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1. Title of the project

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.

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3 Plain English summary

The main function of the kidneys is to filter waste products and excess fluid from the blood and expel them into the urine. Chronic kidney disease is a long-term condition in which the kidneys are only able to function at a reduced level. Chronic kidney disease can lead to kidney failure and the need for a kidney transplant or the waste products and excess fluid being removed from the blood by a process called dialysis. There are two main types of dialysis: i) where blood is removed from the body along a tube and filtered by an external machine before being returned to the body by another tube ("haemodialysis") and ii) where the lining of the abdomen is used to filter the blood ("peritoneal dialysis").

In people having dialysis, it is important to monitor the amount of fluid being removed, as removing too much, or not enough, fluid, can cause other health problems during dialysis or between dialysis sessions. Assessing the fluid levels has traditionally been done by the medical staff using their experience and judgement but this can be unreliable. In recent years, a type of technical device has been introduced to estimate a person's fluid level and provide information on the person's body which is related to the dialysis process. These devices work by sending painless electrical currents through the body by way of pads, which are placed on certain parts of the body (e.g. hand and foot). It is not clear at the present time whether using these devices provides more reliable information than the judgement of medical staff about the fluid levels in people receiving dialysis or whether they represent good value-for-money for the NHS.

The purpose of this assessment is to bring together existing evidence on the effects of these devices for the assessment of fluid levels in people with chronic kidney disease who are on dialysis as compared with the judgment of medical staff. We will also assess whether using the new devices in clinical practice is an appropriate use of NHS resources.

4 Decision problem

4.1 Purpose of the decision to be made

Bioimpedance devices are a technology based on passing a bioelectrical current through the body in order to estimate the body fluid volume by the amount of resistance the current endures in the body tissues.[1] The bioelectrical current used in these devices can have spectral or multi-bioelectrical frequencies.[1, 2] Multiple frequency bioimpedance devices are used to monitor the hydration status of people with chronic kidney disease who are treated with either haemodialysis or peritoneal dialysis. The information provided by the technology can be used to guide how much fluid to remove during dialysis. If too little or too much fluid is removed during dialysis this will lead to underhydration or overhydration (e.g. fluid overload). Short-term complications of fluid overload include oedema of the hands, feet and face, and fluid retention in the lungs (pulmonary oedema), causing shortness of breath. In contrast, short-term complications of underhydration may include cramps, dizziness and tiredness. Long-term fluid imbalance can result in poor blood pressure control, leading to heart disease, further reductions in kidney function and increased mortality. Fluid overload in people receiving dialysis can also cause ventricular hypertrophy which increases the risk of heart attack, stroke and arrhythmia.

Multiple frequency bioimpedance devices aim to improve estimates of the amount of fluid to remove during dialysis, which may reduce complications associated with fluid overload or underhydration. Potential benefits of reduced fluid overload could include reduced use of antihypertensive medicine, reduced numbers of hypertensive episodes and reduced risk of cardiovascular complications and death. Potential benefits of reducing systematic underhydration could include greater preservation of renal function, reduced numbers of hypotensive episodes and a reduction in symptoms such as cramps and post-dialysis fatigue. Further benefits may include reduced hospital admission arising from overhydration and underhydration, and improved quality of life for people with chronic kidney disease (CKD).

The purpose of this assessment is to review the current evidence on the clinical effectiveness and cost-effectiveness of multiple frequency bioimpedance devices for the fluid management of people with chronic kidney disease who are treated with haemodialysis or peritoneal dialysis.

4.2 Clear definition of the intervention

Bioimpedance technology involves assessment of fat-free mass and total body water in people without significant fluid and electrolyte abnormalities.[2] 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 of extracellular and intracellular resistance. 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).[3, 4] 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.[5] 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.[6, 7] As the limbs have a high water content in proportion to their cross-sectional area due to their neuromuscular bundles and muscle matter, they provide a disproportionate amount of information (as compared to the trunk) by way of bioimpedance analysis. Thus, measuring segments of the body, such as the lower leg[8] or chest wall[9] is sometimes preferred.[7]

The technologies relevant to this assessment are the BCM - Body Composition Monitor; the MultiScan 5000, the BioScan 920-II, 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.[7, 10] 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.[11, 12] 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.[6, 10] There are no restrictions on the age of the person that this device can be used on.

