant* 2008;**23:**2965-71.

110. Flythe JE. Ultrafiltration Rate Clinical Performance Measures: Ready for Primetime? *Semin Dial* 2016;**29:**425-34.

111. Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. *Kidney Int* 2016;**90:**262-71.

112. Baek SH, Oh KH, Kim S, Kim DK, Joo KW, Oh YK, et al. Control of fluid balance guided by body composition monitoring in patients on peritoneal dialysis (COMPASS): study protocol for a randomized controlled trial. *Trials [Electronic Resource]* 2014;**15:**432.

113 Grima DT, Bernard LM, Dunn ES, McFarlane PA, Mendelssohn DC. Cost-effectiveness analysis of therapies for chronic kidney disease patients on dialysis: a case for excluding dialysis costs. *Pharmacoeconomics* 2012;**30:**981-9.

114. Davis S. *Assessing technologies that are not cost-effective at a zero price*. School of Health and Related Research, University of Sheffie: NICE Decision Support Unit; 2014. http://www.nicedsu.org.uk/Not_CE_at_zero_price_FINAL_14.07.14.pdf [Accessed November 2016]

115. *Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Technology Appraidal 117*. London: National Institute for Health and Care Excellence; 2007. https://www.nice.org.uk/guidance/ta117 [Accessed November 2016]

116. *NHS reference costs 2014-2015*. London: UK Department of Health; 2015. URL: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 [Accessed November 2016]

117. *Kidney transplantation (adults) - immunosuppressive therapy (review of TA 85) [ID456] GID-TAG348*. London: National Institute for Health and Clinical Excellence; 2015. https://www.nice.org.uk/guidance/GID-TAG348/documents/html-content [Accessed November 2016]

118. *British National Formulary* Medicines Complete; 2016. https://www.medicinescomplete.com/mc/bnf/current/index.htm [Accessed November 2016]

119. Tan BK, Yu Z, Fang W, Lin A, Ni Z, Qian J. Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. *Kidney Int* 2016;**89:**487-97.

120. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int* 2007;**72:**92-9.

121. Curtis L. *Unit Costs of Health and Social Care 2015*. Canterbury: Personal Social Services Research Unit.; 2015. URL: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php [Accessed November 2016]

122 Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. *Value Health* 2008;**11:**733-41.

123 Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. *PLoS Med* 2012;**9:**e1001307.

124. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*;**13:**509-18.

125. *NICE DSU Technical Support Document 11: Alternatives to EQ-5D for generating health state utilitiy values*. School of Health and Related Rese Support Unit; 2011. http://www.nicedsu.org.uk/TSD11%20Alternatives%20to%20EQ-5D_final.pdf [Accessed November 2016]

7 Appendices

Appendix 1 Search strategies

Multiple frequency bioimpedance devices for fluid management in people with CKD having dialysis

Clinical effectiveness

Database: Embase Classic+Embase <1947 to 2016 Week 40>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to 10th October

OVID Multi-file Search URL: https://shibboleth.ovid.com/

Date of Search: 10th October 2016

---

1 exp Renal Insufficiency, Chronic/ use ppez

2 exp chronic kidney disease/ use emcz

3 exp chronic kidney failure/ use emcz

4 ckd.tw,kw.

5 (chronic adj3 (kidney or renal)).tw,kw.

6 or/1-5

7 exp renal dialysis/ use ppez

8 exp renal replacement therapy/ use emcz

9 (haemodialysis or hemodialysis or dialysis).kw,tw.

10 or/7-9

11 6 and 10

12 bioimpedance.tw,kw.

13 bioelectric$ impendance.tw,kw.

14 body composition monitor$.tw,kw.

15 bioscan$.tw,kw.

16 bio scan$.tw,kw.

17 multiscan$.tw,kw.

18 multi scan$.tw,kw.

19 inbody.tw,kw.

20 or/12-19

21 10 and 20

22 hypervol?emi?.tw,kw.

23 euvol?emi?.tw,kw.

24 hypovol?emi?.tw,kw.

25 (fluid adj3 (status or overload or monitor$ or level? or balance or imbalance)).tw,kw.

26 (hydration adj3 (status or monitor$)).tw,kw.

27 ((under or over) adj3 hydration).tw,kw.

28 underhydrat$.tw,kw

29 overhydrat$.tw,kw.

30 normohydrat$.tw,kw.

31 ((dry or target) adj weight).tw,kw.

32 ultrafiltration volume.tw,kw.

33 or/22-32

34 11 and 33

35 21 or 34

36 (editorial or comment or note or letter).pt.

37 35 not 36

38 exp animals/ not humans/ use ppez

39 nonhuman/ not human/ use emcz

40 37 not 38 use ppez

41 37 not 39 use emcz

42 40 or 41

43 remove duplicates from 42

Science Citation Index (1970 - 27th June 2016)

ISI Web of Knowledge URL: http://wok.mimas.ac.uk/
Date of search: 27th June 2016

1 TS=(haemodialysis or hemodialysis or dialysis)

2 TS=bioimpedance

3 TS=bioelectric* impendance

4 TS=body composition monitor$*

5 TS= (bioscan$* or bio scan*)

6 TS=(multiscan* or multi scan*)

7 TS=inbody

8 #2 or #3 or #4 or #5 or #6 or #7

#9 #1 and #8

The Cochrane Library

Cochrane Database of Systematic Reviews : Issue 6 of 12, June 2016

Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2016

URL: http://www3.interscience.wiley.com/
Date of search:27th June 2016

#1 MeSH descriptor: [Renal Dialysis] explode all trees

#2 haemodialysis or hemodialysis or dialysis:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 bioimpedance.:ti,ab,kw (Word variations have been searched)

#5 bioelectric* impendance.ti,ab,kw

#6 body composition monitor*.ti,ab,kw

#7 (bioscan* or bio scan*) .ti,ab,kw.

#8 (multiscan* or multi scan*) .ti,ab,kw

#9 inbody.ti,ab,kw

#10 #4 or #5 or #6 or #7 or #8 or #9

#11 #3 and #10

DARE December 2014

Centre for Reviews & Dissemination URL:http://nhscrd.york.ac.uk/welcome.htm

Date of search: 27th June 2016

1	MeSH DESCRIPTOR Renal Dialysis EXPLODE ALL TREES IN DARE
2	(haemodialysis) OR (hemodialysis) OR (dialysis)
3	#1 OR #2
4	(bioimpedance) OR (impedance)
5	(body composition monitor*) OR (bioscan*) OR (bio scan*)
6	(inbody) OR (multiscan*) OR (multi scan*)
7	#4 OR #5 OR #6
8	#3 AND #7

Additional Conference Proceedings

ERA/EDTA Congress 2014, Amsterdam, 31 May-3rd June

ERA/EDTA Congress 2015, London, 28- 31 May

Kidney Week (JASN) Am Soc Nephrol 2014 Phildelphia, 11-16 Nov

Kidney Week (JASN) Am Soc Nephrol 2015 San Diego, 3 - 8 Nov

Annual Dialysis Conference 2014 Atlanta, 8-11 Feb

Annual Dialysis Conference 2015 New Orleans,31 Jan - 3 Feb

Annual Dialysis Conference 2016 Seattle, 27 Feb – 1 March

Clinical Trials (June 2016)

URL: http://clinicaltrials.gov/ct/gui/c/r

Date of search: 4th July 2016

Bioimpendance AND dialysis

or

Bioimpendance AND hemodialysis

International Clinical Trials Registry Platform (ICTRP) (June 2016)

World Health Organization URL: http://www.who.int/ictrp/en/

Date of search: 4th July 2016

Bioimpendance AND dialysis

or

Bioimpendance AND hemodialysis

EU Clinical Trials Register (June 2016)

URL: https://www.clinicaltrialsregister.eu/

Date of search: 4th July 2016

Bioimpedance

BCM Validation studies

Database: Embase Classic+Embase <1947 to 2016 Week 39>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

OVID Multi-file Search URL: https://shibboleth.ovid.com/

Date of search: 27th September 2016

1 exp Renal Insufficiency, Chronic/ use ppez
2 exp chronic kidney disease/ use emcz
3 exp chronic kidney failure/ use emcz
4 ckd.tw,kw.
5 (chronic adj3 (kidney or renal)).tw,kw.
6 or/1-5
7 exp renal dialysis/ use ppez
8 exp renal replacement therapy/ use emcz
9 (haemodialysis or hemodialysis or dialysis).kw,tw.
10 or/7-9
11 6 and 10
12 bioimpedance.tw,kw.

13 bioelectric$ impendance.tw,kw.
14 body composition monitor$.tw,kw.
15 bioscan$.tw,kw.
16 bio scan$.tw,kw.
17 multiscan$.tw,kw
18 multi scan$.tw,kw.
19 inbody.tw,kw.
20 or/12-19
21 10 and 20
22 hypervol?emi?.tw,kw.
23 euvol?emi?.tw,kw.
24 hypovol?emi?.tw,kw.
25 (fluid adj3 (status or overload or monitor$ or level? or balance or imbalance)).tw,kw
26 (hydration adj3 (status or monitor$)).tw,kw.
27 ((under or over) adj3 hydration).tw,kw.
28 underhydrat$.tw,kw.
29 overhydrat$.tw,kw.
30 normohydrat$.tw,kw.
31 ((dry or target) adj weight).tw,kw.
32 ultrafiltration volume.tw,kw.
33 or/22-32
34 validation studies/
35 measurement accuracy/
36 "reproducibility of results"/
37 (validation or validity).tw,kw.
38 (accuracy or accurate).tw,kw.
39 44 or 45 or 46 or 47 or 48
40 21 and 39
41 11 and 33 and 39
42 40 or 41
43 remove duplicates from 42

Cost Effectiveness

Database: Embase Classic+Embase <1947 to 2016 Week 27>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
OVID Multi-file Search URL: https://shibboleth.ovid.com/
Date of search: 5th July 2016

1 exp Renal Insufficiency, Chronic/ use ppez
2 exp *chronic kidney disease/ use emcz
3 exp *chronic kidney failure/ use emcz
4 ckd.tw,kw.
5 (chronic adj1 (kidney or renal)).tw,kw.
6 or/1-5
7 exp renal dialysis/ use ppez
8 exp renal replacement therapy/ use emcz
9 (haemodialysis or hemodialysis or dialysis).kw,tw.
10 or/7-9
11 6 and 10
12 exp "costs and cost analysis"/ use ppez
13 exp economic evaluation/ use emcz
14 economics/
15 health economics/ use emcz
16 exp health care cost/ use emcz
17 exp economics,hospital/ use ppez
18 exp economics,medical/ use ppez
19 economics,pharmaceutical/ use ppez
20 pharmacoeconomics/ use emcz
21 exp models, economic/ use ppez
22 exp decision theory/
23 monte carlo method/
24 markov chains/
25 exp technology assessment, biomedical/
26 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
27 economics model$.tw.
28 (economic$ or pharmacoeconomic$).tw.
29 (price or prices or pricing).tw.
30 budget$.tw.
31 (value adj1 money).tw.
32 (expenditure$ not energy).tw.
33 markov$.tw.
34 monte carlo.tw.
35 (decision$ adj2 (tree? or analy$ or model$)).tw.
36 or/12-35
37 (metabolic adj cost).tw.
38 ((energy or oxygen) adj (cost or expenditure)).tw.
39 36 not (37 or 38)
40 (letter or editorial or note or comment).pt.

41 39 not 40

42 11 and 41

43 remove duplicates from 42

HTA June 2016/NHS NEED December 2014

Centre for Reviews & Dissemination

URL:http://nhscrd.york.ac.uk/welcome.htm

Date of search: 5th July 2016

1 MeSH DESCRIPTOR Renal Dialysis EXPLODE ALL TREES IN NHSEED

2 (dialysis) OR (hemodialysis) OR (haemodialysis)

3 #1 OR #2

4 MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES IN NHSEED

5 (ckd) OR (chronic renal) OR (chronic kidney)

6 #4 OR #5

7 #3 AND #6

RePEc (Research Papers in Economics)
URL: http://repec.org/

dialysis | hemodialysis |haemodialysis | CKD | renal | kidney

Quality of Life/Utilities

Database: Embase Classic+Embase <1947 to 2016 Week 27>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Ovid Multifile Search URL: https://shibboleth.ovid.com/
Date of search: 8th July 2016

1 exp Renal Insufficiency, Chronic/ use ppez

2 exp chronic kidney disease/ use emcz

3 exp chronic kidney failure/ use emcz

4 ckd.tw,kw.

5 (chronic adj3 (kidney or renal)).tw,kw.

6 or/1-5

7 exp renal dialysis/ use ppez

8 exp renal replacement therapy/ use emcz

9 (haemodialysis or hemodialysis or dialysis).kw,tw.

10 or/7-9

11 6 and 10

12 quality adjusted life year/

13 "Value of Life"/ use ppez

14 (qaly? or qald? or qale? or qtime?).tw,kf.

15 (euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).tw,kf.

16 (eq-sdq or eqsdq).tw,kf.

17 (hye or hyes).tw,kf.

18 health$ year$ equivalent$.tw,kf.

19 (hui or hui1 or hui2 or hui3).tw,kf.

20 (quality adjusted or adjusted life year$).tw,kf.

21 disability adjusted life.tw,kf.

22 daly?.tw,kf.

23 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).tw,kf.

24 (multiattribute$ or multi attribute$).tw,kf.

25 (utility adj3 (score? or scoring or valu$ or measur$ or evaluat$ or scale? or instrument? or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure? or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).tw,kf.

