NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

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

The National Institute for Health and Care Excellence (NICE) is producing guidance on using multiple frequency bioimpedance devices to guide fluid management for people with chronic kidney disease who are on dialysis in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics Assessment Programme manual.

Key dates:

Closing date for comments: 8 March 2017

Second diagnostics advisory committee meeting: 23 March 2017

1 Draft recommendations

1.1 There is currently not enough evidence to recommend the routine adoption of the BCM – Body Composition Monitor to guide fluid management in people with chronic kidney disease having dialysis in the NHS. Further research is recommended to show the effect of using the BCM – Body Composition Monitor on clinical outcomes (see section 6.1).

Centres that are currently using the BCM – Body Composition Monitor to guide fluid management are encouraged to take part in research and data collection (see section 5.18).

Centres that do not currently use the BCM – Body Composition Monitor to guide fluid management should only do so as part of a research study, such as the BISTRO trial.

1.2 There is currently not enough validation or clinical-outcome data to recommend the routine adoption of the InBody S10 or the MultiScan 5000 to guide fluid management in people with chronic kidney disease having dialysis in the NHS.

2 Clinical need and practice

The problem addressed

2.1 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using multiple frequency bioimpedance devices to monitor the hydration status of a person with chronic kidney disease who is having either haemodialysis or peritoneal dialysis treatment.

2.2 Dialysis is used to replace renal function in people with severe chronic kidney disease, including the removal of excess fluid from the blood. It is important that a correct volume of fluid is removed; removing too little will result in the person becoming overhydrated and may lead to oedema, increased blood pressure and an increased risk of cardiovascular events. Alternatively, if too much fluid is removed during dialysis the person will become underhydrated, which can potentially result in the loss of residual renal function and an increased incidence of symptoms such as cramps, nausea and dizziness.

2.3 In current practice the fluid status of a person on dialysis is usually determined by clinical assessment, taking into account clinical features and symptoms that suggest overhydration or underhydration. People who are over or underhydrated are often asymptomatic, so clinical assessment may not identify this. Multiple

frequency bioimpedance devices give an objective assessment of a person's fluid status which, when used alongside clinical assessment, may help make decisions about the amount of fluid to remove in dialysis. Using the devices may help to reduce the incidence of overhydration or underhydration and their associated clinical consequences.

The condition

Chronic kidney disease and dialysis

2.4 Chronic kidney disease can be categorised into 5 stages of severity, in accordance with NICE's clinical guideline on chronic kidney disease. If chronic kidney disease progresses to the most severe stage (stage 5), kidney failure occurs and renal replacement therapy (transplantation or dialysis) is needed for survival.

2.5 Dialysis replicates many of the functions of a healthy kidney, for example, filtering waste products and excess water from the blood, and is available in 2 types: haemodialysis and peritoneal dialysis. When used as a longer-term renal replacement therapy, dialysis can be delivered in an outpatient setting or at home (see NICE's technology appraisal guidance on home compared with hospital haemodialysis for patients with end-stage renal failure).

The diagnostic and care pathways

Management of chronic kidney disease

2.6 The management of chronic kidney disease and renal replacement therapy is described in NICE's guidelines on chronic kidney disease, peritoneal dialysis, anaemia management in chronic kidney disease and hyperphosphatemia management in chronic kidney disease.

Determining fluid volumes to remove by dialysis

2.7 One of the main aims of dialysis is to remove fluid which builds up because of reduced renal function. Determining the volume of fluid to be removed by dialysis involves identifying a target weight for a person. This is often defined as how much a person should weigh at the end of a haemodialysis session or, for people who have peritoneal dialysis, how much they should weigh in the morning. Comparing a person's current and target weight helps to decide the amount of fluid to be removed during dialysis.

2.8 Assessing fluid status to set, or adjust, a person's target dialysis weight is usually based on clinical judgement and identifying symptoms of over or underhydration. Clinical parameters assessed include blood pressure, the presence of oedema, weight and any intradialytic or interdialytic symptoms that could suggest overhydration or underhydration (such as cramps, fatigue or nausea). Identification of a person's first target weight often involves gradually reducing a person's post-dialysis weight over successive dialysis sessions until it is as low as can be tolerated.

3 The diagnostic tests

The assessment compared 3 intervention devices with 1 comparator.

The interventions

3.1 Multiple frequency bioimpedance devices send small, painless electrical signals through the body by way of electrodes. The electrodes also measure the opposition to the flow of the electric current from body tissues (bioimpedance). Each of the devices included in this assessment are portable and could be used by a healthcare professional in either a clinic or the patient's home. Built-in software uses bioimpedance values to calculate parameters relating to hydration, such as volumes of extracellular, intracellular

and total body water. Based on these parameters, multiple frequency bioimpedance devices can also produce estimates of a person's target dialysis weight, using models or algorithms that differ between devices. These outputs should be used alongside clinical assessment to make decisions about the amount of fluid to be removed during dialysis.

BCM – Body Composition Monitor (Fresenius Medical Care)

3.2 The BCM – Body Composition Monitor uses bioimpedance spectroscopy and measures bioimpedance across 50 frequencies between 5 and 1,000 kilohertz (kHz). The technology includes a BCM – Body Composition Monitor unit with an output display screen. It is connected by cables to disposable electrodes which are attached to the body. A computer software application is also provided for further analysis, and external data storage devices (PatientCards) can be used to transfer outputs from the device to a computer using a card reader.

3.3 The device calculates parameters relating to hydration, such as volumes of extracellular, intracellular and total body water, and the ratio of extracellular to intracellular water volumes. It also calculates fluid overload using 2 physiological models adapted from techniques published by Chamney et al. (2007) and Moissl et al. (2006). This is the volume that a person is above, or below, their predicted normally hydrated volume.

InBody S10 (InBody)

3.4 The InBody S10 model is a multifrequency bioimpedance device that measures bioimpedance across 6 different frequencies (1, 5, 50, 250, 500 and 1,000 kHz). The device consists of an InBody S10 unit which contains a display monitor. The unit is connected by cables to electrodes which are attached to the body. Two types of electrode can be used with this device: disposable adhesive type

electrodes and reusable touch type electrodes which can be clipped to a person's hand and foot. As well as whole body measurements, bioimpedance measurements can also be made in 5 areas of the body; right arm, left arm, trunk, right leg, left leg.

3.5 The device calculates hydration-related outputs including water volumes (extracellular water and intracellular water) and ratio of extracellular to total body water. A suggested standard range of values is given, to help identify people who may be overhydrated or underhydrated. Accompanying software can calculate several suggested dry weight values for use, depending on any complications which may alter extracellular fluid volumes, such as diabetes or hypoalbuminaemia.