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.[13, 14] 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[1] identified two RCTs of 131 and 189 participants, respectively,[15, 16] and one observational study of 110 participants, which assessed the use of the BCM - Body Composition Monitor in people receiving haemodialysis.[17] 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 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.[18]

Further information on the BCM - Body Composition Monitor is available from the company's website.[10]

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. Values for extracellular water, intracellular water, total body water, and

volume of over/under-hydration are obtained from the same physiological models as used in the BCM – Body Composition Monitor analysis.[11, 12] 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[19] 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 measured. These parameters can be used to evaluate 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.[19]

The use of the MULTISCAN5000 has been evaluated in a cohort of Chinese patients receiving haemodialysis by Zhou and colleagues.[20] They concluded that the device is a simple and practical method for assessing body fluid status and that the recognition of chronic volume overload facilitated better blood pressure control.[20]

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 provides 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 estimates 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.[21] 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 going to be released during the course of this assessment. As with the BioScan 920-II, it is anticipated that there will be two versions of this device, one suitable for people aged 0-18 and one suitable for people aged 5-99.

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 provided along with a suggested standard range of values to facilitate identification of overhydrated or underhydrated individuals. In addition, the InBody S10 provides outputs 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.

4.3 Target condition: Chronic kidney disease and dialysis

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[6, 22] 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.[23-27] 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.[24, 28] 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.[24] 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.[29]

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.[24, 29]

CKD is classified into a continuum of five stages, based on renal function:[23, 24, 29]

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.[30] 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 in most cases is accompanied by signs and symptoms of uremia, or the need to start kidney replacement therapy (dialysis or transplantation).[24, 31-34]

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.[35]

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 excess salts and water 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.[36]

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).[6, 22, 37]

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 hypervolemia or fluid overload) and underhydration (also referred to as hypovolemia) are associated with negative outcomes, such as mortality, intradialytic morbidity and long-term cardiovascular complications.[7, 37-42] 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.[4, 38, 39, 42-47] A negative association between higher diastolic blood pressure and residual renal function has also been reported.[48]

Complications associated with overhydration can be asymptomatic. Oedema, for example, may not be detectable until interstitial fluid volumes rise to approximately 30% above normal.[44] 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.[20, 49-51] 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.[52, 53]

To enable an assessment of the amount of fluid to be removed during dialysis – the so called 'ultrafiltration volume',[37] - people are assigned a 'dry weight' or 'target weight' (i.e. euvolemic), 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.[38, 40, 54, 55] It can also be defined as how much a person should weigh in the morning, following peritoneal dialysis, or at the end of a haemodialysis session.[6] 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 protocol. Target weight is commonly estimated using methods such as weight gain between dialysis sessions, pre-dialysis and post-dialysis blood pressure and subjective symptoms.[49] However, as methods for assessing target weight are not precise, it has been reported that approximately one-half of people who achieve their 'ideal target weight' are actually overhydrated.[56] Dialysis centres are now increasingly using measurement devices based on bioimpedance technology, as they are non-invasive, simple and relatively inexpensive.[5, 7, 57]

In the UK, on 31 December 2014, there were 58968 adults receiving renal replacement therapy (49842 in England, 2842 in Wales). Of these, 27804 people were on dialysis (23734 in England, 1308 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.[58, 59] In addition, 190 children and young people under the age of 18 years were on dialysis (103 haemodialysis and 87 peritoneal dialysis).[59, 60]

The Hospital Episode Statistics for England for the 2014-2015 period[61] 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.

4.4 Population and relevant subgroups

The population under consideration is people with chronic kidney disease (CKD) who are treated with haemodialysis or peritoneal dialysis.

Relevant subgroups may include:

- People who are treated with haemodialysis;
- People who are treated with peritoneal dialysis;

- People of different ethnic origin;
- 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;
- Children younger than 5 years who may require more frequent monitoring.