26 utility.ab. /freq=2

27 utilities.tw,kf.

28 disutili$.tw,kf

29 (hsuv or hsuvs).tw,af.

30 (illness state$ or health state$).tw,kf.

31 (shortform$ or short form$).tw,kf.

32 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw,kf.

33 (sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).tw,kf.

34 (sf12 or sf 12 or sf twelve or sftwelve).tw,kf.

35 (sf16 or sf 16 or sf sixteen or sfsixteen).tw,kf.

36 (sf20 or sf 20 or sf twenty or sftwenty).tw,kf.

37 (15d or 15-d or 15 dimension).tw,kf.

38 standard gamble$.tw,kf.

39 (time trade off$ or time tradeoff$ or tto or timetradeoff$).tw,kf.

40 (case report or editorial or letter).pt.

41 case report/

42 or/12-39

43 42 not (40 or 41)

44 11 and 43

45 remove duplicates from 44

CEA Registry July 2016

URL https://research.tufts-nemc.org/cear4/default.asp

Date of search: 8th July 2016

Dialysis or hemodialysis or haemodialysis

ScHarrHud July 2016

URL: http://www.scharrhud.org/

Date of search: 8th July

Dialysis or hemodialysis or haemodialysis

WEBSITES CONSULTED

Agency for Healthcare Research and Quality URL: http://www.ahrq.gov/

American Society of Nephrology URL: https://www.asn-online.org/

Belgian Health Care Knowledge Centre (KCE): URL: https://kce.fgov.be/

Bodystat URL: http://www.bodystat.com/products/multiscan

Canadian Agency for Drugs and Technologies in Health URL: http://www.cadth.ca/

ERA-ETDA URL: http://era-edta.org/

French National Authority for Health (HAS) URL: http://www.has-sante.fr/

Fresenius Medical Care URL: http://www.bcm-fresenius.com/

Health Information & Quality Authority:URL: http://www.hiqa.ie/

Inbody Co Ltd. URL: http s://www.inbody.com/eng/product/body-composition-analyzer.aspx

Institute for Clinical and Economic Review URL: http://www.icer-review.org/

Institute for Quality and Efficiency in Health Care URL: https://www.iqwig.de/

Maltron URL: http://maltronint.com/industry/medical/dialysis.php

Medicines and Healthcare Products Regulatory Agency URL: http://www.mhra.gov.uk/

National Institute for Health and Care Excellence URL: http://www.nice.org.uk/

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) URL: https://www.niddk.nih.gov/

NHS Health Improvement Scotland URL: http://www.healthcareimprovementscotland.org/

US Food and Drug Administration URL: http://www.fda.gov/default.htm

Appendix 2 Characteristics of excluded non-randomised studies that focused on a paediatric population

Study details	Participant characteristics	Study aims	Main outcomes
First author, yr: Allinovi 2016 **Country:** UK **No of centres: 1** **Study design:** Prospective observational study **Device used:** BCM - Body Composition Monitor (in children > 2 years of age only (n=11) as the authors stated that the technique has not been validated with appropriate reference algorithms in children under 2 years of age)	**Enrolled, n:** 13 **Age, median (range), yrs:** 4.0 (0.8-14.0) **HD/PD, n:** 5/8 **Inclusion criteria:** All infants and children (age range 0–18 years) with ESRD receiving dialysis [haemodialysis (HD) or peritoneal dialysis (PD)] in our regional paediatric nephrology centre between 1 May 2015 and 1 October 2015 **Exclusion criteria:** Co-existent lung fibrosis, atelectasis, lymphangitis, interstitial lung disease, cardiac failure, acute respiratory distress syndrome or congenital cardiac anomalies	The aim of this study was to evaluate the accuracy of bioimpedance spectroscopy, echocardiographic assessment of inferior vena cava and lung ultrasound in detecting fluid overload in children with ESRD and to compare them with clinical measures, including weight, physical examination and systolic blood pressure.	The correlation of fluid overload by weight and the BCM - Body Composition Monitor measurement was reported as r=0.43 (p=0.2), although it is unclear which parameter(s) assessed by the device was used in the correlation.
First author, yr: Canpolat 2013 **Country:** Turkey **No of centres:** NR **Study design:** Cross-sectional **Device used:** BCM - Body Composition Monitor	**Enrolled, n:** 33 **Age, range, yrs:** 5.7 – 19.9 **HD/PD:** 15/18 **Inclusion criteria:** Patients aged 5–20 years who were on dialysis for at least 3 months **Exclusion criteria:** Patients with overt infections, acute inflammation or active vasculitis at the time of the study and those with congenital or structural heart disease or who were receiving anti-inflammatory	Examine the prevalence of malnutrition and its possible associations with inflammation and vascular disease in children on chronic dialysis	Mean RRF was 0.41 (0.60) mL/min/1.73m^2 in HD patients and 3.41 (2.52) mL/min/1.73m^2 in PD patients (p<0.001). Fat mass, as assessed by the BCM - Body Composition Monitor, was significantly lower in patients than in controls (20.6% vs 24.6%, p=0.048).

Study details	Participant characteristics	Study aims	Main outcomes
	medications, such as corticosteroids and aspirin		
First author, yr: Zaloszyc 2013, Zaloszyc 2016 **Country:** Germany & France **No of centres:** 3 **Study design:** Retrospective **Device used:** BCM - Body Composition Monitor	**Enrolled, n:** 23 **Age, mean (SD), yrs:** 13.9 (5.1) **HD/PD:** 23/0 **Inclusion criteria:** Age of <20 years, on stable HD for at least 3 months, able to cooperate with BCM measurements and devoid of severe malnutrition, defined as a BMI of <2.5 standard deviation score **Exclusion criteria:** NR	To assess the current practice of clinical estimate of hydration status and BP control in children on chronic HD, the frequency of hypertension and its correlation with individual patient hydration status measured by means of BCM were evaluated. In addition, the impact of dialysis prescription on BP control, considering Napl, the prescribed NaD, and the achieved dry weight was evaluated. The urea distribution volume determined by BCM was compared to that obtained from four different anthropometric formulas of which only the Morgenstern equation has been validated in children on PD	Mean (SD) pre-dialytic ROH was 6.3 (7.1)% (range -6.1 to +21%). Of the total 463 dialysis sessions assessed, fifty two sessions (11.2%) were assessed as being moderately overhydrated (i.e. mean ROH > 15%), of which 5.6% of sessions showed pre- and post-HD hypertension; 21% of sessions were in the range +7 to +15%, with 26.8% of sessions having pre- and post-HD hypertension; and 62.4% of sessions were classed as normohydrated (i.e. mean ROH -7 to +7%), of which 20% involved pre- and post-HD hypertension. Urea distribution volume as determined by the BCM - Body Composition Monitor was in agreement with the Morgenstern anthropometric equation

Abbreviations: ESRD, End stage renal disease; HD, Haemodialysis; PD, Peritoneal dialysis; NR, Not reported; RRF, Residual renal function; SD, standard deviation; Napl, plasma sodium; NaD, dialysate sodium concentration; ROH, Relative overhydration; BMI, Body mass index

Appendix 3 Data extraction form: details of outcomes extracted

Data extraction section	**Information provided in each section**								
Study characteristics 1	Publication status	Study design	Country/ies	No of centres	Recruitment method	Allocation method	Study dates		
Study characteristics 2	Secondary outcomes reported	Adverse events reported	Study power & statistical analysis	Funding source					
Intervention characteristics	Study ID	Intervention & comparator names [one per row]	Full details	Length of follow-up					
Participant characteristics	Study ID	Total/ intervention/ comparator [one per row]	Enrolled, n	Randomised, n	Analysed, n	Lost to follow up, n	Lost to follow up, reasons	Age (years), mean (SD); p-value if reported	Sex, male: female; p-value if reported
	BMI (kg/m^2)	Weight (kg), mean (SD)	Dialysis modality	Dialysis vintage (months), mean (SD)	Diabetes, n (%)	Anti-hypertensive medication, n (%)	Dry weight (kg), mean (SD)	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)
	Cause of ESRD, n (%)	Presence of LVH	LVMI (g/m^2)	OH (L), mean (SD)	TBW (L), mean (SD)	ECW (L), mean (SD)	ICW (L), mean (SD)	E/I, mean (SD)	Lean tissue index (kg/m^2)
	Fat tissue mass	Comorbid conditions							

Intermediate outcomes	Study ID	Total/ intervention/ comparator [one per row]	No of haemodialysis sessions	Length of haemodialysis sessions	No of unplanned hospital visits/ admissions due to FO or dehydration	Use of anti-hypertensive medication	Incidence of anaemia	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)
	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Incidence of overhydration	Incidence of underhydration	Change of dialysis modality due to FO	Adherence with recommended fluid intake	Hydration status	Relative hydration status
Clinical outcomes	Study ID	Total/ intervention/ comparator [one per row]	Incidence of CV events (incl stroke & heart attack)	Mortality	Residual renal function	Incidence of oedema	Incidence of peritonitis	Adverse effects associated with hypotensive episodes (incl cramps, fatigue, diarrhoea, nausea, dizziness, fainting)	
Patient reported outcomes	Study ID	Post-dialysis recovery time	Fatigue	HRQoL					
NRS outcomes	Study ID	Summary of outcomes/conclusions	Any other information						

Risk of Bias RCT	Adequate sequence generation?	Allocation concealment?	Blinding: participants?	Blinding: outcome assessment? [report each outcome separately]	Incomplete outcome data addressed? [report each outcome separately]	Free of selective reporting?	Other sources of bias?		
Risk of Bias NRS	Were participants a representative sample selected from a relevant patient population?	Were the inclusion/exclusion criteria of participants clearly described?	Were participants entering the study at a similar point in their disease progression, i.e. disease severity?	Was selection of patients consecutive?	Was data collection undertaken prospectively?	Were the groups comparable on demographic characteristics and clinical features?	Was the intervention (and comparison) clearly defined?	Was the intervention undertaken by an experienced person?	Was the setting appropriate?
	Were the staff, place and facilities where the patients were treated appropriate for performing the procedure?	Were any of the important outcomes considered?	Were objective (valid and reliable) outcome measures used?	Was the assessment of main outcomes blind?	Was follow-up long enough to detect important effects on outcomes of interest?	Was information provided on non-respondents, dropouts, etc?	Did the withdrawals, dropouts, etc have similar characteristics as those who completed the study?	Was length of follow-up similar between comparison groups?	Were the important prognostic factors identified, e.g. age, duration of disease, disease severity?
	Were the analyses adjusted for confounding factors?								

Appendix 4 Risk of bias form: RCTs (Cochrane risk of bias tool)

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix 5 Risk of bias form: non-randomised studies

Criteria	Yes	No	Unclear	Comments
1. Were participants a representative sample selected from a relevant patient population?				
2. Were the inclusion/exclusion criteria of participants clearly described?				
3. Were participants entering the study at a similar point in their disease progression, i.e. severity of disease?				
4. Was selection of patients consecutive?				
5. Was data collection undertaken prospectively?				
6. Were the groups comparable on demographic characteristics and clinical features?				
7. Was the intervention (and comparison) clearly defined?				
8. Was the intervention undertaken by someone experienced at performing the procedure?				
9. Were the staff, place, and facilities where the patients were treated appropriate for performing the procedure? (E.g. access to back-up facilities in hospital or special clinic)				
10. Were any of the important outcomes considered, i.e. on clinical effectiveness, cost-effectiveness, or learning curves?				
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?				
12. Was the assessment of main outcomes blind?				
13. Was follow-up long enough to detect important effects on outcomes of interest?				
14. Was information provided on non-respondents, dropouts?				
15. Was length of follow-up similar between comparison groups				
16. Were the important prognostic factors identified, e.g. age, duration of disease, disease severity?				
17. Were the analyses adjusted for confounding factors?				

Appendix 6 Excluded studies

Ineligible study design: N=34

Antlanger, M, Hecking, M, Haidinger, M, Werzowa, J, Kovarik, JJ, Paul, G, Eigner, M, Bonderman, D, Horl, WH,Saemann, MD. Fluid overload in hemodialysis patients: a cross-sectional study to determine its association with cardiac biomarkers and nutritional status. *BMC Nephrology* 2013;14:266

Bai, Q, Zhang, J, Zhang, AH, Cheng, LT, Duan, JL, He, L, Luo, YJ, Fan, MH, Wang, Y,Wang, T. Role of arachidonoylethanolamine in blood pressure regulation in volume-resistant patients on peritoneal dialysis. *International Urology and Nephrology* 2012;44(6):1855-60.

Bai, Q, Zhang, J, Zhang, AH, Cheng, LT, He, L, Fan, MH, Luo, YJ,Wang, T. Roles of human urotensin II in volume resistance hypertension in peritoneal dialysis patients. *Renal Failure* 2012;34(6):713-17.

Castellano, S, Palomares, I, Moissl, U, Chamney, P, Carretero, D, Crespo, A, Morente, C, Ribera, L, Wabel, P, Ramos, R,Merello, JI. Risk identification in haemodialysis patients by appropriate body composition assessment. *Nefrologia* 2016;36(3):268-74.

Chen, HS, Lee, KC, Cheng, CT, Hou, CC, Liou, HH, Lin, CJ,Lim, PS. Application of Bioimpedance Spectroscopy in Asian Dialysis Patients (ABISAD): Serial follow-up and dry weight evaluation. *Clinical Kidney Journal* 2013;6(1):29-34.