MultiScan 5000 (Bodystat)

3.6 The MultiScan 5000 uses bioimpedance spectroscopy and measures bioimpedance across 50 frequencies between 5 and 1,000 kHz. The system consists of a bioimpedance spectroscopy hardware unit which is connected by leads to disposable electrodes. Outputs are displayed on a colour touchscreen display. Results for up to 1,000 tests can be stored on the device, with additional data storage available through a Wi-Fi or Bluetooth connection to a computer. A calibrator unit and analytical software are also provided. As well as whole body measurements, bioimpedance can also be measured in different body areas by attaching electrodes in different positions on the body.

3.7 The device calculates hydration-related parameters such as the volumes of total body water and intracellular and extracellular water, as well as the ratio of total body to extracellular water volumes. The device also displays an estimate of the volume of fluid excess or deficit in a person, which is reported as the volume of overhydration in litres. This value is determined using models

based on methods set out in published literature (Chamney et al. 2007; Moissl et al. 2006).

The comparator

Clinical assessment

3.8 The comparator is clinical assessment to determine fluid status and set, or adjust, target weights for people with chronic kidney disease who are on dialysis. Clinical assessment may include blood pressure measurements, changes in weight, the presence of oedema, assessment of residual renal function, any pre-existing cardiovascular conditions and also any reported symptoms of overhydration or underhydration (such as dizziness or nausea). There is no generally accepted gold standard for identifying a person's target weight for assessing the accuracy of the comparator or interventions.

4 Evidence

The diagnostics advisory committee (section 9) considered evidence on the use of the BCM – Body Composition Monitor, InBody S10 and MultiScan 5000 to guide fluid management in people with chronic kidney disease having dialysis from several sources. Full details of all the evidence are in the committee papers.

Clinical effectiveness

4.1 Six randomised controlled trials (RCTs) met the inclusion criteria for the systematic review, all of which assessed use of the BCM – Body Composition Monitor (hereafter referred to as the BCM; Huan-Sheng et al. 2016; Hur et al. 2013; Luo et al. 2011; Onofriescu et al. 2012; Onofriescu et al. 2014; Ponce et al. 2014). Two of these trials (Onofriescu et al. 2012 and Onofriescu et al. 2014) may have reported the same trial or outcomes from an overlapping patient population. The possible effect of this was

explored by reporting the meta-analyses with and without Onofriescu et al. (2012). The Cochrane risk of bias tool was used to assess the risk of bias in the included RCTs. One of the RCTs was judged to be at low risk of overall bias (Onofriescu et al. 2012) and 1 was at high risk of bias (Luo et al. 2011). The remaining 4 RCTs did not give enough information to make a judgement on the risk of bias.

4.2 The frequency of BCM use varied between studies, from twice monthly to every 3 months. All of the RCTs were done outside the UK. Only 1 study included people having peritoneal dialysis (Luo et al. 2011), the remaining studies enrolled people having haemodialysis. Five trials included people aged 18 years or over and the remaining trial did not give the age-related exclusion criteria, but the mean age of participants was 52.4 years (standard deviation 13.1 years; Onofriescu et al. 2012). Other groups excluded from some of these studies were people with limb amputations, pregnant women and people with coronary stents, pacemakers or metallic implants. No RCTs were identified for the InBody S10 or the MultiScan 5000.

4.3 Eight non-randomised cohort studies, reported in 9 papers, were also included in the systematic review (Castellano et al. 2014; Hoppe et al. 2015; Kim et al. 2012; Kim et al. 2015; Oei et al. 2016; O'Lone et al. 2014; Onofriescu et al. 2015; Santhakumaran et al. 2016; Wizemann et al. 2009), all of which assessed the BCM device. Studies were included if they involved at least 100 participants. Two of these studies (reported in O'Lone et al. 2014, Oei et al. 2016 and Santhakumaran et al. 2016) may have

overlapping patient populations. All participants included in the non-randomised studies had monitoring using the BCM.

4.4 The frequency of device use varied widely between studies, from just once in the first week of dialysis to 3 assessments per week. Two studies were done in the UK (reported in O'Lone et al. 2014, Oei et al. 2016 and Santhakumaran et al. 2016) and none of the studies enrolled paediatric patients. Most of the studies included people having haemodialysis (6 studies) rather than peritoneal dialysis (2 studies). The risk of bias in the non-randomised studies was assessed using the Review Body for Interventional Procedures tool. None of the studies included blinded participants or study personnel, and the characteristics of participants who withdrew from the studies were not reported.

Evidence on clinical outcomes

Mortality

4.5 Three RCTs reported data on mortality (Onofriescu et al. 2014; Ponce et al. 2014; Huan-Sheng et al. 2016). Use of the BCM device had no significant effect on mortality rates (pooled hazard ratio 0.69; 95% confidence interval [CI] 0.23 to 2.08; p=0.51) and there was moderate statistical heterogeneity between trials.

4.6 Three non-randomised studies had results for the effects of hydration status on mortality in subgroups of participants monitored with the BCM device. Kim et al. (2015) reported a higher incidence of mortality in overhydrated participants (defined by relative hydration state; odds ratio 2.57; 95% CI 1.08 to 6.13; p=0.033). In O'Lone et al. (2014), absolute overhydration had a significant effect on the risk of mortality (hazard ratio 1.10; 95% CI 1.01 to 1.20; p=0.025) and Wizemann et al. (2009) reported that hydration state was an important predictor of mortality in patients having

haemodialysis (adjusted hazard ratio 2.10; 90% CI 1.39 to 3.18; p=0.003).

Patient-reported adverse effects associated with dialysis

4.7 Huan-Sheng et al. (2016) reported significant differences in intradialytic complications between people monitored with and without the BCM device. But incidences were not consistently higher in 1 group. For people monitored using BCM, significantly higher incidences of cramping, chest tightness and headaches were reported. However, significantly lower incidences of complications caused by hypotension during dialysis sessions and skin itching were reported. The difference in the number of patient-reported events of intradialytic fatigue in participants monitored with and without the BCM was not statistically significant (p=0.7).

4.8 Hur et al. (2013) reported no significant difference in the frequency of intradialytic events between groups monitored with and without the BCM device at 12 months (66.6 and 63.9 events per 1,000 dialysis sessions respectively; p=0.4). Similarly, Onofriescu et al. (2014) found no significant difference in the incidence of hypotension or cramps (p=0.6). Ponce et al. (2014) reported no significant difference in the incidence of hypotensive events (defined as a drop in systolic blood pressure during dialysis by at least 30 mm of mercury [Hg] or to below 90 mm Hg) at 12 months.

Incidence of cardiovascular events

4.9 One RCT (Huan-Sheng et al. 2016) reported the incidence of cardiovascular-related events, although this was in combination with the incidence of acute fluid overload events. The incidence rate in people monitored with the BCM device was significantly

lower than the control group (incidence rate ratio 0.50 per patient-year; 95% CI 0.26 to 0.94; p=0.03).