4.5 Relevant comparators

The comparator being considered is standard clinical assessment (without the use of bioimpedance devices) 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.

4.6 Key factors to be addressed

The specific objectives of this assessment are 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 people with CKD receiving dialysis treatment versus standard clinical assessment.

4.7 Areas of agreement at the scoping workshop that are outside the scope of the assessment and therefore do not require any detailed assessment (e.g. key factors for which evidence is already accepted).

We will not carry out a formal assessment and statistical synthesis of the accuracy and validation of multiple frequency bioimpedance devices under assessment as current test accuracy and validation studies are likely to be heterogeneous with regard to the choice of reference standard measurements; the definitions and the cut-off points to designate overhydration and underhydration as well as inclusion/exclusion criteria. However, we will systematically search the literature and contact the companies to gather data on the validation and accuracy of the different multiple frequency bioimpedance devices. Findings of relevant identified studies will be summarised in a narrative way and tabulated for comparison.

It is worth noting that the measurement of the hydration related parameters produced by multiple frequency bioimpedance devices has been validated against various standard measurements (e.g. total body water measurements have been validated against deuterium dilution and extracellular water measurements have been validated against bromide dilution). However, no generally accepted 'gold standard' exists for the measurement of fluid status, which allows identification of whether a person is overhydrated or underhydrated and, if so, to what extent. Often validation of overhydration measures have been made by using clinical assessment and ultrafiltration volume.[13] Other methods used to assess the volume status of people treated with dialysis include lung ultrasound to evaluate extravascular lung water, measurement of inferior vena cava diameter, and the measurement of brain natriuretic peptide levels.

5 Report methods for synthesis of evidence of clinical effectiveness

An objective synthesis of the evidence on the relative clinical effectiveness of multiple frequency bioimpedance devices (i.e. BCM, MultiScan 5000, BioScan 920-II, BioScan touch i8, InBody S10) versus clinical assessment will be conducted according to the general principles of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, the recommendations of the Cochrane Handbook for Systematic

Reviews of Interventions, the PRISMA statement for the reporting of systematic reviews and meta-analyses, and the NICE Diagnostics Assessment Programme Manual.[62-65]

5.1 Inclusion and exclusion criteria

Population

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

Intervention

The interventions being considered in this assessment are the following:

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 being considered is standard clinical assessment, which takes into consideration the following clinical parameters:

- Blood pressure;
- Presence of oedema;
- Changes in weight;
- Residual renal function;
- Pre-existing cardiovascular conditions;
- Any patient reported symptoms of overhydration or underhydration (e.g. cramps, fatigue nausea, dizziness, breathlessness, decreased appetite, visual disturbances).

In additional to these clinical parameters, other factors may be taken into account when setting target weight. These may include any recent admission to hospital or the presence of a new fistula.

Outcomes

Studies will be included if they provide data on any of the following outcomes:

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.

5.2 Study design

We will prioritise RCTs for inclusion in the systematic review of clinical effectiveness. In particular, we will focus on RCTs assessing multiple frequency bioimpedance devices versus standard clinical assessment as well as RCTs assessing the comparative effectiveness of one device versus another. However, if such RCTs are lacking or not sufficient to answer the proposed research question, we will consider non-randomised evidence (including non-randomised comparative studies as well as observational studies), providing they include relevant outcomes for this assessment, suitable to inform UK clinical practice.

Systematic reviews of interventions, if they exist, will be used as a source of relevant evidence for this assessment but will not be formally updated.

5.3 Exclusion criteria

The following types of report will not be considered suitable for inclusion:

i. Narrative reviews, editorials and opinions;
ii. Case reports;
iii. Conference abstracts for which a full publication or further methodological information could not be found;
iv. Non-English language reports for which a translation cannot be organised.

5.4 Search strategy

Extensive sensitive electronic searches will be conducted to identify reports of published and ongoing studies which assess multiple frequency bioimpedance devices' performance and clinical effectiveness in monitoring the hydration status of people receiving either haemodialysis or peritoneal dialysis treatments. The search strategies will combine (AND) two facets: haemodialysis or peritoneal dialysis; and the specified monitors (BCM - Body Composition Monitor; MultiScan 5000, BioScan 920-II, BioScan touch i8, and InBody S10) or fluid status. Search terms will include both controlled vocabulary and free text terms. No study design search filter will be included in the search strategies and no language or date restriction will be applied. Systematic reviews will be also retrieved to check their reference lists for potentially relevant studies.