Davies, SJ, Engel, B, Chan, C, Tan, BK, Yu, ZZ, Asghar, R, John, B, Spanel, P,Smith, D. Breath Analysis and the Measurement of Total Body Water Using Isotope Dilution - Applications in the Dialysis Clinic. *Current Analytical Chemistry* 2013;9(4):593-99.

Dekker, MJ, Marcelli, D, Canaud, B, Konings, CJ, Leunissen, KM, Levin, NW, Carioni, P, Maheshwari, V, Raimann, JG, van der Sande, FM, Usvyat, LA, Kotanko, P,Kooman, JP. Unraveling the relationship between mortality, hyponatremia, inflammation and malnutrition in hemodialysis patients: results from the international MONDO initiative. *European Journal of Clinical Nutrition* 2016;20:20.

Di Gioia MC, GRP, Cobo G, Garcia Lopez F. Body composition changes in hemodialysis patients: implications for prognosis. *Enliven Arch Nephrol Renal Studies* 2014;1(1):1-7 http://enlivenarchive.org/nephrology-renal-studies-001.pdf.

Furusho, M, Weng, J, Mori, T,Wang, T. Impact of hydration and nutrition status on the Watson formula in peritoneal dialysis patients. *Advances in Peritoneal Dialysis* 2014;30:110-4.

Hassan, MO, Duarte, R, Dix-Peek, T, Vachiat, A, Dickens, C, Grinter, S, Naidoo, S, Manga, P,Naicker, S. Volume overload and its risk factors in South African chronic kidney disease patients: an appraisal of bioimpedance spectroscopy and inferior vena cava measurements. *Clinical Nephrology* 2016;10:10.

Kalainy, S, Reid, R, Jindal, K, Pannu, N,Braam, B. Fluid volume expansion and depletion in hemodialysis patients lack association with clinical parameters. *Canadian Journal of Kidney Health & Disease* 2015;2:54.

Kang, SH, Cho, KH, Park, JW, Yoon, KW,Do, JY. Characteristics and clinical outcomes of hyponatraemia in peritoneal dialysis patients. *Nephrology* 2013;18(2):132-37.

Kaysen, GA, Larive, B, Painter, P, Craig, A, Lindsay, RM, Rocco, MV, Daugirdas, JT, Schulman, G,Chertow, GM. Baseline physical performance, health, and functioning of participants in the Frequent Hemodialysis Network (FHN) trial. *American Journal of Kidney Diseases* 2011;57(1):101-12.

Kwan, BCH, Szeto, CC, Chow, KM, Law, MC, Cheng, MS, Leung, CB, Pang, WF, Kwong, VWK,Li, PKT. Bioimpedance spectroscopy for the detection of fluid overload in chinese peritoneal dialysis patients. *Peritoneal Dialysis International* 2014;34(4):409-16.

Lu, Q, Cheng, LT, Wang, T, Wan, J, Liao, LL, Zeng, J, Qin, C,Li, KJ. Visceral Fat, Arterial Stiffness, and Endothelial Function in Peritoneal Dialysis Patients. *Journal of Renal Nutrition* 2008;18(6):495-502
.

Marcelli, D, Usvyat, LA, Kotanko, P, Bayh, I, Canaud, B, Etter, M, Gatti, E, Grassmann, A, Wang, Y, Marelli, C, Scatizzi, L, Stopper, A, Van Der Sande, FM,Kooman, J. Body composition and survival in dialysis patients: Results from an international cohort study. *Clinical Journal of the American Society of Nephrology* 2015;10(7):1192-200.

Marcelli, D, Brand, K, Ponce, P, Milkowski, A, Marelli, C, Ok, E, Merello Godino, JI, Gurevich, K, Jirka, T, Rosenberger, J, Di Benedetto, A, Ladanyi, E, Grassmann, A, Scatizzi, L, Bayh, I, Kooman, J,Canaud, B. Longitudinal Changes in Body Composition in Patients After Initiation of Hemodialysis Therapy: Results From an International Cohort. *Journal of Renal Nutrition* 2016;26(2):72-80.

Mathew, S, Abraham, G, Vijayan, M, Thandavan, T, Mathew, M, Veerappan, I, Revathy, L,Alex, ME. Body composition monitoring and nutrition in maintenance hemodialysis and CAPD patients--a multicenter longitudinal study. *Renal Failure* 2015;37(1):66-72

Passauer, J, Petrov, H, Schleser, A, Leicht, J,Pucalka, K. Evaluation of clinical dry weight assessment in haemodialysis patients using bioimpedance spectroscopy: a cross-sectional study. *Nephrology Dialysis Transplantation* 2010;25(2):545-51.

Paudel, K, Visser, A, Burke, S, Samad, N,Fan, SL. Can Bioimpedance Measurements of Lean and Fat Tissue Mass Replace Subjective Global Assessments in Peritoneal Dialysis Patients? *Journal of Renal Nutrition* 2015;25(6):480-7.

Perez-Garcia, R, Palomares, I, Merello, JI, Ramos, R, Maduell, F, Molina, M, Aljama, P, Marcelli, D,Group, ORD. Hyponatraemia, mortality and haemodialysis: An unexplained association. *Nefrologia* 2016;36(1):42-50

Piccoli, A,Italian, C-BIASG. Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status. *Kidney International* 2004;65(3):1050-63.

Rosenberger, J, Kissova, V, Majernikova, M, Straussova, Z,Boldizsar, J. Body composition monitor assessing malnutrition in the hemodialysis population independently predicts mortality. *Journal of Renal Nutrition* 2014;24(3):172-6.

Tsai, YC, Chiu, YW, Kuo, HT, Chen, SC, Hwang, SJ, Chen, TH, Kuo, MC,Chen, HC. Fluid Overload, Pulse Wave Velocity, and Ratio of Brachial Pre-Ejection Period to Ejection Time in Diabetic and Non-Diabetic Chronic Kidney Disease. *Plos One* 2014;9(11).

Unal, A, Kavuncuoglu, F, Duran, M, Oguz, F, Kocyigit, I, Sipahioglu, MH, Tokgoz, B,Oymak, O. Inflammation is associated to volume status in peritoneal dialysis patients. *Renal Failure* 2015;37(6):935-40.

van Biesen, W, Williams, JD, Covic, AC, Fan, S, Claes, K, Lichodziejewska-Niemierko, M, Verger, C, Steiger, J, Schoder, V, Wabel, P, Gauly, A,Himmele, R. Fluid status in peritoneal dialysis patients: The European body composition monitoring (EuroBCM) study cohort. *PLoS ONE* 2011;6 (2) (no pagination)(e17148).

Van Biesen, W, Claes, K, Covic, A, Fan, S, Lichodziejewska-Niemierko, M, Schoder, V, Verger, C,Wabel, P. A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. *Nephrology Dialysis Transplantation* 2013;28(10):2620-28.

Vega, A, Ruiz, C, Abad, S, Quiroga, B, Velazquez, K, Ampuero, J,Lopez-Gomez, JM. Body Composition Affects Urea Distribution Volume Estimated by Watson's Formula. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation* 2015;25(5):420-25.

Vega, A, Ruiz, C, Abad, S, Quiroga, B, Velazquez, K, Yuste, C, Aragoncillo, I,Lopez Gomez, JM. Body composition affects the response to erythropoiesis-stimulating agents in patients with chronic kidney disease in dialysis. *Renal Failure* 2014;36(7):1073-7.

Vega, A, Quiroga, B, Abad, S, Ruiz, C,Lopez-Gomez, JM. Study on overhydration in dialysis patients and its association with inflammation. *Nefrologia* 2014;34(5):579-83.

Voroneanu, L, Cusai, C, Hogas, S, Ardeleanu, S, Onofriescu, M, Nistor, I, Prisada, O, Sascau, R, Goldsmith, D,Covic, A. The relationship between chronic volume overload and elevated blood pressure in hemodialysis patients: use of bioimpedance provides a different perspective from echocardiography and biomarker methodologies. *International Urology & Nephrology* 2010;42(3):789-97

Wabel, P, Moissl, U, Chamney, P, Jirka, T, Machek, P, Ponce, P, Taborsky, P, Tetta, C, Velasco, N, Vlasak, J, Zaluska, W,Wizemann, V. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrology Dialysis Transplantation* 2008;23(9):2965-71.

Wabel, P, Chamney, P, Moissl, U,Jirka, T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purification* 2009;27(1):75-80.

Yao, YH, Fu, CH, Ho, SJ, Tsai, SH, Ng, YY, Chuang, CL, Lin, CC,Chen, JY. Peritoneal dialysis as compared with hemodialysis is associated with higher overhydration but non-inferior blood pressure control and heart function. *Blood Purification* 2012;34(1):40-47.

Ineligible device N=67

Abreo, AP, Chertow, GM, Dalrymple, LS, Kaysen, GA,Johansen, KL. Association of bioimpedance spectroscopy-based volume estimation with postdialysis hypotension in patients receiving hemodialysis. *Hemodialysis International* 2015;19(4):536-42.

Abreo, AP, Herzog, CA, Kutner, NG, Lea, J,Johansen, KL. Estimated pulmonary artery systolic pressure and self-reported physical function in patients on hemodialysis. *American Journal of Nephrology* 2015;41(4-5):313-9.

Alijanian, N, Naini, AE, Shahidi, S, Liaghat, L,Samani, RR. The comparative evaluation of patients' body dry weight under hemodialysis using two methods: Bioelectrical impedance analysis and conventional method. *Journal of Research in Medical Sciences* 2012;17(10):923-27

Barros, A, Costa, BE, Mottin, CC,d'Avila, DO. Depression, quality of life, and body composition in patients with end-stage renal disease: a cohort study. Revista *Brasileira de Psiquiatria* 2016;5:5.

Basile, C, Vernaglione, L, Di Iorio, B, Bellizzi, V, Chimienti, D, Lomonte, C, Rubino, A,D'Ambrosio, N. Development and validation of bioimpedance analysis prediction equations for dry weight in hemodialysis patients. *Clinical journal of the American Society of Nephrology : CJASN* 2007;2(4):675-80.

Basile, C, Vernaglione, L, Bellizzi, V, Lomonte, C, Rubino, A, D'Ambrosio, N,Di Iorio, B. Total body water in health and disease: Have anthropometric equations any meaning? *Nephrology Dialysis Transplantation* 2008;23(6):1997-2002.

Beberashvili, I, Sinuani, I, Azar, A, Yasur, H, Feldman, L, Averbukh, Z,Weissgarten, J. Longitudinal study of leptin levels in chronic hemodialysis patients. *Nutrition Journal* 2011;10:68.

Beberashvili, I, Azar, A, Sinuani, I, Shapiro, G, Feldman, L, Stav, K, Sandbank, J,Averbukh, Z. Bioimpedance phase angle predicts muscle function, quality of life and clinical outcome in maintenance hemodialysis patients. *European Journal of Clinical Nutrition* 2014;68(6):683-9.

Beberashvili, I, Azar, A, Sinuani, I, Shapiro, G, Feldman, L, Sandbank, J, Stav, K,Efrati, S. Geriatric nutritional risk index, muscle function, quality of life and clinical outcome in hemodialysis patients. *Clinical Nutrition* 2016;13:13.

Booth, J, Pinney, J,Davenport, A. The effect of vascular access modality on changes in fluid content in the arms as determined by multifrequency bioimpedance. *Nephrology Dialysis Transplantation* 2011;26(1):227-31.

Chen, YC, Chen, HH, Yeh, JC,Chen, SY. Adjusting dry weight by extracellular volume and body composition in hemodialysis patients. *Nephron* 2002;92(1):91-6.

Chen, YC, Lin, CJ, Wu, CJ, Chen, HH,Yeh, JC. Comparison of extracellular volume and blood pressure in hemodialysis and peritoneal dialysis patients. *Nephron* 2009;113(2):c112-6.

Cheng, LT, Chen, W, Tang, W,Wang, T. Residual renal function and volume control in peritoneal dialysis patients. *Nephron* 2006;104(1):c47-54.

Cheng, LT, Jiang, HY, Tang, LJ,Wang, T. Seasonal variation in blood pressure of patients on continuous ambulatory peritoneal dialysis. *Blood Purification* 2006;24(5-6):499-507.

Cigarran, S, Barril, G, Cirugeda, A, Bernis, C, Aguilera, A, Sanz, P, Herraez, I, Alegre, L,Selgas, R. Hypoalbuminemia is also a marker of fluid excess determined by bioelectrical impedance parameters in dialysis patients. *Therapeutic Apheresis and Dialysis* 2007;11(2):114-20

Cox-Reijven, PL, Kooman, JP, Soeters, PB, Van der Sande, FM,Leunissen, KML. Role of bioimpedance spectroscopy in assessment of body water compartments in hemodialysis patients. *American Journal of Kidney Diseases* 2001;38(4):832-38.

Davenport, A,Willicombe, M. Comparison of fluid status in patients treated by different modalities of peritoneal dialysis using multi-frequency bioimpedance. *International Journal of Artificial Organs* 2009;32(11):779-86.

Davenport, A,Willicombe, MK. Does diabetes mellitus predispose to increased fluid overload in peritoneal dialysis patients? *Nephron* 2010;114(1):c60-6.

Davenport, A, Sayed, RH,Fan, S. Is extracellular volume expansion of peritoneal dialysis patients associated with greater urine output? *Blood Purification* 2011;32(3):226-31.

Davenport, A, Sayed, RH,Fan, S. The effect of racial origin on total body water volume in peritoneal dialysis patients. *Clinical Journal of the American Society of Nephrology* 2011;6(10):2492-98.