4.10 Three non-randomised studies gave the incidence of cardiovascular events among subgroups of people monitored using the BCM device. Kim et al. (2015) reported no statistically significant difference in the number of cardiovascular events per year between overhydrated and non-overhydrated subgroups as determined by the level of relative overhydration (p=0.13). Onofriescu et al. (2015) also found no statistically significant difference in the incidence of coronary heart disease, peripheral vascular disease, heart failure or stroke between subgroups with lower relative fluid overload (less than 17.4%) and higher relative fluid overload (over 17.4%). Hoppe et al. (2015) reported a non-significant difference in the incidence of acute myocardial infarction and stroke between people who had been having dialysis for a shorter length of time (short dialysis vintage) and people who had been having dialysis for a longer length of time (long dialysis vintage).

Residual renal function

4.11 No RCTs gave data on residual renal function, although 2 reported urinary output which could be used as a surrogate measure. Hur et al. (2013) found a significant increase in the proportion of patients with anuria, that is when the kidneys no longer produce urine, and a significant decrease in urine output in patients without anuria in a group monitored using the BCM device. In the corresponding control group, there was no change in the proportion of patients with anuria and the decrease in urine output seen in patients without anuria was not significant. Luo et al. (2011) reported non-

significant decreases in urine volume in groups monitored with and without the BCM device.

Evidence on intermediate outcomes

Blood pressure

4.12 All 6 included RCTs reported systolic blood pressure measurements. Use of the BCM device was associated with a significantly lower systolic blood pressure in a meta-analysis (pooled mean difference −3.48 mm Hg; 95% CI −5.96 to −1.00; p=0.006). When data from Onofriescu et al. (2012) was removed from the meta-analysis, the effect size of BCM-guided monitoring was reduced and was no longer significant (pooled mean difference −2.46 mm Hg; 95% CI −5.07 to 0.15; p=0.06).

4.13 The external assessment group (EAG) also did a subgroup analysis of systolic blood pressure according to the type of dialysis: peritoneal dialysis (1 RCT) or haemodialysis (5 RCTs). In the haemodialysis subgroup, use of the BCM device was associated with a significant decrease in systolic blood pressure (pooled mean difference −3.09 mm Hg; 95% CI −5.88 to −0.31; p=0.03). For patients having peritoneal dialysis, Luo et al. (2011) reported a mean decrease in systolic blood pressure of −6.08 mm Hg (95% CI −12.57 to 0.41) associated with use of the BCM device.

4.14 Four non-randomised studies gave data on blood pressure among subgroups of people monitored using the BCM device. No statistically significant differences in blood pressure were seen in the following subgroup comparisons: patients in whom the average overhydration decreased within 6 months compared with those in whom it did not decrease (Castellano et al. 2014), patients who had been having dialysis for a short length of time compared with those who had been having it for longer (Hoppe et al. 2015), and patients with a high relative fluid overload (more than 17.4%) compared with

those in whom it was low (less than 17.4%; Onofriescu et al. 2015). Kim et al. (2012) reported that systolic blood pressure was higher in hyperhydrated patients when compared with dehydrated patients (significance not stated).

Arterial stiffness

4.15 Three RCTs gave data on carotid-femoral pulse wave velocity as a surrogate for arterial stiffness (Hur et al. 2013; Onofriescu et al. 2012; Onofriescu et al. 2014) and were included in a meta-analysis. Arterial stiffness is thought to be associated with an increased risk of cardiovascular events in the longer term. Pulse wave velocity was significantly reduced in patients who were monitored using the BCM device and standard clinical assessment compared with standard clinical assessment alone (mean difference −1.53 meters per second [m/s]; 95% CI −3.00 to −0.07; p=0.04). There was high statistical heterogeneity between the studies. If data from Onofriescu et al. (2012) were removed from the meta-analysis, the pooled effect was no longer significant (mean difference −1.18 m/s; 95% CI −3.14 to 0.78; p=0.24).

Absolute overhydration

4.16 Five RCTs (Huan-Sheng et al. 2016; Hur et al. 2013; Luo et al. 2011; Onofriescu et al. 2012; Ponce et al. 2014) assessed absolute overhydration; that is, the volume of fluid by which the participants were above their target volume (as assessed by the BCM device). No data on underhydration were available. A meta-analysis of the mean difference in absolute overhydration volumes showed that absolute overhydration was significantly lower in groups monitored with the BCM device (mean difference = −0.39 litres, 95% CI −0.62 to −0.15, p=0.001).

4.17 The EAG did a subgroup analysis for absolute overhydration, as assessed by the BCM device, according to type of dialysis. They

compared the pooled effect of using the BCM device on absolute overhydration in the overall group (all 5 studies) and a subgroup of studies on people having haemodialysis (4 of these studies). A difference in effect between the overall and haemodialysis subgroup was seen, but the EAG stated that this was not large enough to suggest a significant dialysis effect.

Relative overhydration

4.18 Four RCTs had results for relative overhydration (Huan-Sheng et al. 2016; Onofriescu et al. 2012; Onofriescu et al. 2014; Ponce et al. 2014); that is, a person's absolute overhydration volume normalised against their total extracellular body water volume (both volumes assessed by the BCM device). A meta-analysis of the reported mean differences in the relative overhydration between groups monitored with and without the BCM device showed that relative overhydration was significantly lower when the BCM device was used (mean difference = −1.54; 95%CI −3.01 to −0.07; p=0.04).

Hospitalisation

4.19 Three RCTs gave data on hospitalisations. Huan-Sheng et al. (2016) reported that the difference in all-cause hospitalisation in patient groups monitored with and without the BCM device was not significant (hazard ratio 1.19; 95% CI 0.79 to 1.80). Hur et al. (2013) found that the difference in rates of hospitalisation caused by new cardiovascular events in the control and BCM monitored groups was not statistically significant. In Ponce et al. (2014), 39.6% of participants in the BCM monitored group and 31.8% of the standard clinical assessment group were hospitalised at least once.

4.20 Two non-randomised studies gave data on hospitalisation. Kim et al. (2015) found no significant differences in the number of hospital

days per event between overhydrated and non-overhydrated groups (as determined by the BCM device). Onofriescu et al. (2015) found a significantly higher all-cause hospitalisation rate for patients classified as overhydrated when a relative overhydration value of 17.4% was used as a cut-off to define people as overhydrated, but not when a value of 15% was used.

Left ventricular hypertrophy and left ventricular mass index

4.21 Measures of left ventricular hypertrophy, and surrogates of this, such as left ventricular mass index, may be associated with longer-term cardiac morbidity. Hur et al. (2013) reported that left ventricular hypertrophy was present at 12 months in 44% of participants monitored using the BCM device and in 50% of participants monitored using standard clinical assessment alone. This was a non-significant reduction from baseline in both groups (67% and 53% respectively). But there was a statistically significant reduction in left ventricular mass index from baseline in the group monitored using the BCM device ($p<0.001$), although not in the group monitored using standard clinical assessment ($p=0.9$).