The main databases to be searched will include: MEDLINE, MEDLINE In-Process, Embase, Science Citation Index and the Cochrane Controlled Trials Register. A preliminary MEDLINE search strategy is provided in Appendix A and will be adapted to search other relevant databases. The Cochrane Database of Systematic Reviews, the HTA Database and DARE will be searched for reports of systematic reviews as well as for background publications.

Current research registers, including Current Controlled Trials, Clinical Trials and WHO International Clinical Trials registry will be searched. Recent conference proceedings (2014-2016) including those of the European Renal Association, American Society of Nephrology ad the Annual Dialysis Conferences will also be screened.

In addition, relevant websites of key professional organisations, registries and device manufacturers will be checked for additional data and relevant information.

5.5 Study selection and data extraction strategies

Two reviewers will independently screen all titles and abstracts identified by the search strategies. Full text versions of all potentially relevant reports will be retrieved and assessed independently by two reviewers using a study eligibility screening form based on the pre-

specified inclusion criteria. Any disagreements will be resolved by discussion or arbitration by a third reviewer.

A data extraction form will be designed and piloted for the purpose of this assessment. One reviewer will extract information on study design, characteristics of participants, characteristics of the interventions and outcome measures as described above. A second reviewer will check the information and data extracted by the first reviewer. Any disagreements will be resolved by discussion or arbitration by a third reviewer.

5.6 Quality assessment strategy

A single reviewer will assess the methodological quality of the included studies and findings checked by a second reviewer. Any disagreements will be resolved by consensus or arbitration by a third party. Studies will not be included or excluded on the basis of their methodological quality.

The quality of all the included RCTs will be evaluated using Cochrane Risk of Bias tool.[63] Non-randomised studies will be assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions), which is based on the Cochrane Risk of Bias tool for randomised trials.[66]

5.7 Methods of analysis/synthesis

We will provide a summary of the data relevant to the purpose of this assessment using tables and graphs as these will be useful for identifying differences in outcomes between studies, which could represent potential biases.

If appropriate, meta-analysis will be performed to estimate a summary measure of effect of the relevant outcomes. Summary statistics of binary data will be calculated as relative risk (RR) using mantel-Haenszel method while summary statistics for continuous data will be calculated as weighted mean difference (WMD) using inverse-variance method. For the estimates of RR and WMD 95% confidence intervals (CIs) and p-values will be calculated. A random effects model will be used to calculate the pooled estimates. The statistical heterogeneity across studies will be explored by making use of appropriate plots and using both Chi squared and I-squared statistics.

Risk factors such as age, diabetes, blood pressure, diet, cardiovascular disease and smoking will be tabulated so that differences both within and between studies could be easily seen.

If data permit, outcomes for people who are overhydrated and people who are underhydrated will be summarised and analysed separately.

We are planning to perform subgroup analyses according to the type of dialysis (haemodialysis, peritoneal dialysis), to the type of patient population (children younger than 5 years), to ethnicity groups, and to certain characteristics of the patient population (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).

If data permit, we will perform sensitivity analyses based on:

- Low risk of bias studies only;
- According to the type of multiple frequency bioimpedance devices (i.e. BCM, MultiScan 5000, BioScan 920-II, BioScan touch i8, InBody S10).

6 Report methods for synthesising evidence of cost-effectiveness

The aim of the economic evaluation for this assessment is 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 specific objectives are 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 for fluid management in people with chronic kidney disease having dialysis - from a UK NHS and personal social services perspective.

Relevant economic literature will be systematically identified, appraised for quality and summarised. Following this, an economic model will be developed using data from the literature supplemented with expert opinion. The model will be populated using data from the systematic clinical effectiveness review of randomised and observational studies, further focussed reviews to inform key parameters (e.g. utilities, costs), routine sources of unit cost data, and where necessary study specific cost estimates (based on expert opinion). The model will be used to estimate the cost-effectiveness of using bioimpedance technology to guide fluid management decisions in people with CKD on dialysis, compared with the standard practice of clinical assessment.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Scoping searches have identified no existing economic evaluations directly addressing the decision problem described in the final scope for this assessment.