Davenport, A. Differences in prescribed Kt/V and delivered haemodialysis dose-why obesity makes a difference to survival for haemodialysis patients when using a 'one size fits all' Kt/V target. *Nephrology Dialysis Transplantation* 2013;28(SUPPL.4):iv219-iv23.

Davison, SN, Jhangri, GS, Jindal, K,Pannu, N. Comparison of volume overload with cycler-assisted versus continuous ambulatory peritoneal dialysis. *Clinical Journal of The American Society of Nephrology: CJASN* 2009;4(6):1044-50.

de Araujo Antunes, A, Vannini, FD, de Arruda Silveira, LV, Barretti, P, Martin, LC,Caramori, JC. Associations between bioelectrical impedance parameters and cardiovascular events in chronic dialysis patients. *International Urology & Nephrology* 2013;45(5):1397-403.

Demirci, C, Ozkahya, M, Demirci, MS, Asci, G, Kose, T, Colak, T, Duman, S, Toz, H, Ergin, P, Adam, SM,Ok, E. Effects of three times weekly eight-hour nocturnal hemodialysis on volume and nutritional status. *American Journal of Nephrology* 2013;37(6):559-67

Demirci, C, Asci, G, Demirci, MS, Ozkahya, M, Toz, H, Duman, S, Sipahi, S, Erten, S, Tanrisev, M, Impedance ratio: a novel marker and a powerful predictor of mortality in hemodialysis patients. *International Urology & Nephrology* 2016;19:19.

Dumler, F,Kilates, C. Body composition analysis by bioelectrical impedance in chronic maintenance dialysis patients: comparisons to the National Health and Nutrition Examination Survey III. *Journal of Renal Nutrition* 2003;13(2):166-72.

Dumler, F,Kilates, MC. Body composition analysis in chronic dialysis patients: A longitudinal study. *Hong Kong Journal of Nephrology* 2003;5(1):24-28.

Essig, M, Escoubet, B, de Zuttere, D, Blanchet, F, Arnoult, F, Dupuis, E, Michel, C, Mignon, F, Mentre, F, Clerici, C,Vrtovsnik, F. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrology Dialysis Transplantation* 2008;23(1):239-48.

Fagugli, RM, Pasini, P, Quintaliani, G, Pasticci, F, Ciao, G, Cicconi, B, Ricciardi, D, Santirosi, PV, Buoncristiani, E, Timio, F, Valente, F,Buoncristiani, U. Association between extracellular water, left ventricular mass and hypertension in haemodialysis patients. *Nephrology Dialysis Transplantation* 2003;18(11):2332-38.

Fan, S,Davenport, A. The importance of overhydration in determining peritoneal dialysis technique failure and patient survival in anuric patients. *International Journal of Artificial Organs* 2015;38(11):575-79.

Fisch, BJ,Spiegel, DM. Assessment of excess fluid distribution in chronic hemodialysis patients using bioimpedance spectroscopy. *Kidney International* 1996;49(4):1105-9.

Furstenberg, A,Davenport, A. Assessment of body composition in peritoneal dialysis patients using bioelectrical impedance and dual-energy X-ray absorptiometry. *American Journal of Nephrology* 2011;33(2):150-56.

Genctoy, G, Arikan, S,Eldem, O. Pulmonary hypertension associates with malnutrition and body composition hemodialysis patients. *Renal Failure* 2015;37(2):273-9.

Guo, Q, Lin, J, Li, J, Yi, C, Mao, H, Yang, X,Yu, X. The effect of fluid overload on clinical outcome in southern chinese patients undergoing continuous ambulatory

peritoneal dialysis. *Peritoneal Dialysis International* 2015;35(7):691-702.

Hung, SC, Lin, YP, Huang, HL, Pu, HF,Tarng, DC. Aldosterone and Mortality in Hemodialysis Patients: Role of Volume Overload. *PLoS ONE* 2013;8 (2) e57511

Jha, V, Jairam, A, Sharma, MC, Sakhuja, V, Piccoli, A,Parthasarathy, S. Body composition analysis with bioelectric impedance in adult Indians with ESRD: comparison with healthy population. *Kidney International* 2006;69(9):1649-53.

Kang, SH, Cho, KH, Park, JW, Yoon, KW,Do, JY. Change in body composition in accordance with residual renal function in patients on peritoneal dialysis. *Journal of Renal Nutrition* 2013;23(6):438-44.

Katzarski, K, Charra, B, Laurent, G, Lopot, F, Divino-Filho, JC, Nisell, J,Bergstrom, J. Multifrequency bioimpedance in assessment of dry weight in haemodialysis. *Nephrology Dialysis Transplantation* 1996;11(SUPPL. 2):20-23.

Katzarski, KS, Charra, B, Luik, AJ, Nisell, J, Divino Filho, JC, Leypoldt, JK, Leunissen, KML, Laurent, G,Bergstrom, J. Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrology Dialysis Transplantation* 1999;14(2):369-75.

Koh, KH, Wong, HS, Go, KW,Morad, Z. Normalized bioimpedance indices are better predictors of outcome in peritoneal dialysis patients. *Peritoneal Dialysis International* 2011;31(5):574-82.

Kumar, S, Khosravi, M, Massart, A,Davenport, A. Is there a role for n-terminal probrain-type natriuretic peptide in determining volume status in haemodialysis patients? *Nephron - Clinical Practice* 2013;122(1-2):33-37.

Kumar, S, Khosravi, M, Massart, A, Potluri, M,Davenport, A. Haemodiafiltration results in similar changes in intracellular water and extracellular water compared to cooled haemodialysis. *American Journal of Nephrology* 2013;37(4):320-24.

Kumar, S, Khosravi, M, Massart, A, Potluri, M,Davenport, A. Are serum to dialysate sodium gradient and segmental bioimpedance volumes associated with the fall in blood pressure with hemodialysis? *International Journal of Artificial Organs* 2014;37(1):21-28.

Lee, SW, Song, JH, Kim, GA, Lee, KJ,Kim, MJ. Assessment of total body water from anthropometry-based equations using bioelectrical impedance as reference in Korean adult control and haemodialysis subjects. *Nephrology Dialysis Transplantation* 2001;16(1):91-97.

Lin, YP, Yu, WC, Hsu, TL, Ding, PYA, Yang, WC,Chen, CH. The Extracellular Fluid-to-Intracellular Fluid Volume Ratio Is Associated with Large-Artery Structure and Function in Hemodialysis Patients. *American Journal of Kidney Diseases* 2003;42(5):990-99.

Maggiore, Q, Nigrelli, S, Ciccarelli, C, Grimaldi, C, Rossi, GA,Michelassi, C. Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. *Kidney International* 1996;50(6):2103-08.

McCafferty, K, Fan, S,Davenport, A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. *Kidney International* 2014;85(1):151-7.

Nongnuch, A, Panorchan, K,Davenport, A. Predialysis NTproBNP predicts magnitude of extracellular volume overload in haemodialysis patients. *American Journal of Nephrology* 2014;40(3):251-57.

Nongnuch, A, Campbell, N, Stern, E, El-Kateb, S, Fuentes, L,Davenport, A. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in hemodialysis outpatients. *Kidney International* 2015;87(2):452-57.

Ohashi, Y, Tai, R, Aoki, T, Mizuiri, S, Ogura, T, Tanaka, Y, Okada, T, Aikawa, A,Sakai, K. The associations of malnutrition and aging with fluid volume imbalance between intra- and extracellular water in patients with chronic kidney disease. *Journal of Nutrition, Health and Aging* 2015;19(10):986-93.

Omichi, Y, Srivareerat, M, Panorchan, K, Greenhall, GH, Gupta, S,Davenport, A. Measurement of Muscle Strength in Haemodialysis Patients by Pinch and Hand Grip Strength and Comparison to Lean Body Mass Measured by Multifrequency Bio-Electrical Impedance. *Annals of Nutrition & Metabolism* 2016;68(4):268-75.

Panorchan, K, Nongnuch, A, El-Kateb, S, Goodlad, C,Davenport, A. Changes in muscle and fat mass with haemodialysis detected by multi-frequency bioelectrical impedance analysis. *European Journal of Clinical Nutrition* 2015;69(10):1109-12.

Papakrivopoulou, E, Booth, J, Pinney, J,Davenport, A. Comparison of volume status in asymptomatic haemodialysis and peritoneal dialysis outpatients. *Nephron Extra* 2012;2(1):48-54

Pillon, L, Piccoli, A, Lowrie, EG, Lazarus, JM,Chertow, GM. Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. *Kidney International* 2004;66(3):1266-71

Santi Xavier, P, Perez Vogt, B, Cuadrado Martin, L, Vaninni, F, Araujo Antunes, A, Ponce, D, Costa Teixeira Caramori, J, Dos Santos, ESMR, da Silva Franco, RJ,Barretti, P. Total body water and failure to control blood pressure by medication in hemodialysis patients. *Nephron Extra* 2014;4(2):95-100.

Segall, L, Moscalu, M, Hogas, S, Mititiuc, I, Nistor, I, Veisa, G,Covic, A. Protein-energy wasting, as well as overweight and obesity, is a long-term risk factor for mortality in chronic hemodialysis patients. *International Urology and Nephrology* 2014;46(3):615-21.

Sezer, S, Karakan, S, Sasak, G, Tutal, E,Acar, FNO. Body Fat Percentage as a Risk Factor for Atherosclerosis but not for Inflammation for Hemodialysis Patients: Differences Between Genders. *Journal of Renal Nutrition* 2012;22(5):490-98.

Sivalingam, M, Vilar, E, Mathavakkannan, S,Farrington, K. The role of natriuretic peptides in volume assessment and mortality prediction in Haemodialysis patients. *BMC Nephrology* 2015;16:218.

Sugano, N, Yokoyama, K, Kato, N, Hara, Y, Endo, S, Mitome, J, Kin, T, Tokudome, G, Kuriyama, S, Hosoya, T,Yokoo, T. Monitoring of body water composition by the simultaneous use of bioelectrical impedance analysis and Crit-Line during hemodialysis. *Clinical and Experimental Nephrology* 2014;18(6):944-51.

Tan, BK, Yu, Z, Fang, W, Lin, A, Ni, Z, Qian, J, Woodrow, G, Jenkins, SB, Wilkie, ME,Davies, SJ. Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. *Kidney International* 2016;89(2):487-97.

Tian, N, Guo, QY, Yao, FJ, Zhou, Q, Yang, X, Lin, JX,Yu, XQ. Bioimpedance-guided fluid management can improve clinical outcomes in peritoneal dialysis patients: A prospective randomized control trial. *Hong Kong Journal of Nephrology* 2015;17(Suppl 2):S123.

Tian, N, Guo, Q, Zhou, Q, Cao, P, Hong, L, Chen, M, Yang, X,Yu, X. The impact of fluid overload and variation on residual renal function in peritoneal dialysis patient. *PLoS ONE* 2016;11 (4) e0153115

Unal, A, Sipahioglu, M, Oguz, F, Kaya, M, Kucuk, H, Tokgoz, B, Buyukoglan, H, Oymak, O,Utas, C. Pulmonary hypertension in peritoneal dialysis patients: prevalence and risk factors. *Peritoneal Dialysis International* 2009;29(2):191-8.

Wang, X, Axelsson, J, Lindholm, B,Wang, T. Volume status and blood pressure in continuous ambulatory peritoneal dialysis patients. *Blood Purification* 2005;23(5):373-78.

Yashiro, M, Ochiai, M, Fujisawa, N, Kadoya, Y,Kamata, T. The evaluation of filtration coefficients of microvasculature for the assessment of fluid status in hemodialysis patients. *International Journal of Artificial Organs* 2013;36(1):7-16.

Zhou, YL, Liu, J, Sun, F, Ma, LJ, Han, B, Shen, Y,Cui, TG. Calf bioimpedance ratio improves dry weight assessment and blood pressure control in hemodialysis patients. *American Journal of Nephrology* 2010;32(2):109-16.

Zhou, YL, Liu, J, Ma, L, Sun, F, Shen, Y, Huang, J,Cui, T. Impact of dry weight determined by calf bioimpedance ratio on carotid stiffness and left ventricular hypertrophy in hemodialysis patients. *Artificial Organs* 2014;38(4):327-34.

Zimmerman, DL, Ruzicka, M, Hebert, P, Fergusson, D, Touyz, RM,Burns, KD. Short daily versus conventional hemodialysis for hypertensive patients: a randomized cross-over study. *PLoS ONE [Electronic Resource]* 2014;9(5):e97135.

Ineligible participants: N=3

Keane, DF,Lindley, E. Use of hand-to-hand measurements for body composition monitoring in patients with inaccessible or amputated feet. *Journal of Renal Care* 2015;41(1):28-32.

Hung, SC, Kuo, KL, Peng, CH, Wu, CH, Lien, YC, Wang, YC,Tarng, DC. Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. *Kidney International* 2014;85(3):703-9.

Tsai, YC, Tsai, JC, Chiu, YW, Kuo, HT, Chen, SC, Hwang, SJ, Chen, TH, Kuo, MC,Chen, HC. Is fluid overload more important than diabetes in renal progression in late chronic kidney disease? *PLoS ONE* 2013;8 (12) (e82566).

Ineligible outcomes: N=8

Broers, NJH, Usvyat, LA, Marcelli, D, Bayh, I, Scatizzi, L, Canaud, B, Van Der Sande, FM, Kotanko, P, Moissl, U,Kooman, JP. Season affects body composition and estimation of fluid overload in haemodialysis patients: Variations in body composition; A survey from the European MONDO database. *Nephrology Dialysis Transplantation* 2015;30(4):676-81.