Use of antihypertensive medication

4.22 Two non-randomised studies gave data on the use of antihypertensive medication in subgroups of people monitored using the BCM device. In Castellano et al. (2014), consumption of antihypertensive medication was significantly higher in a subgroup of patients who did not have reduced relative overhydration after 6 months of monitoring. Kim et al. (2012) found no significant difference in medication use between people who were dehydrated or hyperhydrated.

People under 18 years

4.23 Three non-randomised studies that enrolled people under 18 years were identified by the EAG (all of which assessed the BCM). One

of these studies (reported in Zaloszyc et al. [2013] and Zaloszyc et al. [2016]) investigated the association between relative hydration status (measured using the BCM device) and blood pressure in children having dialysis. The study authors concluded that hypertension was not always related to overhydration; and that using bioimpedance spectroscopy could prevent incorrect reduction of a child's target weight to try and reduce hypertension, when it is not caused by excess fluid.

Ongoing trials

4.24 Four ongoing trials that will report outcomes which may be relevant to this assessment were identified. One of these trials, the BioImpedance Spectroscopy to maintain Renal Output (the BISTRO trial; ISRCTN11342007), will be UK based. This multi-centre study, funded by the National Institute for Health Research, has a primary outcome of time to anuria (loss of urine output). The study will involve random allocation of participants (adults starting haemodialysis because of chronic kidney disease stage 5) for either regular assessment with a bioimpedance device plus standard treatment or standard treatment alone. Secondary outcomes will include the rate of kidney function reduction, vascular access failure, cardiovascular events, hospital admissions, death and patient-reported outcomes, such as quality of life, dialysis symptoms and functional status (measured at baseline, then every 3 months for up to 24 months). The trial is scheduled to start recruiting in March 2017, with a planned publication date of February 2020.

Cost effectiveness

Review of economic evidence

4.25 The EAG did a systematic review to identify existing studies on the cost effectiveness of using multiple frequency bioimpedance

devices to monitor the fluid status of people with chronic kidney disease who are on dialysis. No studies reporting full economic evaluations relevant to the scope of this assessment were identified.

Modelling approach

4.26 The EAG developed a de novo economic model to assess the cost effectiveness of using multiple frequency bioimpedance testing to help guide fluid management decisions in people having dialysis for chronic kidney disease. The model took the perspective of NHS and personal social services.

Model structure

4.27 A Markov model was developed to simulate the effects of monitoring the fluid status of cohorts of people on dialysis, using a multiple frequency bioimpedance device with standard assessment or by standard assessment alone. The model was run as a cohort simulation over a 30-year time horizon for a 66 year old mixed dialysis population in the base-case analyses. All future costs and benefits included in modelling were discounted at a rate of 3.5% per annum.

4.28 In the model, people started in a stable state on either haemodialysis or peritoneal dialysis and over time could either stay in that state or move to others when events (such as a kidney transplant, cardiovascular event or death) happened. These events could occur in each cycle of the model, which was set as 3 months. The characteristics of the cohort of patients modelled (for example, their age, the proportion of people on haemodialysis or peritoneal dialysis, gender, and incidence of comorbidities) were based on the UK Renal Registry Report (2015). Mortality rates and hospitalisation rates were informed by a combination of European

(ERA-EDTA Registry Annual Report 2013*)* and UK Renal Registry data, and other published sources.

4.29 The model also had an option to allow people in the 'stable' and 'post-CV event' dialysis states to be further classified as either severely overhydrated or normohydrated (based on their relative overhydration). This allowed scenarios to be run in the model in which mortality and hospitalisation rates were increased for dialysis patients who were overhydrated. No 'underhydrated' state was included because of a lack of evidence on the prevalence of underhydration in UK dialysis cohorts, the effect of underhydration on the risk of adverse events and quality of life, and the effectiveness of the BCM device in reducing the incidence of underhydration.

Model inputs

4.30 Parameter values used in the model were taken from focused reviews of the literature to identify baseline risks for mortality and hospitalisation, and also sources for cost and utility data, and the clinical-effectiveness review. Several possible outcomes that may be affected by using the BCM device were not included in base-case modelling because of a lack of evidence. These included changes in quality of life (independent of effects of hospitalisation and cardiovascular events), maintenance of residual renal function and effects on dialysis requirements (number and duration of sessions).

4.31 The clinical-effectiveness review only found data on using the BCM, therefore only this device has been assessed in base-case analyses. Several scenarios were used to model the effect of BCM-guided fluid management on baseline model parameters. Direct evidence was only available for the effect of BCM-guided monitoring on all-cause mortality. Several identified trials also

reported the effects of BCM-guided monitoring on surrogate endpoints, such as pulse wave velocity as a measure of arterial stiffness. The EAG did a further literature search to identify evidence that could be used to link changes in these surrogate endpoints to final health outcomes. Using this linked approach, estimated effects of BCM-guided monitoring on mortality and non-fatal cardiovascular events were calculated. The EAG also modelled an effect of assuming that BCM-guided monitoring reduced the proportion of people who were seriously overhydrated (with relative overhydration over 15%). This was applied by classifying people in dialysis states in the model as either severely overhydrated or normohydrated, which allowed mortality and hospitalisation rates to be adjusted upwards for proportions of people in the dialysis cohorts who were estimated to be severely overhydrated. Table 1 gives a summary of the relative effects applied to different parameters in the base-case scenario analyses.

Table 1 Summary of effect estimates for BCM-guided monitoring used in base-case scenario analyses

Scenario	Relative effect on all-cause mortality (HR; 95% CI)	Relative effect on hospitalisation for non-fatal CV (HR; 95% CI)	Effect on blood pressure medication costs (£ mean reduction)	Proportional reduction in severe overhydration
Scenario 1	0.69 (0.23 to 2.08)	1.00	0.00	-
Scenario 2	0.69 (0.23 to 2.08)	0.91 (0.82 to 1.01)	0.00	-
Scenario 3	0.91 (0.82 to 1.01)	0.91 (0.82 to 1.01)	0.00	-
Scenario 4	0.91 (0.82 to 1.01)	0.91 (0.82 to 1.01)	−12.98	-
Scenario 5	-	-	-	0.28
Scenario 6	-	-	-	0.38

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Costs

4.32 The model incorporates health service costs associated with maintenance dialysis, blood pressure medication, erythropoietin stimulating agents, all-cause inpatient hospitalisation, renal transplantation (including work-up, surgery and follow-up), post-transplantation immunosuppression and outpatient visits. Dialysis costs, per session (haemodialysis) or per day (peritoneal dialysis), were taken from NHS reference costs (2014-2015). For haemodialysis, the average cost of £154 per haemodialysis session was calculated based on the cost per type of session, at home or at a unit, weighted by relative incidence. For peritoneal dialysis, the average cost per day of £69 was taken from the NHS reference costs.