Electronic searches will be undertaken to identify reports of economic evaluations. The following bibliographic databases will be included: MEDLINE, MEDLINE in process, Embase, Science Citation Index, NIHR Economic Evaluations Database (NEED) and the HTA Database. No date or language restrictions will be imposed. A draft MEDLINE strategy is detailed in Appendix A and will be adapted to search other relevant databases. 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 will also be screened. Relevant websites of key professional organisations, registries and device manufacturers will be checked for additional data and information.

Any identified full economic evaluations addressing the decision problem defined in the final scope, will be appraised against the NICE reference case[67] and quality assessed using the 10-point Drummond checklist[68] and, if applicable, the Philips checklist for good practice in decision modelling.[69] The main findings of existing economic evaluations will be summarised in a narrative review and tabulated for comparison.

To inform the de novo economic model, broader searches will be 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 will also be developed for health state utility data relevant to the health states included in the economic model. Databases that will be searched will include MEDLINE, EMBASE, SCI and the CEA registry. No date or language restrictions will be imposed. Priority will be given to utility data that is consistent with the NICE reference case (i.e. descriptive health related quality of life data elicited from UK patients using the EQ-5D, and valued using general population preferences).

6.2 Evaluation of costs and cost effectiveness

Following the synthesis of cost effectiveness evidence, an economic model will be developed to assess multiple frequency bioimpedance devices (i.e. BCM, MultiScan 5000, BioScan 920-II, BioScan touch i8, InBody S10) as an alternative to standard clinical assessment. The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. utilities), routine sources of cost data, and if necessary some study specific cost estimates (based on expert opinion). This model will be

used to estimate the effectiveness and cost-effectiveness of alternative strategies for fluid management in people with CKD treated with haemodialysis or peritoneal dialysis. The evidence on costs and cost-effectiveness will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[65]

6.3 Development of a health economic model

The proposed research will evaluate, using a decision analytic model, the clinical and cost-effectiveness of using multiple frequency bioimpedance devices to help guide fluid management decisions in people with CKD who are treated with dialysis. The comparator will be clinical assessment alone, as defined in the final scope for this assessment and in section 5.1 above. The economic model will incorporate the pathways of care that individuals follow under standard practice in the UK NHS, as well as the proposed new pathways involving the identified bioimpedance devices. It will simulate the incidence of overhydration and underhydration in cohorts on haemodialysis or peritoneal dialysis, and associated adverse health outcomes (e.g. cardiovascular events, loss of residual renal function, and mortality).

To help structure the model and clinical event pathways, previous economic models in the area of CKD and ESRD will be reviewed. The advice of clinical experts and the availability of supporting evidence will also guide decisions on the key morbidity/mortality events to include in the economic model. It is anticipated that the event pathways will be modelled through a number of mutually exclusive Markov health states. Transition probabilities between the health states (expressed on a constant cycle length) will govern the flow of cohorts through the model. However, we will retain the flexibility to move to an individual simulation approach if the preferred conceptual model becomes too complex to implement as a Markov cohort model. Risks (probabilities) of the included events under standard practice will be informed by a review of published observational/registry data applicable to the UK clinical setting. The control arms of identified randomised controlled trials (identified in the systematic review of clinical effectiveness) will also be assessed for generalisability to the UK context.

Alternative approaches to modelling the impact of bioimpedance technology on the baseline event rates will be considered depending on the types and extent of evidence available. Where direct evidence of impact on final health outcomes is available from RCTs, this will be the preferred source of evidence for incorporating effects in the model. Alternatively, if there are no direct data on the effects of using bioimpedance technology on important health outcomes (e.g. non-fatal CV events), we will consider using estimated effects on an appropriate surrogate endpoint (e.g. left ventricular hypertrophy; left ventricular mass index; loss of

residual renal function) to model effects of bioimpedance technology on longer term health outcomes. This will depend on whether there is an appropriate source of evidence to link the available surrogate endpoints to health outcomes in the relevant patient populations.