Ferrario, M, Moissl, U, Garzotto, F, Signorini, MG, Cruz, D, Tetta, C, Ronco, C, Gatti, E,Cerutti, S. Study of the autonomic response in hemodialysis patients with different fluid overload levels. *Annual International Conference of the IEEE Engineering in Medicine & Biology Society* 2010;2010:3796-9.

Gracia-Iguacel, C, Gonzalez-Parra, E, Perez-Gomez, MV, Mahillo, I, Egido, J, Ortiz, A,Carrero, JJ. Prevalence of protein-energy wasting syndrome and its association with mortality in haemodialysis patients in a centre in Spain. *Nefrologia* 2013;33(4):495-505

Ronco, C, Verger, C, Crepaldi, C, Pham, J, De Los Rios, T, Gauly, A, Wabel, P,Van Biesen, W. Baseline hydration status in incident peritoneal dialysis patients: The initiative of patient outcomes in dialysis (IPOD-PD study). *Nephrology Dialysis Transplantation* 2015;30(5):849-58.

Santos, PR, Monteiro, DL, de Paula, PH, Monte Neto, VL, Coelho, ML, Arcanjo, CC, Aragao, SM, Gondim, CB, Tapeti, JT, Mendes, HS, Vieira, LV,Prado Rde, C. Volaemic status and dyspepsia in end-stage renal disease patients. *Nephrology* 2015;20(8):519-22.

Schwermer, K, Hoppe, K, Radziszewska, D, Klysz, P, Sawatiuk, P, Nealis, J, Kaluzna, M, Kaczmarek, J, Baum, E, Lindholm, B, Pawlaczyk, K,Oko, A. N-terminal pro-B-type natriuretic peptide as a marker of hypervolemia and predictor of increased mortality in patients on hemodialysis. *Polskie Archiwum Medycyny Wewnetrznej* 2015;125(7-8):560-69.

Siriopol, D, Voroneanu, L, Hogas, S, Apetrii, M, Gramaticu, A, Dumea, R, Burlacu, A, Sascau, R, Kanbay, M,Covic, A. Bioimpedance analysis versus lung ultrasonography for optimal risk prediction in hemodialysis patients. *International Journal of Cardiovascular Imaging* 2016;32(2):263-70.

Yuste, C, Abad, S, Vega, A, Barraca, D, Bucalo, L, Perez-De Jose, A,Lopez-Gomez, JM. Assessment of nutritional status in haemodialysis patients. *Nefrologia* 2013;33(2):243-49.

Non-English language & unable to obtain translation: N=2

Castellano-Gasch, S, Palomares-Sancho, I, Molina-Nunez, M, Ramos-Sanchez, R, Merello-Godino, JI,Maduell, F. [New reliable methods for the diagnose of protein-energy wasting in hemodialysis patients]. *Nutricion Hospitalaria* 2014;30(4):905-10.

Diez, GR, Del Valle, E, Negri, AL, Crucelegui, S, Luxardo, R, Zambrano, L, Algranati, S, Ryba, J, Peri, P, Puddu, M, Bravo, M, Sintado, L, Bevione, P, Canalis, M, Leon, L, Marini, A, Marelli, C,Heguilen, R. Hypovitaminosis D in patients on hemodialysis (HD): Related factors and influence on muscle strength. *Revista de Nefrologia, Dialisis y Trasplante* 2013;33(3):134-40.

Appendix 7 Characteristics of included studies

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Randomised control trials (A = Study Group, B = Control Group, C = Total, both groups)			
First author, yr: Huang-Sheng, 2016 **Secondary reports:** No **Language:** English **Publication type:** Full-text **No of centres:** 6 **Setting:** Dialysis centres **Country:** Taiwan **Start-end dates:** Oct 2013 – Sept 2013 **Prospective/retrospective data collection:** Prospective **Study design:** RCT **Randomisation method:** Using a computer-generated sequence **Length of follow-up:** 12 months Source of funding: NephroCare Asia Pacific, Taiwan Division (Grand No 102030) **Type of device used:** The BCM-BIS (Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany)	**Enrolled:** C = 322 **Randomised:** A = 148, B = 150, C = 298 **Analysed:** A = 148, B = 150, C = 298 **Age mean yrs (SD):** A = 62.7 (12.1), B = 62.1 (11.5), C = 62.4 (11.8) **Sex n (%) Male:** A = 65 (43.9%), B = 80 (53.3%), C = 145 (48.7%) **Diabetes n (%):** A = 56 (37.8%), B = 56 (37.3%), C = 112 (37.6%) **Inclusion criteria:** MHD patients with age ≥18 and dialysis vintage ≥3 months **Exclusion criteria:** Coronary stents or pacemaker implantation; metallic devices in body, such as artificial joints or pins; contralateral or bilateral amputations; pregnancy	**A:** Post dialysis target weight (PDTW) was adjusted according to bioimpedance spectroscopy (BSM-BIS) algorithm. All the parameters relevant to fluid were revealed to the primary care staff and they adjusted PDTW according to these data. **B:** PDTW was adjusted according to clinical symptoms and signs by one or two fixed experienced dialysis staff in each centre. The data about fluid were not disclosed to primary care staff **Frequency of measurement:** Both groups received monthly measurements before their mid-week dialysis sessions.	**Aims:** To determine if the algorithm for adjusting PDTW with BCM-BIS is beneficial on the hospitalisation rate and other pivotal clinical outcomes in maintenance haemodialysis patients. **Outcomes:** Incidence of intra-dialysis hypotension was significantly lower in the study group. The incidence of acute fluid overload (AFO) or cardiovascular (CV) related events were lower in the study group and lower among non-diabetes patients in study group. Post-dialysis target weight was achieved in 88.38% of months where adjustment of PDTW was in the same direction as the BCM - Body Composition Monitor results
First author, yr: Hur, 2013 **Secondary reports:** No **Language:** English **Publication type:** Full text	**Enrolled:** C = 327 **Randomised:** A = 78, B = 78, C = 156 **Analysed**: A = 64, B = 62, C = 126	**A:** Fluid overload information was provided to treating physicians and used to adjust fluid removal during	**Aims:** Whether objective measurement of fluid overload with bioimpedance spectroscopy

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
No of centres: 2 **Setting:** Dialysis centres (operated by Fresenius Medical Care) **Country:** Turkey **Start/end dates:** NR **Prospective/retrospective data collection:** Prospective **Study design:** RCT **Randomisation method:** NR **Length of follow-up:** 12 months **Source of funding:** Unrestricted grant from European Nephrology and Dialysis Institute **Type of device used:** Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany	**Age mean yrs (SD):** A = 50.9 (13.2), B = 52.4 (11.4) **Sex n (%) Male:** A = 44/64, B = 43/62, C =87/127 **Diabetes n (%):** A = 15/78 (19.2%), B = 12/78 (15.4%), C=27/156 **Inclusion criteria:** Patients who were willing to participate in the study with written informed consent, older than 18 years, and on maintenance HD therapy scheduled thrice weekly (12 hours weekly) for 3 months or longer were included. **Exclusion criteria:** Exclusion criteria were the presence of a pacemaker or defibrillator, artificial joints or pins, amputation, permanent or temporary catheters, being scheduled for living donor kidney transplantation, presence of serious life-limiting comorbid situations (eg, malignancy, uncontrollable infection, and end-stage cardiac, pulmonary, or hepatic disease), being pregnant, or lactating.	dialysis. Fluid overload was assessed twice monthly. **B:** Fluid overload information was not provided to treating physicians and fluid removal during dialysis was adjusted according to usual clinical practice. **C:** Dry weight was assessed by routine clinical practice. Echocardiography, 48-ambulatory BP measurement and pulse wave analysis were performed at baseline and 12 months. **Frequency of intervention:** For study group, fluid overload was assessed 2x monthly; for control group, every 3 months before the mid or end week haemodialysis session.	is helpful in optimising fluid status. **Outcomes:** Left ventricular mass index (LVMI) (g/m^2) decreased significantly in the intervention group and had no statistical significant change in the control group. The LVMI decrease in the intervention group was significantly higher than in the control group. Urine output: significant increase in proportion of anuric patients and significant decrease in urine output in nonanuric patients at 12 months in the bioimpedance group. No change in proportion of anuric patients in control group and decrease in urine output in nonanuric patients was not significant at follow-up.
First author, yr: Luo, 2011 **Secondary reports:** No **Language:** English **Publication type:** Full text	**Enrolled:** C = 165 **Randomised:** A=80, B = 85, C = 165 **Analysed:** A = 78, B = 82, C =160	**A:** The patients and their primary nurses were informed of the overhydration value (OH) provided by bioimpedance spectroscopy.	**Aims:** To test if the recent use of OH provided by bioimpedance spectroscopy and patients'

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
No of centres: NR **Setting:** Peritoneal dialysis clinic in the hospital **Country:** China **Start-end dates:** Sept 2008 - NR **Prospective/retrospective data collection:** Prospective **Study design:** RCT **Randomisation method:** NR **Length of follow-up:** 3 months (terminated 3 months early) **Source of funding:** Grants from National Natural Science Foundation of China (Project 30900681) and Beijing Municipal Science & Technology Commission (D09050704310905). **Type of device used:** Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany	**Age mean yrs (SD):** A = 59.63 (13.89), B = 60.28 (16.01) **Sex n (%) Male:** A = 34 (43.6), B = 40 (48.8) **Diabetes n (%):** A = 21 (26.9), B = 23 (28.0) **Inclusion criteria:** Stable continuous ambulatory peritoneal patients. At the recruitment, all patients were older than 18 years, had been on PD for a minimum of 3 months and had no acute infection or new cardiovascular event in the prior month. **Exclusion criteria:** Patients who had been on 1 or 2 exchanges a day due to economic limitation were not included in the present study.	**B:** Values provided by bioimpedance spectroscopy were not revealed and patients' volumes were measured by the standard methods. **C:** All the recruited patients were closely followed and assessed by an experienced dietitian and bioimpedance assessment during each clinic visit. All patients, investigators and dialysis staff were not blinded to treatment assignment. At the outpatient review, the dietitian and primary nurse educated all of the patients in the same ways. **Frequency of measurement:** For all patients, every 6 weeks or less.	education would help to control overhydration. **Outcomes:** OH and extracellular water (ECW) were significantly different in pre and post with both study and control groups. OH and intracellular (ICW) were significantly different between study and control groups post at 12 weeks. Urine volume: non-significant decrease in urine volume in both bioimpedance and control groups at 12 weeks, but larger decrease in bioimpedance group
First author, yr: Onofriescu, 2012 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** Dr C.I. Parhon University Hospital dialysis centre **Country:** Romania **Start-end dates:** 1 Jan 2008 – 1 Jan 2009	**Enrolled:** C = 170 **Randomised:** A = 71, B = 64, C = 135 **Analysed:** A = 71, B = 64, C = 135 **Age mean yrs (SD):** C = 52.4 (13.1) **Sex n (%) Male:** C = 69/135 (51.1%) M **Diabetes n (%):** C: 14/135 (10.3%) **Inclusion criteria:** Prevalent patients (n = 170) with ESRD treated by HD for at least 3 months in the ‘‘Fresenius Nephrocare—Dr. C. I. Parhon Hospital’’ HD Centre in Iaşi, Romania	**A:** Target dry weight was determined by bioelectrical impedance analysis (BIA) measurements **B:** The target dry weight was set according to clinical criteria by the attending physicians from the dialysis unit (i.e., target BP equal to or less than 140/90 mm Hg, absence of oedema, and absence of	**Aims:** To study the effect BIA-guided versus clinical-guided ultrafiltration on various cardiovascular disease risk factors and markers in HD patients. **Outcomes:** The PWV significantly decreased in the study group and increased in the control group.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Prospective/retrospective data collection: Prospective **Study design:** RCT **Randomisation method:** Computer-generated randomisation list prepared by the chief investigators. Study subjects were randomised in blocks of 10 **Length of follow-up:** 12 months **Source of funding:** NR **Type of device used:** Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany	**Exclusion criteria:** Those with metallic joint prostheses (n = 4), cardiac pacemakers (n = 5), and limb amputations (n = 10) were subsequently excluded.	intra-dialytic or inter-dialytic hypotension or other symptoms). **C:** Biochemistry and haematology analyses, serum NT-pro-BNP, anthropometric and BP measurements, BIA, and applanation tonometry were performed at baseline in all participants, before a mid-week HD session. BIA and tonometry were performed each by a single investigator, blinded to the patients' randomization. **Frequency of measurement:** BIA measurements were taken every three months from the start.	Statistically significant changes from baseline for Systolic BP and Diastolic BP in study group; NS statistical changes in control group (p value not provided).
First author, yr: Onofriescu, 2014 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** Dr C.I. Parhon University Hospital dialysis centre **Country:** Romania **Start-end dates:** July 2008 – Dec 2011 **Prospective/retrospective data collection:** Prospective **Study design:** RCT	**Enrolled:** NR **Randomised:** A= 62, B=69, C = 131 **Analysed:** A= 62, B=69, C = 131 **Age mean yrs (SD):** A=52 (13), B=54 (13), p=0.5 **Sex n (%) Male:** A=33/62, B=36/69, p=0.7 **Diabetes n (%):** A = 6 (10%), B = 6 (9%) **Inclusion criteria:** All adult patients (>= 18 years) from the Dr C.I. Parhon University Hospital dialysis centre already on maintenance HD therapy for more than 3 months.	**A:** Target dry weight was prescribed exclusively based on readouts from the bioimpedance device measurements. Results were disclosed to clinicians for only the bioimpedance intervention arm, in the form of a strict target interval (bioimpedance-recommended dry weight 6 1.1 kg) to be achieved during the next month. Thus, in the bioimpedance arm, all patients, either under- or overhydrated, were brought to the	**Aims:** To compare strict volume control based on bioimpedance versus clinical methods for guiding ultrafiltration prescriptions in HD patients. **Outcomes:** All-cause mortality (both unadjusted and multivariate adjusted) was significantly lower in the bioimpedance group compared to the clinical-methods group.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Randomisation method: Block randomisation technique **Length of follow-up:** 30 months **Source of funding:** Part of this study was funded by the University of Medicine and Pharmacy Iaşi, grant IDEI-PCE 2011, PN-II-IDPCE-2011-3-0637 **Type of device used:** Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany	**Exclusion criteria:** Patients with limb amputations, metallic joint prostheses, absence of a permanent vascular access, decompensated cirrhosis, pregnancy, or a cardiac stent or pacemaker were excluded from the study because bioimpedance assessment cannot be performed accurately in such cases. In addition, patients with life expectancy less than 1 year were not considered.	bioimpedance- recommended dry weight, with 200-g weight adjustments per dialysis session. **B:** Dry weight was determined/ adjusted in the clinical- methods group by clinical reference criteria (BP value, presence of oedema, intradialytic hypotension, cramps etc.) **C:** After the 2.5 year intervention period, during the last year of the study, all patients were left free of any intervention and managed according to the standard medical practice of the dialysis centre. At the end of the study, at 3.5 years, a third PWV measurement was performed in all patients. **Frequency of measurement:** Every 3 months	Proportion of patients maintained within 1.1kg of the bioimpedance-recommended dry weight was statistically significantly higher in the bioimpedance group than in the clinical methods group at around half of the quarterly assessments
First author, yr: Ponce, 2014 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 23 **Setting:** Dialysis units **Country:** Portugal **Start-end dates:** 2010 - 2012 **Prospective/retrospective data collection:** Prospective	**Enrolled:** C=218 **Randomised:** A = 101, B = 88, C = 189 **Analysed:** A = 101, B = 88, C = 189 Consecutive: **Age mean yrs (SD):** A = 65.8 (14.6), B = 66.7 (15.1) **Sex n (%) Male:** A = 72/101, B = 72/88, C = 144/189 **Diabetes n (%):** A = 39 (38.6%0, B = 35 (39.8%)	**A:** Data of pre-dialysis measurements were only accessible to the treating physicians of the study group **B:** Patients' fluid status as measured by BCM was not communicated to physicians or nurses in the blinded centre. Used all conventional fluid management techniques according	**Aims:** To compare the performance of bioimpedance spectroscopy device versus conventional clinical judgement in assessing the hydration status of HD patients and determine their ideal weight. **Outcomes:** The reduction of PH after 12 months compared to the baseline was significant in both