4.33 Costs of bioimpedance monitoring included in modelling were purchase costs for devices (annuitised over 5 years), maintenance costs, staff costs related to using the device, training costs and device consumable costs (such as electrodes). The costs of the bioimpedance devices are shown in table 2.

Table 2 Costs of the multiple frequency bioimpedance devices

Bioimpedance device	Cost	Expected service life	Maintenance cost	Estimated annual cost of device consumables	Estimated annual cost per patient per year [e]
BCM – Body Composition Monitor	£5,750	5 years	£250	£13.26 [c]	£96.50 [f]
InBody S10	£8,100	5 years	–[a]	£2.08 [d]	£93.03
MultiScan 5000	£7,600	5 years	£70[b]	£4.40	£91.22

[a] No maintenance costs provided.

[b] Assumes a replacement set of leads annually.

[c] Assumes use of patient cards

[d] Assumes use of reusable electrodes and cost of results sheets.

[e] Assumes testing every 3 months

[f] Including maintenance contract without parts and labour.

Health-related quality of life and quality-adjusted life year decrements

4.34 Health state utility values for people on dialysis and post-renal transplant were identified through a focused search of the literature. Two systematic reviews were found that published EQ-5D data for UK patients (Liem et al. 2008; Wyld et al. 2012). Further searches did not identify any other studies reporting EQ-5D data for UK patients after 2010 (the end date for searches in the most recent systematic review). Short and longer-term utility multipliers associated with cardiovascular events were calculated based on data from the Health Survey for England (2003 and 2006). Decreases in health state utilities resulting from hospitalisations were taken from the NICE guideline on peritoneal dialysis.

Base-case results

4.35 The following main assumptions were applied in the base-case analysis:

- Hydration status was assessed with a bioimpedance device every 3 months and, if needed, people had their target weight modified in line with the results.
- Any effect of BCM-guided monitoring on the length and frequency of dialysis sessions was assumed to be cost neutral.
- In the starting cohort of modelled patients, 87% were having haemodialysis and 13% were having peritoneal dialysis.
- The starting age of the cohort was 66 years.
- Survival on haemodialysis and peritoneal dialysis was assumed to be equivalent, and patients did not switch between dialysis modes.
- Fixed proportions of the cohort were on a waiting list for transplant, and waited a median of about 3 years, depending on survival. No transplants were done in patients over 75 years.
- It was assumed that 17.6% of all inpatient hospitalisations were because of cardiovascular events.
- Health state utility decrements were applied in the acute period for all hospitalisation events, and ongoing health state utility decrements were also applied after hospitalisation for a cardiovascular event.
- Effects of bioimpedance monitoring on all-cause mortality were applied for 10 years in the model.
- Effects of bioimpedance monitoring on cardiovascular-related or all-cause hospitalisation were applied over the lifetime of the cohort.

4.36 Six base-case scenarios were modelled, each differing in the assumed effects of BCM-guided monitoring, as described above in table 1. Incremental cost-effectiveness ratios (ICERs) were

calculated both with and without dialysis costs (table 3), because including BCM-guided monitoring in the model prolonged life expectancy, so dialysis was needed over a longer period which increased dialysis costs.

Table 3 Deterministic cost-effectiveness scenarios for BCM-guided fluid management compared with standard practice (with and without dialysis costs)

Intervention	Including dialysis costs		Without dialysis costs	
	ICER (cost per QALY gained)	Net monetary benefit*	ICER (cost per QALY gained)	Net monetary benefit*
Scenario 1				
Standard assessment	-	−£104,097	-	£7,793
BCM	£62,532	−£128,366	£16,378	£9,859
Scenario 2				
Standard assessment	-	−£104,097	-	£7,793
BCM	£60,855	−£127,786	£15,435	£10,440
Scenario 3				
Standard assessment	-	−£104,097	-	£7,793
BCM	£59,144	−£109,983	£15,636	£8,449
Scenario 4				
Standard assessment	-	−£104,097	-	£7,793
BCM	£58,721	−£109,919	£15,212	£8,513
Scenario 5				
Standard assessment	-	−£106,708	-	£8,285
BCM	£66,013	−£109,858	£21,206	£8,203
Scenario 6				
Standard assessment	-	−£106,708	-	£8,285
BCM	£64,157	−£110,810	£19,350	£8,346

Abbreviations: BCM, BCM – Body Composition Monitor; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

* Calculated at a willingness to pay threshold of £20,000 per QALY gained.

4.37 Cumulative costs per patient monitored with and without the BCM device in scenario 3 were calculated. Costs were higher for BCM-

guided monitoring because people on average lived for longer, with dialysis costs making up most (74%) of the increase in cost.

Analysis of alternative scenarios

4.38 Several further scenario analyses, based on varying parameters in the base-case scenario 3 model, were done. Results were generally reported without considering the costs of dialysis (unless otherwise stated) and in relation to the ICER produced in base-case scenario 3 when dialysis costs were excluded (£15,636 per quality-adjusted life year [QALY] gained). The results were as follows:

- Increasing the frequency of BCM monitoring to every month (from every 3 months) increased the ICER to £19,818 per QALY gained.
- Applying the estimated costs associated with monitoring in paediatric centres (which have a lower throughput of patients and so higher estimated costs of bioimpedance monitoring) to the modelled adult population increased the ICER to £20,329 per QALY gained (assuming testing every 3 months). This was increased to £23,647 per QALY gained if testing was assumed to be done every month.
- Assuming that BCM-guided fluid management resulted in a 2% improvement in health state utility over a patient's lifetime reduced the ICER to £11,758 per QALY gained (£44,477 if dialysis costs were included). If this improvement was increased to 5%, the ICER reduced further to £8,570 per QALY gained (£32,418 if dialysis costs were included).
- If BCM-guided monitoring was assumed to result in a 10% reduction in lifetime dialysis costs, BCM-guided care dominated standard care (that is, it costs less but produces more QALYs). If a 5% reduction in lifetime dialysis costs was assumed, the ICER for BCM-guided care (including dialysis costs) was £19,759 per

QALY gained (compared with £59,144 per QALY gained in the base-case analysis when including dialysis costs).

- If BCM-guided monitoring was assumed to have no effect on mortality (that is, the effects were only as a result of changes in the incidence of non-fatal cardiovascular events), the ICER including the cost of dialysis was £21,327 per QALY gained (compared with £59,144 per QALY gained in base-case analysis).
- If BCM-guided monitoring was assumed to have no effect after 3 years, the ICER for BCM-guided monitoring increased to £18,324 per QALY gained.