To capture modelled benefits in terms of quality adjusted life years, a focused search for utility values for the health states included in the model will be undertaken. This search will focus primarily on studies reporting EQ-5D values for UK patients with CKD on dialysis. However, if appropriate values cannot be identified for all the modelled event states in this population (e.g. post CV event states for those with ESRD), we will consider combining estimated health state utility multipliers obtained from wider cohorts (e.g. CV disease cohorts) with identified utility multipliers for ESRD. If the evidence supports an improvement in health related quality of life with the use of bioimpedance devices, through reductions in symptoms associated with overhydration/underhydration, the estimated utility increment will also be applied in the model.

Costs associated with health states and events included in the model will be informed by a focussed search of published cost studies applicable the UK NHS, supplemented with expert opinion and routine sources of unit cost data.[70, 71] In terms of the costs associated with the standard fluid management pathways, these will be based on a review of current clinical guidelines and any published data on the frequency of dialysis and monitoring visits in the UK NHS. Costs associated with the pathways involving the use of bioimpedance technology will be informed by any available sources of data on the frequency of testing and the experience/opinions of the specialist committee members for the assessment. Unit costs for the alternative bioimpedance devices and any associated consumables will be provided by the companies. Capital equipment costs will be amortised over the estimated useful lifespan of the device, and allocated on a per patient or per test basis using estimates of annual throughput per device.

The impact of applying different assumptions with respect to testing frequency and throughput will be explored through sensitivity analyses. Scenario analyses will explore the impact on cost-effectiveness of dialysis location (at home or at a renal unit) and of the grade of staff carrying out the monitoring. If the evidence for multiple frequency bioimpedance assessments supports a reduction in the number of dialysis sessions or a reduced rate of hospitalisation, then these cost savings will be factored into the model. Similarly, if the evidence supports the postulated reduction in the rate of adverse health outcomes, the associated costs savings will be captured. The costing perspective will be that of the NHS and Personal Social Services.

The results of the model will be presented in terms of a cost-utility analysis the lifetime of simulated cohorts. Each strategy will be compared incrementally to its next less effective non-dominated comparator, to estimate its incremental cost per quality adjusted life year gained (QALY). The modelling exercise will use the net benefit framework 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 will be undertaken.[72] The results of these analyses will be presented in the form of cost-effectiveness acceptability curves (CEACs) and frontiers (CEAFs). Further deterministic sensitivity analyses will be used to address other forms of uncertainty. The primary analysis will be conducted for a mixed cohort of patients on haemodialysis or peritoneal dialysis. Subgroup analyses will be conducted to explore any differences in cost-effectiveness by mode of dialysis and, where data allow, by characteristics of the patient population.

7. Handling information from the companies

Following a request for information, any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined.

8. Competing interests of authors

None

9. REFERENCES

1. *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 May 2016]

2. 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.

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

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

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

6. *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 May 2016]

7. 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.

8. 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.

9. 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 Meas* 2006;**27:**961-71.

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

11. 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.

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

13. 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.

14. 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. *Pediatr Nephrol* 2016;**31:**991-9.

15. 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.

16. 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.

17. 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.

18. 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.

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

20. 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.

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

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

23. *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 May 2016]

24. 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.

25. Levey AS, De Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. *Kidney Int* 2011;**80:**17-28.

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

27. 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.

28. 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.

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

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

31. 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.

32. 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.

33. 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.

34. 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.

35. *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 May 2016]

36. *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 May 2016]

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

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

39. 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.

40. 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.

41. 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.

42. 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.

43. 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.

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

45. 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.

46. 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.

47. 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.

48. 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 May 2016]

49. 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.

50. 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.

51. 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.

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

53. 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.

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

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

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

57. 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.

58. 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.

59. 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.

60. Hamilton AJ, Braddon F, Casula A, Inward C, Lewis M, Mallett T, et al. UK Renal Registry 18th Annual Report: Chapter 4 Demography of Patients Receiving Renal Replacement Therapy in Paediatric Centres in the UK in 2014. *Nephron* 2016;**132 Suppl 1:**99-110.