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Study design: RCT **Randomisation method:** NR **Length of follow-up:** 12 months **Source of funding:** NR **Type of device used:** Body Composition Monitor: Fresenius Medical Care, Bad Homburg, Germany	**Inclusion criteria:** Incident and prevalent HD patients were included if they were older than 18, with a relative predialytic overhydration (OH) (relative OH [%] = OH [l] / extracellular water [l]*100) at baseline of > 15% (on average > 2.5 litres) as assessed by the body composition monitor (BCM©). **Exclusion criteria:** Patients with an implanted electronic medical device or who were connected to an external electronic medical device were excluded. Further exclusion criteria were: Any kind of metal implants or metal prosthetic joints, e.g., implanted defibrillators, cardiac pacemakers. On the other hand, dental implants and piercings were allowed. Patients with major amputations, pregnant women, and patients with symptomatic aortic valve stenosis were also excluded.	to traditional centre standards, in order to assess dry weight of their patients and to adjust ultrafiltration. **Frequency of measurement:** In both groups, the hydration status of patients was measured once monthly by the BCM at midweek dialysis treatment, prior to dialysis session.	groups. Hospitalisation and survival rate was not significantly different between the two groups.
Non-randomised studies			
First author, yr: Castellano, 2014 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 29 **Setting:** HD units in the Fresenius Medical Care network	**Analysed:** Total: 2959 **Age mean yrs (SD):** 68.20 (14.51) **Sex n (%) Male:** 62.1% **Diabetes n (%):** 27.10% **Inclusion criteria:** Patients over the age of 18, dialysed with high permeability membrane three times a week on average	All patients had a monthly measuring with the BCM and the first six measurements were assessed. Patients classified as overhydrated or normohydrated and aim was to	**Aims:** To identify the characteristics of patients with maintained hyperhydration status and to show the hemodynamic and analytical changes that are related to the reduction in hydration status.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Country: Spain **Start-end dates:** December 2011 to December 2012 **Prospective/retrospective data collection:** NR **Study design:** Longitudinal cohort **Randomisation method:** N/A **Length of follow-up:** 6 months **Source of funding:** NR **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	and with an average effective time of 240 minutes per session. All of them had a monthly measuring with the BCM. **Exclusion Criteria:** Amputees or patients with pacemakers were excluded.	move overhydrated patients into the normohydrated zone. **Frequency of measurement:** Monthly measurements and first six measurements were assessed.	**Outcomes:** Those that had a reduced hydration status also show a better control in blood pressure and anaemia with less hypotensive drugs (AHT) and erythropoiesis stimulating agents (ESA).
First author, yr: Hoppe, 2015 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** NR **Country:** Poland **Start-end dates:** NR **Prospective/retrospective data collection:** Prospective **Study design:** Cohort study with follow-up **Randomisation method:** N/A **Length of follow-up:** 30 months **Source of funding:** Grant from Baxter Healthcare Corporation to Karolinska Institutet **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	**Analysed:** Short dialysis vintage group: 119, Long dialysis vintage group: 122 **Age mean yrs (SD):** SDVG: 62 (13.1), LDVG: 61.7 (12), p = 0.65 **Sex n (%) Male:** SDVG: 77/119, LDVG: 83/122, p = 0.65 **Diabetes n (%):** SDVG: 47 (39.5%), LDVG: 29 (23.8%), p <0.01 **Inclusion criteria:** Patients on maintenance HD **Exclusion Criteria:** NR **Frequency of measurement:** Before midweek dialysis session	Value of cardiac troponin T and hydration parameters (according to BCM) of short-dialysis vintage patients and long-dialysis vintage participants were compared.	**Aims:** To assess cardiac troponin T (cTnT) and hydration stat as cardiovascular (CV) risk markers in haemodialysis patients. **Outcomes:** The long dialysis group was associated with a significantly higher rate of deaths.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
First author, yr: Kim 2012 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 3 **Setting:** Dialysis centre **Country:** Korea **Start-end dates:** NR **Prospective/retrospective data collection:** Prospective **Study design:** Interventional cohort study **Randomisation method:** N/A **Length of follow-up:** 16 weeks **Source of funding:** In part by Fresenius Medical Care (FMC), Korea **Length of follow-up:** 16 weeks	**Analysed:** Total: 120, Dehydrated: 18, Hyperhydrated: 44, Normohydrated: N/A **Age mean yrs (SD):** Total: 56.4 (13.2), Dehydrated: 53.3 (14.3), Hyperhydrated: 58.4 (11.3), Normohydrated: 55.9 (14.1) **Sex n (%) Male:** Total: 67 (55.4%), Dehydrated: 8 (42.1%), Hyperhydrated: 28 (63.6%), Normohydrated: 30 (52.6%) **Diabetes n (%):** NR **Inclusion criteria:** 18 years or older, no change in dialysate composition, and less than a 5% change in dry weight within 3 months. Clinically euvolaemic for at least three months **Exclusion Criteria:** Any diagnosed acute or inflammatory state within 3 months, hospitalisation-related dialysis within 3 months, diseases that produce local fluid accumulation and oedema, active malignancy, currently taking diuretics or any medication with the potential to influence body composition, malnutrition, pregnancy, cardiac pacemaker, or amputation of any extremity.	Patients were divided into two groups: hyperhydrated (fluid overload>=1.1L) or dehydrated (fluid overload <-1.1L). Normohydrated patients were not subsequently included in the analyses. **Frequency of measurement:** Before and 30 minutes after HD sessions every 4 weeks.	**Aims:** Whether the objective measurement and optimisation of fluid status could be beneficial for haemodynamic and biochemical parameters in haemodialysis patients. **Outcomes:** After 16 weeks, systolic blood pressure and pulse pressure decreased in the hyperhydrated group, while there was no increase in blood pressure in the dehydrated group after the intervention
First author, yr: Kim 2015 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** Hospital	**Analysed:** Overhydrated: 160, Nonoverhydrated: 80, total: 240 **Age mean yrs (SD):** Overhydrated: 65.6 (12.8), nonoverhydrated: 65.7 (12.6)	Extent of overhydration and dry body weight were assessed with the BCM. Patients were classified into 2 groups: Overhydrated group (OG) - OH/ECW>15%	**Aims:** To evaluate the clinical usefulness of bioimpedance analysis (BIA) for predicting the survival rate of haemodialysis patients in Korea.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Country: Korea **Start-end dates:** Jun 2009 – Apr 2014 **Prospective/retrospective data collection:** Prospective **Study design:** Cohort study **Randomisation method:** N/A **Length of follow-up:** Mean (SD) for survival analysis: Mean for admissions rates analysis: OG: 20.6 (15.8); NOG: 16.2 (15.2)mo (p=0.04) OG: 20.6 (15.8), NOG: 16.2 (15.2) **Source of funding:** Chungnam National University Hospital in 2009 and Chungnam National University in 2010 **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	**Sex n (%) Male:** Total: 67 (55.4%), Dehydrated: 8 (42.1%), Hyperhydrated: 28 (63.6%), Normohydrated: 30 (52.6%) **Diabetes n (%):** Overhydrated: 112 (71.3%), nonoverhydrated: 49 (61.3%)* *Diabetic nephropathy **Inclusion criteria:** All patients were diagnosed with ESRD and started maintenance haemodialysis between June 2009 and April 2014 **Exclusion Criteria:** Patients who started dialysis due to acute kidney injury; a patient whose date of dialysis start and death were in the same admission period; and a patient with a history of renal transplantation, a history of peritoneal dialysis longer than 1 month, or active malignancy (all solid organ cancer and hematologic malignancy).	Nonoverhydrated group (NOG) - OH/ECQ<15% The value of initial overhydration measured with BCM was used without modification if it was measured on the 1st dialysis day. If it was measured with BCM after the 1st dialysis day, the value of initial overhydration was calculated by difference between initial body weight and dry body weight measured with BCM. **Frequency of measurement:** BCM was performed within the 1st week from the start of haemodialysis.	**Outcomes:** The ratio of OH/ECW volume measured with body composition monitor is related to the overall survival of end-stage renal disorder patients who started maintenance haemodialysis. Admission rates analysis (no significant difference between overhydrated group (OG) and nonoverhydrated group (NOG. Patients in OG had a higher risk for all-cause mortality.
First author, yr: O'Lone, 2014 **Secondary reports:** Santhakumaran, 2016 **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** NR **Country: UK** **Start-end dates:** 1 Jan 2008 – 30 Mar 2012	**Analysed:** Incident (enrolment into study was within 90 days of PD initiation): 225, prevalent: 304, total: 529 **Age mean yrs (SD):** Incident: 53.7 (42.9-66.9), prevalent: 58.6 (48.4 - 69.8), p-value: <0.01, total: 57.0 (46.7 - 68.8) **Sex n (%) Male:** NR Incident: 131 (60%), prevalent: 198 (65%), total: 329: 62%	Different parameters (overhydration (OH), extra- cellular water/total body water (ECW/TBW) or OH/ECW) have been proposed to indicate hydration status. We wished to determine which parameter (if any) was most predictive of all-cause mortality, and if this was independent of nutritional indices.	**Aims:** To determine which parameter (if any) was most predicative of all-cause mortality and if this was independent of nutritional indices. **Outcomes:** OH index (OH and OH/ECW) was the independent predictor of mortality in multi-variate analysis. ECW/TBW as a