4.39 Further scenario analyses produced little change in the base-case scenario ICERs, with ICER values (not including dialysis costs) of between £9,000 and £19,000 per QALY gained.

InBody S10 and MultiScan 5000

4.40 No clinical-effectiveness data were found for the InBody S10 or MultiScan 5000. These devices were therefore not included in base-case cost-effectiveness modelling. But they were included in scenario analyses which assumed that these devices reduced mortality and non-fatal cardiovascular events to the same extent as the BCM device in scenario 3 (but with different costs). The ICERs produced for these devices were very similar, being between £15,000 and £16,000 per QALY gained.

Subgroup analyses

4.41 Subgroup analysis were also done with the dialysis population grouped by comorbidity status (none or at least 1), dialysis modality (haemodialysis or peritoneal dialysis), starting age of the cohort, whether a person was on a transplant list or not, and whether or not they were chronically overhydrated. No large differences in cost effectiveness by subgroup were identified. ICERs for all subgroups

stayed below £16,500 per QALY gained (when dialysis costs were not included), except for people listed for a transplant who had an ICER of £20,297 per QALY gained.

Sensitivity analyses

Deterministic sensitivity analyses

4.42 One-way sensitivity analyses were done on model parameters for base-case scenario 3 (both with and without dialysis costs). When dialysis costs were included, adjusting the hazard ratio for all-cause mortality to 1.00 resulted in the most favourable ICER for BCM-guided monitoring. This was because these people have the same survival as those having standard monitoring, and therefore do not have higher dialysis costs, but do have the benefit of a reduced cardiovascular hospitalisation rate. When dialysis costs are included, ICERs produced by varying model parameters within their specified ranges generally stayed above £30,000 per QALY gained.

4.43 When dialysis costs were not included, the ICERs stayed sensitive to varying all-cause mortality. But, in this case, the least favourable ICER occurs when the hazard ratio is equal to 1.00.

Probabilistic sensitivity analyses

4.44 The EAG did probabilistic sensitivity analyses for base-case scenarios 1, 3 and 4 (both with and without dialysis costs included). Results are shown in table 4. The probabilistic ICERs produced for all 3 base-case scenarios were similar to the deterministic ICERs (shown in table 3 above). If dialysis costs were included, the probability of BCM-guided monitoring being cost effective at a maximum acceptable ICER of £20,000 per QALY gained was 26% in scenario 1 and less than 6% in scenarios 3 and 4. If dialysis costs were excluded, BCM-guided monitoring was 67% to 75% likely to be cost effective at this maximum acceptable ICER in the 3

scenarios. The EAG warned that the uncertainty in the parameters produced by linking the effects of monitoring with the BCM device on arterial stiffness to mortality and non-fatal cardiovascular events (as in base-case scenarios 3 and 4) may not be fully captured in the probabilistic modelling.

Table 4 Probabilistic cost-effectiveness scenarios for BCM-guided fluid management compared with standard assessment (both with and without dialysis costs included)

Intervention	With dialysis costs		Without dialysis costs	
	ICER (cost per QALY gained)	Probability of cost effectiveness at £20,000 per QALY gained	ICER (cost per QALY gained)	Probability of cost effectiveness at £20,000 per QALY gained
Scenario 1				
Standard assessment	–	0.737	–	0.328
BCM	£63,983	0.263	£16,269	0.672
Scenario 3				
Standard assessment	–	0.941	–	0.306
BCM	£58,396	0.059	£15,579	0.694
Scenario 4				
Standard assessment	–	0.952	–	0.255
BCM	£58,011	0.048	£15,015	0.745

Abbreviations: BCM, BCM – Body Composition Monitor; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

4.45 As noted in the clinical-effectiveness section, removing the Onofriescu et al. (2012) data from meta-analysis reduced the estimated effect of BCM-guided monitoring on reducing arterial stiffness. Because the pooled estimate of arterial stiffness was used to estimate the relative treatment effects of the BCM in modelling (in base-case scenarios 2, 3 and 4), a revised cost-effectiveness analyses was done with BCM modelling assumed to have a smaller and more uncertain effect on hospitalisation for cardiovascular events and mortality. Similar ICERs were produced

for revised base-case scenarios 2, 3 and 4 and also for most of the further revised sensitivity, subgroup and scenario analyses. But there was greater uncertainty about the cost-effectiveness results in the revised probabilistic analyses. When dialysis costs were included, the probability of BCM being cost effective increased from less than 6% to about 13% for scenarios 3 and 4. When dialysis costs were excluded, the probability of BCM being cost effective decreased for revised scenarios 3 and 4 (from about 72% to about 62%). This reflected the greater uncertainty in the effect of BCM-guided monitoring on reducing arterial stiffness, and so the linked effect on all-cause mortality and hospitalisation for cardiovascular events.

5 Committee discussion

5.1 The committee discussed current practice in the NHS for monitoring the fluid status of people with chronic kidney disease who are having dialysis. It heard from clinical experts that target weights are set to determine how much fluid should be removed during a dialysis session. A person's target weight is usually set and adjusted based on clinical assessment, which takes into account the person's clinical history and any reported symptoms that may suggest fluid overload or dehydration. It heard that there is currently no standardised approach to clinical assessment of fluid status and that there is variation both in how it is done and also the frequency with which it occurs. The committee concluded that current practice for monitoring fluid status in people having dialysis is highly subjective and results in variation in practice both in and between centres.

5.2 The committee discussed the effect of fluid imbalances on the quality of life of a person having dialysis. It heard from a patient expert that the consequences of fluid overload can include oedema

and difficulty breathing. In contrast, removing too much fluid during haemodialysis can lead to painful muscle cramps and hypotension, which can cause a person to faint during or shortly after dialysis sessions. It can also cause more prolonged side effects such as headaches and fatigue after a haemodialysis session. The committee heard from clinical experts that in the shorter term, fluid overload can result in hypertension whereas dehydration can lead to hypotension and decreased blood flow to organs, such as the heart and brain. The longer-term consequences of persistent or intermittent fluid overload and dehydration in adults can include cognitive decline, reduced residual renal function and major adverse cardiovascular events. In children, who often have dialysis as a bridge to a renal transplant, it may contribute to developmental delay and increase their risk of adverse cardiovascular events in later life, particularly if they go on to have dialysis as an adult after transplant failure. The committee concluded that technologies that aim to provide a more objective assessment of fluid status in people having dialysis may be a way of improving the quality of life for this population.

Clinical effectiveness

5.3 The committee reviewed the available evidence on the clinical effectiveness of using multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis. It noted that in total, 14 studies were included in the review, 6 of which were randomised controlled trials (RCTs). All of the studies reported data for the BCM – Body Composition Monitor (BCM) device only, and 5 of the RCTs were noted to be at a high or uncertain risk of bias. No studies reported data for the InBody S10 or MultiScan 5000. The committee heard from clinical experts that the devices use different models to calculate how overhydrated or underhydrated a person is. Also, no data were available to

determine the equivalence of fluid overload or target weight calculated by these devices and values calculated by the BCM. The committee noted that without device-specific or equivalence data, the InBody S10 or MultiScan 5000 could not be considered further in this assessment.