61. *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 May 2016]

62. *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 May 2016]

63. 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 May 2016]

64. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* 2009;**339:**332-6.

65. *NICE Diagnostic Assessment Programme Manual* Manchester: 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 May 2016]

66. Sterne JA, Higgins JP, Reeves BC. *The ROBINS-I tool a tool for assessing Risk Of Bias In Non-randomized Studies of Interventions, Version 7* The Cochrane Collaboration; 2016. URL: www.riskofbiastool.info/ [Accessed May 2016]

67. *Guide to the methods of technology appraisal*. London: National Institute for Health and Care Excellence; 2013. https://www.nice.org.uk/article/pmg9/chapter/Foreword [Accessed May 2016]

68. Drummond MF, O'Brien B, Sitoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes Oxford: Oxford University Press; 2005

69. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8(36).**.

70. *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 May 2016]

71. 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 May 2016]

72. Briggs A, Claxton K, Sculpher M. Analysing and presenting simulation output from probabilistic models. New York: Oxford Univerisity Press; 2006

APPENDIX 1

Draft MEDLINE STRATEGY FOR CLINICAL EFFECTIVENESS EVIDENCE

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp renal dialysis/
2 (haemodialysis or hemodialysis or dialysis).kw,tw.
3 1 or 2
4 bioimpedance.tw,kw.
5 body composition monitor$.tw,kw.
6 bioscan$.tw,kw.
7 bio scan$.tw,kw.
8 multiscan$.tw,kw.
9 multi scan$.tw,kw
10 inbody.tw,kw.
11 hypervol?emia.tw,kw.
12 hypovol?emia.tw,kw.
13 (fluid adj3 (status or overload or monitor$)).tw,kw.
14 (hydration adj3 (status OR monitor$)).tw,kw.
15 ((under or over) adj3 hydration).tw,kw.
16 underhydration.tw,kw.
17 overhydration.tw,kw
18 or/4-17
19 3 and 18
20 (editorial or comment or note or letter).pt.
21 19 not 20
22 exp animals/ not humans/
23 21 not 22

DRAFT MEDLINE STRATEGY FOR COST-EFFECTIVENESS EVIDENCE

Database: Ovid MEDLINE(R) without Revisions <1996 to May Week 2 2016>

Search Strategy:

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1 exp "costs and cost analysis"/
2 economics/
3 exp economics,hospital/
4 exp economics,medical/
5 economics,pharmaceutical/
6 exp models, economic/
7 exp decision theory/
8 monte carlo method/
9 markov chains/
10 exp technology assessment, biomedical/
11 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
12 economics model$.tw.
13 (economic$ or pharmacoeconomic$).tw.
14 (price or prices or pricing).tw.
15 budget$.tw.
16 (value adj1 money).tw.
17 (expenditure$ not energy).tw.
18 markov$.tw.
19 monte carlo.tw.
20 (decision$ adj2 (tree? or analy$ or model$)).tw.
21 or/1-20
22 (metabolic adj cost).tw.
23 ((energy or oxygen) adj (cost or expenditure)).tw.
24 (letter or editorial or note or comment).pt.
25 21 not (22 or 23 or 24)
26 exp animals/ not humans/
27 25 not 26
28 exp renal dialysis
29 (haemodialysis or hemodialysis or dialysis).kw,tw.
30 28 or 29
31 bioimpedance.tw,kw.
32 body composition monitor$.tw,kw.
33 bioscan$.tw,kw.

34 bio scan$.tw,kw.
35 multiscan$.tw,kw
36 multi scan$.tw,kw
37 inbody.tw,kw.
38 hypervol?emia.tw,kw.
39 hypovol?emia.tw,kw.
40 (fluid adj3 (status or overload or monitor$)).tw,kw
41 (hydration adj3 (status or monitor$)).tw,kw.
42 ((under or over) adj3 hydration).tw,kw.
43 underhydration.tw,kw.
44 overhydration.tw,kw
45 or/31-44
44 27 and 30 and 45