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Prospective/retrospective data collection: Prospective **Study design:** Cohort study with follow-up **Randomisation method:** N/A **Length of follow-up:** 57 months **Source of funding:** NR **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	**Diabetes n (%):** Incident: 78 (35%), prevalent: 95 (28%), total: 173 (33%) **Inclusion criteria:** All continuous ambulatory peritoneal dialysis (CAPD) and automated PD (APD) patients who had at least one BCM reading. **Exclusion Criteria:** All patients with amputations, cardiac pacemakers or defibrillators were excluded.	OH index (OH and OH/ECW) was the independent predictor of mortality in multi-variate analysis. **Frequency of measurement:** BCM measurements were usually performed during their PD training but if this was not possible, it was performed quarterly for stable patients and more frequently as clinically dictated.	continuous variable was not associated with increased risk of death. In contrast, patients that were severely overhydrated (highest 33%) had hazard ratios (HRs) that were statistically significant irrespective of the parameter used to define hydration.
First author, yr: Oei, 2016 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** NR **Country:** UK **Start-end dates:** 1 Jan 2008 – 20 Mar 2012 **Prospective/retrospective data collection:** Retrospective **Study design:** Cohort study **Randomisation method:** N/A **Length of follow-up:** Mean, 23.9 months **Source of funding:** NR **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	**Analysed:** All: 336, Survivors: 288, Non-cardiac death: 35, Cardiac death: 13, Severe OH: 66 **Age Median (IQR):** All: 57.9 (48.1-69.0), Survivors: 55.4 (46.9-66.6), Non-cardiac death: 68.9 (61.8 - 77.0), Cardiac death: 68.9 (62.9 - 76.5), Severe OH: 60.1 (51.1 - 71.1) **Sex n (%) Male:** All: 207 (62%) Survivors: 167 (58%) Non-cardiac death: 27 (77%) Cardiac death: 13 (100%) Severe OH: 44 (67%) **Diabetes n (%):** All: Survivors: 288, Non-cardiac death: 35, Cardiac death: 13, Severe OH: 66 **Inclusion criteria:** A cohort of patients from a single PD unit, consisting of all continuous ambulatory PD (CAPD) and automated PD (APD) patients between 1	Wished to explore if PD patients who died from cardiac causes were more severely OH compared to patients that died from other causes. Also wished to determine if OH in PD patients predicted cardiac mortality, and if there was a correlation between OH and cardiac troponin-T (cTnT). Thus, studied patients to determine if severe OH did improve, did it lead to a corresponding decrements of cTnT. **Frequency of measurement:** NR	**Aims:** To study the relationship between overhydration (OH) in peritoneal dialysis (PD) patients and cardiac mortality. **Outcomes**: Patients with cardiac causes of death had significantly shorter dialysis vintage and were significantly more overhydrated by BSM measurement. In the severely overhydrated patients, reduction in OH values over 6mo correlated with lowering of cTnT levels.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
	January 2008 and 30 March 2012 who had contemporaneous baseline BIS/cTnT readings. **Exclusion Criteria:** All patients with amputations, cardiac pacemakers or defibrillators were excluded as we were unable to perform BIS measurements. Only patients that recovered renal function or who were transferred to another dialysis unit for geographic relocation reasons were censored at that time point as their survival follow-up could not be accurately determined.		
First author, yr: Onofriescu, 2015 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** Haemodialysis unit **Country:** Romania **Start-end dates:** May 2008 – Dec 2010 **Prospective/retrospective data collection:** Prospective **Study design:** Cohort study with follow-up **Randomisation method:** N/A **Length of follow-up:** Median 66.2 (42.4-70.2) months **Source of funding:** University of Medicine and Pharmacy "Gr. T. Popa"	**Analysed:** Total: 221 **Age mean yrs (SD):** Total: 53.8 (13.9) **Sex n (%) Male:** 116/221 **Diabetes n (%):** 23/221 (10.4%) **Inclusion criteria:** All patients (N = 298) undergoing chronic HD treatment for at least 3 months in the "Dr. C. I. Parhon" haemodialysis unit **Exclusion Criteria:** Bioimpedance was not performed in patients with metallic joint prostheses (N = 11), cardiac pacemakers (N = 8), decompensated cirrhosis (N = 5) and limb amputations (N = 13). Other exclusion criteria were refusal to take part in the study, age<18 years old, active systemic infections and terminal illnesses (N = 40).	Investigate the impact of overhydration on all-cause mortality and cardiovascular events by using a previously reported cut-off value for overhydration and also investigating a new cut-off value derived from our analysis of this specific cohort. **Frequency of measurement:** BCM was used before dialysis. Dialysis was performed three times per week.	**Aims:** To assess if the relationship between bioimpedance assessed overhydration and survival is maintained when adjustments for echocardiographic parameters are considered. **Outcomes:** In the entire study population, patients considered overhydrated had a significant increased risk for all-cause mortality in both univariate and multivariate Cox survival analysis. The number of cardiovascular events was significantly higher in

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
Iasi, grant no. 1643/01.02.2013 and UEFISCDI IDEI PCE, Grant nr. PN-II-ID-PCE-2011-03-0637 **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)			overhydrated patients in both univariate and multivariate Cox regression analysis.
First author, yr: Santhakumaran, 2016 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 1 **Setting:** NR **Country: UK** **Start-end dates:** 1 Jan 2008 – 1 Oct 2012 **Prospective/retrospective data collection:** Prospective **Study design:** Cohort study with follow-up **Randomisation method:** N/A **Length of follow-up:** 78 months **Source of funding:** research grants from Fresenius medical company and Baxter healthcare. **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care)	**Analysed:** Below Median (<6.1) Time averaged hydration status (OH/ECW): 90 Above median (<6.1) time average hydration status (OH/EC): 290 **Age mean yrs (SD):** Below median (<6.1 OH/ECW): 54.5 (0.9), above median (>6.1 OH/ECW): 59.1 (0.9), p<0.0005 total: 55.8 (0.6) **Sex n (%) Male:** Below median: 46.9%, above median: 80.7%, total: 63.8% **Diabetes n (%):** Below median: 23.80%, above median: 45.9%, p<0.0001 total: 34.80% **Inclusion criteria:** Same cohort of patients as in O'Lone 2014 but with slightly longer recruitment period and 51 extra participants. Consisting of all continuous ambulatory Pd and automated PD patients who had at least one contemporaneous BCM **Exclusion Criteria:** All patients with amputations, cardiac pacemakers or defibrillators were excluded as we were unable to perform BIS measurements.	Looked at the relationship between hydration parameters and PD-related peritonitis as well as the variables likely to impact peritonitis rates Compared peritonitis rates of patients with above or below the median time- averaged hydration parameter (OH/extracellular water, OH/ECW). **Frequency of measurement:** NR	**Aims:** To determine if OH is an independent risk factor for peritonitis **Outcomes:** Overhydration was a predictor of peritonitis-free survival from enteric organisms on univariate analysis. This may partly be due to the high co-morbidity of patients (advanced age and diabetes). Only inclusion of nutritional parameters reduced this association.

Study details	Participant characteristics	Intervention characteristics	Aims and Outcomes
First author, yr: Wizemann, 2009 **Secondary reports:** No **Language:** English **Publication type:** Full text **No of centres:** 3 **Setting:** Dialysis centre **Country:** Europe **Start-end dates:** 2003 to 1 Jan 2007 **Prospective/retrospective data collection:** Prospective **Study design:** Cohort study with follow-up **Randomisation method:** N/A **Length of follow-up:** 42 months **Source of funding:** NR **Type of device:** Body Composition Monitor (BCM, Fresenius Medical Care).	**Analysed:** Hyperhydrated: 58, normohydrated: 211, Total: 269 **Age mean yrs (SD):** Hyperhydrated: 65 (14.8), Normohydrated: 66 (15.2), Total: 65 (15) **Sex n (%) Male:** NR Diabetes n (%): Hyperhydrated: 15%, Normohydrated: 32%, Total: 28% **Inclusion criteria:** All patients that received HD treatment in the three study centres in 2003 **Exclusion Criteria:** The patients with pacemakers/implanted defibrillators or amputation of a major limb were excluded.	Measurements taken once only, before dialysis, and patients divided into hyperhydrated (relative hydration>15%) or normohydrated groups, which were then compared on hydration parameters and mortality. **Frequency of measurement:** Three times per week, before the start of HD treatment	**Aims:** To investigate how the magnitude of the prevailing overhydration influences long terms survival in haemodialysis patients. **Outcomes:** Significant predictors of mortality: age, systolic BP, diabetes, peripheral vascular disease, relative hydration status pre-dialysis.

Appendix 8 Risk of bias assessment: non-randomised studies

REBIP criteria	Castellano 2014	Hoppe 2015	Kim 2012	Kim 2015	Oei 2016	O'Lone 2014	Onofriescu 2015	Santhakumaran 2015	Wizemann 2009
Representative sample	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion/exclusion criteria clearly defined	✓	×	✓	×	✓	✓	✓	✓	×
Participants at similar point in disease progression	✓	×	✓	✓	✓	×	✓	×	✓
Consecutive selection of participants	?	?	?	?	?	?	?	?	?
Prospective data collection	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clearly defined intervention	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intervention delivered by experienced person	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intervention delivered in appropriate setting	✓	✓	✓	✓	✓	✓	✓	✓	✓
Important outcomes considered	✓	✓	✓	✓	✓	✓	✓	✓	✓
Objective outcome measured	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blind assessment of main outcomes	×	×	×	×	×	×	×	×	×
Long enough follow-up	✓	✓	×	✓	✓	✓	✓	✓	✓
Information on non-respondents, dropouts	✓	✓	✓	✓	×	✓	?	×	✓
Withdrawals likely to introduce bias	✓	✓	?	×	?	?	?	?	?
Important prognostic factors identified	✓	✓	✓	✓	✓	✓	✓	✓	✓

Appendix 9 Outcome measures extracted from the included RCTs

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
Huan-Sheng 2016									
Indicator	Incidence, incidence rate (IR) ratio and hazard (per patient-year) ratio for all, diabetes mellitus and non-diabetes mellitus patients. CI=95%.		Pre-dialysis SBP					FO and FO_{post} for all, FO≥ 2.5L, FO≤2.5L patients; change with baseline	FOR for all, FO≥ 2.5L, FO≤2.5L patients; change with baseline
Total									
Study (bioimpedance)	**Overall**: 71 events; IR = 0.52, (0.44-0.61) **DM:** 30 events; IR =0.58, 95%CI (0.46-0.73) **Non-DM**: 41 events; IR = 0.48, 95%CI (0.39-0.60)		**All:** 136 (23)/ **FO≤2.5L:** 136 (23) **FO≥2.5L:** 133 (21), *p<0.05*					**All**: FO =1.49 (1.04); FO_{post}: -0.50 (1.21), *p<0.05* **FO≤2.5L**: FO = 1.40 (1.00), *p<0.01*; FO_{post} = -.56 (1.21), *p<0.001* **FO≥2.5L:** FO = 2.21 (1.07), *p <0.001*; FO_{post}= 0.02 (1.07), *p < 0.05*	**All:** 0.10 (0.07) **FO≤2.5L**: 0.09 (0.06), *p<0.05* **FO≥2.5L**: 0.14 (0.006), *p <0.001*
Control	**Overall:** 73 events; incidence = 0.54, (0.46-		**All:** 136 (22) **FO≤2.5L:** 134 (21)					**All:** FO =1.64 (1.40); FO_{post}: -0.23 (1.52)	**All:** FOR: 0.11 (0.09) **FO≤2.5L**: FOR =

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
	0.63); IR = 0.97 (0.70-1.34); HR= 1.19 (0.79-1.80) **DM:** 38 events; incidence = 0.76, (0.65-0.89); IR = 0.76 (0.47-1.23); HR= 1.13 (0.61-2.09) **Non-DM:** 35 events; incidence = 0.41 (0.32-0.53); IR= 1.18 (0.75-1.85); HR= 1.23 (0.70-2.14)		**FO≥2.5L**: 143 (22)					**FO≤2.5L:** FO = 1.25 (1.16); FO_{post} = -.53 (1.39), *p<0.05* **FO≥2.5L:** FO = 3.07 (1.27*), p <0.05*; FO_{post}= 0.89 (1.48)	0.09 (0.09) **FO≥2.5L**: 0.19 (0.07), *p <0.05*
Luo 2011									
Indicator		Total daily defined dose, mean (SD) at 12 weeks						**OH**	**ECW/ICS**
Total (n=160)									
Bioimpedance (n=78)		2.33 (1.76)	132.99 (19.47), *p<0.5,* change with baseline AND between groups	77.63 (12.04) *p<0.5,* change with baseline				1.72 (1.51), *p<0.05*, change with baseline	0.95 (0.13), *p <0.05* change with baseline
Control (n=82)		2.94 (1.87)	139.07 (22.40) *p<0.5,* change with baseline	80.85 (14.15) *p<0.5* , change with baseline				2.52 (1.83), *p<0.05*, change with baseline	1.00 (0.14), *p <0.05,* change with baseline

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
			AND between groups					AND between groups	
Hur 2013									
Indicator	Hospitalisation rate/100 patients		Pre and post-dialysis; p – change from baseline	Pre-and post-dialysis; p – change from baseline	P – change from baseline	P – change from baseline		FO_{pre} and FO_{post}, change with baseline	
Total	10 hospitalised due to new CV events during study period								
Study (bioimpedance)	Hospitalised = 6; Hospitalisation rate/100 patient-y: 12.5		Predialysis: 120 (19) *p<0.001* Postdialysis: 105 (18) *p<0.001*	Predialysis: 73 (9) *p<0.001* Postdialysis: 65 (9) *p<0.001*	28/64 (43.8%) *p=0.4*	116 (29) *p<0.001*	-0.52 (1.38)	FO_{pre}=0.87 (0.88) FO_{post}=-1.33 (0.99) *p<0.001* Change with baseline: FO_{pre} = -0.6 (0.8) FO_{post}= -0.5 (0.9)	
Control	Hospitalisation = 4; Hospitalisation rate/100 patient-y: 30.9 *p=NS*, difference between groups		Predialysis: 125 (19) *p=0.006* Postdialysis: 113 (21) *p=0.03*	Predialysis: 76 (9) *p=0.2* Postdialysis: 70 (10) *p=0.07*	31/62 (50%) *p=0.9*	120 (30) *p=0.9*	0.11 (1.31) Difference between groups= -0.5, CI=95% (-0.9 to -0.0), *p=0.04*	FO_{pre}=1.41 (1.26) FO_{post}=-1.01 (1.44) Change: FO_{pre} = 0.2 (1.2): FO_{post}= 0.0 (1.3)	

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
Between group changes (CI=95%)								FO_{pre}: -0.4 (-0.6 to -0.3), *p<0.001* FO_{post}: -0.5 (-0.8 to-0.1), *p=0.01*	
Onofriescu 2012									
Indicator							Change with baseline	AFO (L) (SD), change with baseline	RFO % (SD), change with baseline
Bioimpedance			Baseline: 144.3 (14.5) 12mo: 135.4 (17.8) Change from baseline statistically significant	Baseline: 79.3 (9.5) 12mo: 73.2 (11.1) Change from baseline statistically significant			6.9 (2.3) p=statistically significant	1.5 (1.4), *p =NS*	9.3 (7.8), *p = NS*
Control			Baseline: 146.6 (16.3) 12mo: 142.8 (13)	Baseline: 77.7 (11.5) 12mo: 75.3 (9.6)			9.2 (3.6) p= statistically significant	1.7 (1.5), p =NS	9.7 (8.3), *p = NS*
Onofriescu 2014 – did not report Diastolic BP									
Indicator		N=Patients not treated with antihypertensives, within group change	Change with baseline						RFO % (SD) change within groups (CI=95%)

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
Bioimpedance		n=45, *p=0.05*	138.9 (14.7): -6.54 (-13.62 to -4.53) *p=0.04*						7.46 (5.77), -2.05 (-5.70 to -1.10), *p = 0.03*
Control		n=NR, *p=NS*	140.5 (11.4) -4.00 (-10.83 to 2.63) *p=0.4*						11.24 (7.62), 0.94 (-2.50 to 4.40), *p = 0.9*
Between group changes			Between group mean difference (end of intervention): 1.67 (-5.24 to 8.60) *p=0.9* Between group mean difference (change from baseline to end of intervention): -2.43 (-7.70 to 2.84) *p=0.4*						End of intervention:3.77 (2.20 - 7.35), *p = 0.03* change from baseline to end of intervention: -2.99 (-5.00 to -0.89), *p=0.05*
Ponce, 2014									
Indicator	Hospitalised at least once		Pre- and post-dialytic	Pre- and post-dialytic				OH (L) (SD), compared with baseline	ROH % (SD) compared with baseline
Total									
Study (bioimpedance)	40/101 (39.6%)		Pre-dialytic SBP: 134.6 (27.3) Post-dialytic SBP: 132.8 (28.6)	Pre-dialytic DBP: 65.4 (15.8) Post-dialytic				2.92 (1.47), *p<0.0001*	15.40 (6.36), *p = NS*

	Hospitalisation	**Anti-hypertensive medication**	Systolic BP (mm HG), mean (SD)	Diastolic BP (mm HG), mean (SD)	Presence of Left ventricular hypertrophy	LVMI (g/m2), mean (SD)	Arterial stiffness PWV (m/s), mean (SD)	Absolute hydration status	Relative hydration status
				DBP: 63.4 (15.0)					
Control	28/88 (31.8%)		Pre-dialytic SBP: 136.5 (24.7) Post-dialytic SBP: 129.3 (24.0)	Pre-dialytic DBP: 64.5 (16.2) Post-dialytic DBP: 61.4 (12.9)				Mean OH: 3.36 (1.75), *p = 0.0216*	16.26 (8.48), *p = NS*
Between group difference								(CI= 95%) 0.4184 (-0.02 to 0.86), *p = 0.0622*	*p=NS*

Appendix 10 Characteristics of ongoing trials

Study details	Participant characteristics	Aims and Outcomes
Study title: Probing the Dry Weight (DW) by Bioimpedance (BIA): Which is the Gold Standard Between Clinical DW and BIA DW? (REST) **ClinicalTrials.gov Identifier:** NCT02446535 **Responsible Party:** Carlo Basile, M.D., Scientific Director of the Division of Nephrology, Miulli General Hospital **Last updated:** May 13, 2015 **(Estimated) study completion date:** December 2016 **Trial status:** This study is currently recruiting participants. **Study type:** Interventional **Country:** Italy **Setting:** NR **Allocation:** NR	**Estimated Enrolment:** 60 **Inclusion criteria:** Patients older than 18 years who have had maintenance HD three times weekly. **Exclusion criteria:** Dialysis vintage <3 months; overt edema; liver cirrhosis; cardiac failure; serum albumin < 3 g/dl; pregnancy; metallic implants or pacemaker; limb amputation **Intervention model:** Single Group Assignment	**Aims:** To verify if BIA-based DW (BIA DW) control is truly superior to current volume management in HD patients. **Primary Outcomes:** The definition for each patient of the gold standard DW when comparing the Clinical and the BIA DW **Secondary outcomes:** NR
Study title: Fluid Management Guided by Bioimpedance Analysis in Peritoneal Dialysis (PD) Patients. **ClinicalTrials.gov Identifier:** NCT02000128 **Responsible Party:** Xue Qing Yu, Director, Institute of Nephrology, Sun Yat-sen University, Sun Yat-sen University **Last updated:** May 19, 2015 **(Estimated) study completion date:** April, 19 2016 **Trial status:** This study has been completed **Study type:** Interventional **Country:** China **Setting:** The First Affiliated Hospital of Sun Yat-Sen University	**Estimated Enrolment:** 240 **Inclusion criteria:** Patients who are undergoing peritoneal dialysis and clinically stable for at least 3 months; 18 Years and older; ratio extracellular water (ECW)/total body water(TBW)≧0.4; signed the informed consent **Exclusion criteria:** patients who have mental graft; amputation; patients who is unable to accomplish the BIA measurement in standing position for 3 minutes; patients whose heart function are class IV estimated by New York Heart Association (NYHA) standard; Patients who have acute complications within 30 days prior to study enrollment; patients whose life expectancy is within 6	**Aims:** To investigate the effect of bioimpedance analysis (BIA) guided fluid management versus experiential way on clinical outcome in peritoneal dialysis patients. **Primary Outcomes:** All-cause; mortality; cardiovascular related mortality **Secondary Outcomes:** Technique survival, cardiovascular events, peritonitis, residual renal function

Study details	Participant characteristics	Aims and Outcomes
Allocation: Randomised	months; patients who are pregnant; patients who are unable to give consent. **Intervention model:** Parallel Assignment	
Study title: Control Of Fluid Balance Guided by Body Composition Monitoring in Patients on PeritoneAl dialySiS (COMPASS) **ClinicalTrials.gov Identifier:** NCT01887262 **Responsible Party:** Kook-Hwan Oh, Associate Professor, Seoul National University Hospital **Last updated:** June 17, 2014 **Estimated study completion date:** July 2015 **Trial status:** This study is currently recruiting participants. **Study type:** Interventional **Country:** Korea **Setting:** Seoul National University Hospital Clinical Trial Center **Allocation:** Randomised	**Estimated Enrolment:** 138 **Inclusion criteria:** age between 20 and 75; peritoneal dialysis > 4 weeks duration; written consent; daily urine output > 500 ml **Exclusion criteria:** subjects who are contraindicated to the bioimpedance measurement (pacemaker insertion state, defibrillator state, amputee, prosthesis, metal implants); pregnant women; subjects who are expected to discontinue peritoneal dialysis with one year; mixed dialysis modality (peritoneal + hemodialysis); hypoalbuminemic subjects (serum albumin < 3.3 g/dL); high blood pressure (> 160/100 mmHg despite antihypertensive medications); severe heart failure (NYHA FC III, or IV) **Intervention model:** Parallel Assignment	**Aims:** Bioimpedance-guided fluid management in peritoneal dialysis patients may provide better protection of residual renal function over 1 year period, compared with management guided by clinical information alone. **Primary Outcomes:** change of glomerular filtration rate from baseline to the 12th month **Secondary Outcomes:** glomerular filtration rate measured by urine collection; Time to the anuric; parameters obtained by echocardiographic measurements such as left ventracular mass index (LVMi);left vetricular end-diastolic volume (LVEDP); left ventracular ejection fraction (LVEF); left atrial volume indx (LAVI); systolic, diastolic blood pressure pulse pressure; fatal and nonfatal cardiovascular events - acute myocardial infarction (AMI); stroke; unstable angina, amputation, cardiovascular revascularization; parameters measured by body composition monitoring (BCM)

Study details	Participant characteristics	Aims and Outcomes
Study title: Bio-impedance spectroscopy to maintain renal output (BISTRO) **ClinicalTrials.gov Identifier:** ISRCTN11342007 **Responsible Party:** Kidney Unit, Royal Stoke University Hospital University Hospital of North Midlands NHS Trust **Last updated:** July 4, 2016 **(Estimated) study completion date:** Recruitment until 02-01-2018 **Trial status:** Recruitment starts 02-01-2017 **Study type:** Interventional **Country:** UK (30 UK dialysis units) **Setting:** Keele University **Allocation:** Randomised	**Estimated Enrolment:** 516 **Inclusion criteria:** Adults aged >18 years commencing centre-based maintenance haemodialysis due to advanced kidney disease CKD stage 5, planned or unplanned, via arterio-venous fistula, graft or central venous catheter (i.e. with or without permanent vascular access); commencing dialysis on any regimen, including having incremental dialysis initiation; residual kidney function: For patients who have not yet started dialysis treatment they should have a daily urine volume > 500ml/day and/or a or a measured mean urea and creatinine clearance >3ml/min/1.72m2 determined from a 24 hour collection; for patients already on dialysis they should have a urine volume >500ml during the short inter-dialytic period and/or a measured mean urea and creatinine clearance >3ml/min/1.72m2, determined from the same timed inter-dialytic urine collections and an average of the post- and pre-dialysis plasma urea and creatinine concentrations. **Exclusion criteria:** Unable or unwilling to give informed consent; unable to comply with trial procedures, e.g. collection of urine output; likely survival prognosis or planned modality transfer < 6 months; subjects with limb amputations when the foot is not accessible AND it is not possible to take hand to hand measurements **Intervention model:** NR	**Aims:** To test whether taking regular measurements with a bioimpedance device improves outcomes for people who have recently started haemodialysis treatment for kidney failure. **Primary Outcomes:** Time to anuria (loss of urine output), <100ml/day or 200ml in the short inter-dialytic period confirmed by a further collection after 2 weeks to exclude temporary illness. **Secondary Outcomes:** The rate that kidney function reduces; vascular access failure; cardiovascular events; hospital admissions, death

Appendix 11 Questions for clinical experts on bioimpedance testing

Multiple frequency bioimpedance devices for fluid management in people with chronic kidney disease having dialysis

Questions from the assessment group on monitoring the fluid status of dialysis patients:

Questions relating to routine practice

1. How many people is your centre responsible for providing dialysis for
    a. Number on HD? _____
    b. Number on PD? _____

2. How many satellite units are linked with your centre?

3. What cadre/grade of staff is generally responsible for establishing the post dialysis target weight for haemodialysis patients under the care of your centre?

4. What cadre/grade of staff is generally responsible for establishing the target weight for peritoneal dialysis patients under the care of your centre?

5. How many bioimpedance devices do you estimate it would require to enable (on average) quarterly monitoring of the fluid status of all your centre's eligible haemodialysis and peritoneal dialysis patients?

Please answer the following questions if bioimpedance devices are currently being used in your dialysis centre to help guide fluid management decisions:

Haemodialysis patients

a. How many of your centre's **haemodialysis** patients are currently monitored using bioimpedance testing?

b. How frequently on average are these **haemodialysis** patients monitored using a bioimpedance device? (i.e number of times per year)

c. Where does the bioimpedance testing of your centre's **haemodialysis** patients take place? (Please state percentage of testing being conducted at the following locations)

Location	**Percentage of bioimpedance testing performed at this location**
Main hospital unit	
Satellite unit	
Patient's home	
Other	

If other, please state where this is:

d. Who normally performs the bioimpedance testing on your centre's **haemodialysis** patients? (i.e. please state cadre/grade of staff who generally performs the procedure)

e. Who generally interprets the results of bioimpedance tests in order to help establish the appropriate target weight for your centre's **haemodialysis** patients? (i.e. please state cadre/grade of staff who interprets the results)

Peritoneal dialysis patients

f. How many of your centre's **peritoneal dialysis** patients are currently monitored using a bioimpedance device?

g. How frequently on average are these **peritoneal dialysis** patients monitored using a bioimpedance device? (i.e. number of times per year)

h. Where does the bioimpedance testing of your centre's **peritoneal dialysis** patients take place? (Please state percentages of testing being conducted at the following locations)

Location	**Percentage of bioimpedance testing performed at this location**
Hospital unit	
Satellite unit	
Patient's home	
Other	

If other, please state where this is:

i. Who normally performs the bioimpedance testing on your centre's **peritoneal dialysis** patients? (i.e. please state the cadre/grade of staff who generally performs the procedure)

j. Who generally interprets the results of bioimpedance tests in order to help establish the target weight for your centre's **peritoneal dialysis** patients? (i.e. please state cadre/grade of staff)

Overall dialysis population

k. How many bioimpedance devices does your centre require to enable all of the above monitoring (of haemodialysis and peritoneal dialysis patients) to take place?

l. Are there any annual measures/requirements in place to quality assure/maintain the bioimpedance device(s) in use at your centre? (please provide details)

m. How many of the following grades of staff has your centre had to train in the use of bioimpedance testing/monitoring?

Cadre/grade of staff	**Number trained**
Consultant nephrologists	
Trainee nephrologists	
Nurses	
Technicians	
Dieticians	
Others	

n. What is the average time-commitment for staff to attend training on the use of bioimpedance testing?

o. Over and above the device, staffing and consumable costs for bioimpedance testing, are there any additional software costs that your unit incurs in order to use this technology?

p. Please provide any other information that you think may be relevant for estimating the cost of monitoring the fluid status of haemodialysis and peritoneal dialysis patients using bioimpedance testing.

Thank you very much for taking the time to answer these questions