5.4 The committee discussed the generalisability of data from the included studies to the NHS. It noted that none of the RCTs and 2 of the non-randomised studies (reported in 3 papers) were done in the UK. The committee heard from clinical experts that current practice varies widely between countries, particularly on whether fluid status is assessed by nursing or medical staff and how frequently assessments are done. It also noted that many of the studies did not give enough details to determine how standard clinical assessment was done, making it difficult to determine whether they were representative of UK practice. The committee therefore concluded that the effect estimates reported by the included studies may not be generalisable to clinical practice in England.

5.5 The committee discussed the evidence available on the effect of BCM-guided monitoring on mortality. The committee noted that the pooled effect estimate (pooled hazard ratio 0.69; 95% confidence interval [CI] 0.23 to 2.08; p=0.51) of BCM-guided monitoring on mortality was not significant. It noted that the total number of mortality events in the 3 included studies was small (42 events) and that the methods used for randomisation were not adequate. It heard from clinical experts that these studies were not powered to show an effect on mortality because this is not the main aim of using the BCM device to guide fluid management. The committee concluded that there is likely to be substantial bias underlying the meta-analysis of mortality data and so there is great uncertainty about the pooled effect estimate.

5.6 The committee discussed the effect of BCM-guided monitoring on intermediate outcomes such as blood pressure control and arterial stiffness. The committee noted that 3 RCTs reported data on arterial stiffness measured by pulse wave velocity and questioned the methods used to get the data. It heard from clinical experts that measurements of pulse wave velocity in these studies were carotid-femoral pulse wave velocity, which is not considered an appropriate surrogate for cardiac morbidity. The committee also noted that 2 of the studies included in the meta-analyses for blood pressure and arterial stiffness (Onofriescu et al. 2012 and 2014) seemed to have overlapping patient populations. When both of these studies are included in the meta-analyses, BCM-guided monitoring results in a significant improvement in blood pressure ($p=0.006$) and arterial stiffness ($p=0.04$), but if Onofriescu et al. (2012) is removed the effect is no longer significant. The committee concluded that there was substantial uncertainty around the effect of BCM-guided monitoring on reducing arterial stiffness and blood pressure, and so on cardiovascular outcomes.

5.7 The committee considered the data available on the effect of BCM-guided monitoring on patient-reported adverse effects associated with dialysis. It noted that data from identified studies did not show a clear benefit to using the device. A patient expert commented that since their fluid levels had been monitored using the BCM device, they had experienced fewer side effects associated with fluid imbalance, and that if they have symptoms possibly related to dialysis a reading with the device can be used to check if they are because of fluid levels. The committee concluded that there is considerable uncertainty about the effect of BCM-guided monitoring on reducing the number of patient-reported adverse effects associated with fluid imbalance and dialysis.

5.8 The committee noted that the studies included reported data on the effect of fluid overload, but did not consider the effect of underhydration. It heard from a clinical expert that the BCM device may identify people, who have previously been identified as normally hydrated by clinical assessment, as underhydrated. Underhydration can lead to clotting in dialysis fistulas, muscle cramps and nausea. It heard that identifying people who are underhydrated, or preventing underhydration, could help to preserve residual renal function in people having dialysis. The committee concluded that more data is needed in this subgroup and noted that this will be collected in the National Institute for Health Research (NIHR) funded BISTRO trial (see section 5.17).

5.9 The committee discussed the likely effect of BCM-guided monitoring on peritoneal dialysis. The committee noted that most of the studies included in the clinical-effectiveness analyses reported data for haemodialysis. Only 1 RCT assessed use of the BCM device in people having peritoneal dialysis, and reported that BCM-guided monitoring reduced systolic blood pressure (mean difference −6.08 mm Hg; 95% CI −12.57 to 0.41) and absolute overhydration (−0.80 litres; 95% CI −1.32 to −0.28). The committee questioned whether BCM-guided monitoring could be expected to have a similar effect in both types of dialysis. The committee heard from clinical experts that the effect of BCM-guided monitoring for people on haemodialysis will not necessarily be the same for people having peritoneal dialysis because the pattern of fluid accumulation which occurs between sessions may be more pronounced with haemodialysis, which is done less often. Also, peritoneal dialysis may preserve residual renal function for a longer period of time, so any effect on this outcome could be more pronounced. The committee therefore concluded that there are

insufficient data to determine the clinical effectiveness of BCM-guided monitoring for people having peritoneal dialysis.

5.10 The committee discussed the clinical effectiveness of BCM-guided monitoring in people under 18 years (that is, babies, children and young people). It noted that none of the identified studies assessed the use of the device in this group. The committee heard from clinical experts that because of physiological differences, and differences in comorbidities, between adults and babies, young people and children, the available data in adults cannot be considered applicable. It heard from clinical experts that a higher proportion of children who have dialysis have peritoneal dialysis rather than haemodialysis. The committee noted that any benefits or negative effects associated with managing fluids in children could influence outcomes and future treatments when they are adults, and so it is plausible that the effects of the BCM device may be greater in this population. The committee concluded that more data are needed on the clinical effectiveness of BCM-guided monitoring for people under 18 years having both haemodialysis and peritoneal dialysis.

Cost effectiveness

5.11 The committee considered the results of the cost-effectiveness analyses for BCM-guided fluid monitoring. It noted that several scenarios had been modelled to investigate the uncertainties in estimates of effect on mortality and hospitalisation events that had been identified in the clinical-effectiveness review. The committee heard that the model was based on data from UK and European renal registries, supplemented with data from the clinical-effectiveness review. It heard from clinical experts that the baseline population risk data and clinical-effectiveness data reflected outcomes for adults only and concluded that the results of the cost-

effectiveness analyses could not be considered applicable to children.

5.12 The committee questioned the impact of excluding the effect of prolonged underhydration, and related outcomes, from the model. It heard from the external assessment group that they had not been able to identify appropriate data sources for the prevalence of prolonged underhydration or its effect on mortality and hospitalisation rates. Also, data were not available to include an effect of BCM-guided monitoring on the incidence of prolonged underhydration or on the maintenance of residual renal function in the model. Clinical experts noted that this could either over- or underestimate the benefits of using the BCM, depending on whether its use increased or decreased the occurrence of prolonged underhydration. The committee concluded that the effect of BCM-guided monitoring on the incidence of prolonged underhydration, and associated outcomes such as residual renal function, is likely to be an important factor in assessing the cost effectiveness of the device and that, because of an absence of data, this has not been captured in the analyses.

5.13 The committee discussed the use of quality-of-life data in the model. It noted that the base-case model did not include an effect of BCM monitoring on quality of life, beyond its assumed effect on reducing mortality and hospitalisation events. The committee heard from clinical and patient experts that if using the BCM improved fluid management there would be reductions in dialysis-related side effects and improved recovery after dialysis, which would be of substantial benefit to patients. The committee concluded that, because of an absence of data, the effect of BCM-guided fluid

management on quality of life had not been captured in the analyses.

5.14 The committee discussed the mortality estimates included in the model. It noted that the pooled-effect estimate from the clinical-effectiveness review showed no significant effect on this outcome (see section 5.5), but that BCM-guided monitoring was assumed to increase survival in the base-case scenarios. The committee considered that, based on the available evidence, it is uncertain whether BCM-guided monitoring has any effect on mortality. It also questioned whether this uncertainty had been captured in probabilistic analyses. The committee determined that the most plausible scenario modelled is further scenario 17, which assumes no difference in mortality between BCM-guided monitoring and clinical assessment alone. This scenario produced an incremental cost-effectiveness ratio (ICER) of about £20,000 per quality-adjusted life year (QALY) gained. The committee noted that this scenario results in very small QALY gains and so its ICER is sensitive to small changes in the non-fatal cardiovascular event rate. Decreasing the effect of BCM-guided monitoring on this parameter by a small amount (changing the applied hazard ratio from 0.91 to 0.93) increased the ICER to over £40,000 per QALY. The committee concluded that the results of further scenario analysis 17 were the most plausible, but that there was considerable uncertainty about the results of this analysis, and whether they show that BCM-guided monitoring is a cost-effective intervention based on a reduction in cardiovascular-event rates alone.

5.15 The committee discussed the effect of including dialysis costs in the model. It noted that 2 sets of ICERs had been calculated, one with and one without dialysis costs. It noted that when dialysis costs are included, BCM-guided monitoring is unlikely to be

considered cost effective, even if the device is provided at no cost. When dialysis costs are excluded the ICERs generally drop below £20,000 per QALY gained. The committee noted that despite the high costs of dialysis, these results were largely driven by the assumption that BCM-guided monitoring increases survival and therefore the duration of dialysis treatment. For scenarios which include a survival benefit, the committee concluded that it would be appropriate to exclude costs related to the extended period of survival because dialysis has been generally available in the health service for a long time and it has therefore already been accepted that the benefits gained by providing dialysis outweigh the cost of delivering the intervention.

5.16 The committee discussed the level of uncertainty in both the clinical- and cost-effectiveness analyses. It noted that there was considerable uncertainty about the effectiveness of BCM-guided monitoring to reduce the incidence of adverse outcomes, such as cardiovascular events. Also, no data were available for potentially important outcomes, such as residual renal function. Because of this uncertainty in clinical effectiveness, there was insufficient evidence to determine the cost effectiveness of the BCM at present with any certainty. However, the committee noted that exploratory cost-effectiveness analyses done for the BCM device suggested that it could be cost effective, although this was sensitive to small changes in the estimated effect of BCM-guided monitoring. The committee concluded that there was too much uncertainty at present to recommend the BCM for routine use, but wished to encourage further research (see section 6).

Research considerations

5.17 The committee considered ongoing research on the clinical effectiveness of multiple frequency bioimpedance devices. It noted that the multi-centre, UK-based BISTRO RCT funded by the NIHR

designed to assess the effectiveness of the BCM device for monitoring people over 18 years on haemodialysis, will begin recruitment in 2017. The trial is scheduled to report in 2020. The committee heard from clinical experts that the primary outcome will be loss of renal function and noted that the effect of BCM-guided monitoring on this outcome had not been included in cost-effectiveness analyses because of a lack of data (see section 5.12). The committee concluded that the BISTRO study is highly relevant to this assessment and data from this ongoing study are therefore likely to be important when the guidance is considered for updating in the future.

5.18 The committee noted that BCM-guided monitoring is routinely used alongside standard clinical assessment in about 25% of UK dialysis services for people with chronic kidney disease having dialysis. It heard from clinical experts that these centres have developed experience of the benefits and limitations of using the BCM device to help manage dialysis-related symptoms associated with fluid imbalance. The committee encouraged centres currently using the BCM device to continue using it and participate in relevant data collection and research.

5.19 The committee considered the feasibility of further research on the clinical effectiveness of BCM-guided fluid management in babies, children and young people having dialysis. It heard from clinical experts that this age group makes up less than 1% of the total population of people on dialysis, and that people in this group typically stay on dialysis for a relatively short period of time, until they have a renal transplant. Therefore multi-centre studies are likely to be needed to recruit enough participants to show an effect on clinical outcomes. In the shorter term, the committee wished to encourage paediatric renal services to collect and publish data on

cognitive function and quality of life in patients having BCM-guided fluid management.

5.20 The committee noted that there were no data to determine the clinical effectiveness of the InBody S10 or MultiScan 5000 devices for guiding fluid management in people with chronic kidney disease who are having dialysis. The committee wished to encourage the companies to collect and publish data on both the validity of their device's underlying fluid model to calculate fluid overload and its associated clinical outcomes. The committee further noted the importance of validating the accuracy of all the multiple frequency bioimpedance devices included in this assessment for people with amputations, people for whom recommended electrode configurations cannot be used and people who are unable to assume recommended positioning for measurements to be made. Also, validation data will be important for people with extremes of body composition, and across different ethnicities, because normal ranges of lean or adipose tissue body composition may differ between ethnicities. It wished to encourage the publication of data on the validity of multiple frequency bioimpedance devices to calculate fluid overload and target weight in these groups.

6 Draft recommendations for further research

6.1 The committee recommended further research into the clinical effectiveness of BCM-guided fluid management in people with chronic kidney disease having dialysis. It noted that the ongoing BISTRO study will assess the effect of the device in people aged 18 years or over having haemodialysis. Further research should collect clinical outcome data in the following populations:

- adults (aged 18 years and over) having peritoneal dialysis
- babies, children and young people (aged under 18 years) having haemodialysis

- babies, children and young people (aged under 18 years) having peritoneal dialysis.

6.2 The committee recommended that data on the effect of BCM-guided monitoring on health-related quality of life is collected and published. Prospective within-patient studies, which record quality of life and symptoms before and after having BCM-guided fluid management should be considered.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, diagnostics advisory committee
February 2017

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland

Chair, diagnostics advisory committee

Dr Mark Kroese

Vice Chair, diagnostics advisory committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Mr John Bagshaw

In-vitro Diagnostics Consultant

Dr Sue Crawford

GP Principal, Chillington Health Centre

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

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NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Thomas Walker

Topic Lead

Rebecca Albrow

Technical Adviser

Robert Fernley

Project Manager

ISBN: