

# Multiple-frequency bioimpedance devices for fluid management in people with chronic kidney disease receiving dialysis: a systematic review and economic evaluation

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## Scientific summary

### Multiple-frequency bioimpedance devices in chronic kidney disease

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# Scientific summary

## Background

Chronic kidney disease (CKD) is a long-term condition in which the kidneys do not function effectively. In the most severe stage of CKD, the kidneys operate at  $\leq 15\%$  of their normal function, and treatment in the form of conservative management, kidney transplantation or dialysis will be required. Dialysis involves removing waste products and excess fluid from the bloodstream, and there are two main types:

1. Haemodialysis (HD), in which the person is connected to a dialysis machine that uses a semipermeable membrane to filter out excess salts and water in the blood; HD is commonly prescribed for 4 hours, three times per week, administered either in hospital, in a satellite unit or at home.
2. Peritoneal dialysis (PD), in which dialysis fluid is passed into the peritoneal cavity through a permanent catheter and waste products and excess fluid are drawn from the blood into the dialysis fluid by the blood vessels lining the cavity. The process of fluid exchange can either be carried out overnight by a machine (automated PD) or conducted manually, four times daily, taking 30–40 minutes for each fluid exchange (continuous ambulatory PD).

To optimise the volume of fluid to be removed during dialysis (to avoid underhydration or overhydration, both of which are associated with potentially serious complications), people are assigned a 'target weight', which is commonly assessed using clinical methods, such as weight gain between dialysis sessions, pre- and post-dialysis blood pressure and patient-reported symptoms. However, these methods are not precise, and measurement devices based on bioimpedance technology, which are non-invasive, simple and inexpensive, are increasingly used in dialysis centres. There is currently limited evidence on the clinical effectiveness and cost-effectiveness of bioimpedance devices compared with standard clinical assessment for fluid management in people with CKD receiving dialysis.

## Objectives

The specific objectives of this assessment were to:

- systematically review the evidence on the clinical effectiveness of multiple-frequency bioimpedance devices [i.e. Body Composition Monitor (BCM; Fresenius Medical Care, Bad Homburg vor der Höhe, Germany), MultiScan 5000 (Bodystat, Douglas, Isle of Man), BioScan 920-II (Maltron International, Essex, UK), BioScan touch i8 (Maltron International, Essex, UK) and InBody S10 (InBody, Seoul, South Korea)] compared with that of 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 or InBody S10) for fluid management in people with CKD receiving dialysis treatment versus standard clinical assessment.

## Methods

### Clinical effectiveness

Comprehensive electronic searches were undertaken between June and October 2016 to identify relevant reports of published studies. There were no date restrictions. Databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index and Cochrane Central Register of Controlled Trials (CENTRAL). Evidence was considered from randomised controlled trials (RCTs) assessing multiple-frequency bioimpedance devices versus standard clinical assessment, and non-randomised cohort studies. The population was people with CKD being treated with HD or PD. The comparator was standard clinical assessment, consisting of blood pressure, presence of oedema, changes in weight, residual renal function, pre-existing cardiovascular (CV) conditions and/or patient-reported symptoms of overhydration or underhydration.

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

### Cost-effectiveness

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

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

## Results

### Clinical effectiveness

A total of five RCTs (published in six papers) analysing a total of 904 participants, and eight non-randomised studies (published in nine papers) analysing a total of 4915 participants were included in the review of clinical effectiveness. All included studies investigated the use of the BCM in the relevant population, all of which were adults. Of the RCTs, one trial was rated as having a high risk of bias, and four trials did not provide sufficient information to make a robust judgement. We further identified four ongoing trials.

The results of the meta-analyses conducted for this assessment showed that both absolute overhydration and relative overhydration were significantly lower in the BCM group than in the standard clinical assessment group [weighted mean difference  $-0.44$ , 95% confidence interval (CI)  $-0.72$  to  $-0.15$ ,  $p = 0.003$ ,  $I^2 = 49\%$ ; and weighted mean difference  $-1.84$ , 95% CI  $-3.65$  to  $-0.03$ ,  $p = 0.05$ ,  $I^2 = 52\%$ , respectively]. The pooled effects of bioimpedance monitoring on blood pressure (mean difference  $-2.46$ , 95% CI  $-5.07$  to  $0.15$ ;  $p = 0.06$ ,  $I^2 = 0\%$ ), arterial stiffness (mean difference  $-1.18$ , 95% CI  $-3.14$  to  $0.78$ ;  $p = 0.24$ ,  $I^2 = 92\%$ ) and mortality (HR  $0.689$ , 95% CI  $0.23$  to  $2.08$ ;  $p = 0.51$ ,  $I^2 = 54\%$ ) were not statistically significant.

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

### **Cost-effectiveness**

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

When dialysis costs were included in the model, the incremental cost-effectiveness ratios (ICERs) for bioimpedance-guided fluid management ranged from £58,723 to £66,007 per QALY gained. These ICERs related to mean incremental costs that varied between £4518 and £35,676, and corresponding lifetime incremental QALY gains that varied from 0.07 to 0.58. The costs of dialysis in added years made up the vast majority of the incremental costs. When dialysis costs were excluded from the model, the base-case ICERs ranged from £15,215 to £21,201.

### **Sensitivity analyses**

Beyond the inclusion/exclusion of dialysis costs, the cost-effectiveness results were found to be most sensitive to the effect of bioimpedance-guided fluid management on all-cause mortality. When dialysis costs were included in the model, the ICER was most favourable ( $\approx$  £40,300) when the HR for all-cause mortality was set equal to one, that is, no reduction in mortality leading to no extra dialysis costs, but retained benefits on non-fatal hospitalisation events. With dialysis costs and an effect on mortality included in the model, there would need to be an accompanying effect of bioimpedance monitoring on the cost of dialysis and/or health state utility over the lifetime of patients receiving dialysis. There is currently limited available evidence to justify such scenarios.

When dialysis costs were excluded from the model, the ICER for bioimpedance-guided fluid management remained below £20,000 in most scenarios assessed. Given the relatively low cost of adding bioimpedance testing four times a year, the ICERs remained favourable with modest effects on mortality and hospitalisation rates. With dialysis costs excluded, probabilities of cost-effectiveness ranged from 61% to 67% at a willingness-to-pay threshold of £20,000 per QALY gained.

## **Discussion**

### **Strengths, limitations of the analyses and uncertainties**

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

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

### **Generalisability of the findings**

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

### **Conclusions**

Our findings indicate that both absolute overhydration and relative overhydration are significantly lower among people with CKD receiving dialysis who are managed using the BCM instead of standard clinical methods. The use of bioimpedance monitoring may reduce systolic blood pressure (SBP), although the pooled estimates of effects show a certain degree of heterogeneity and a non-significant effect. The current evidence does not demonstrate a significant effect on arterial stiffness and on mortality. There is currently no evidence to indicate that these findings are generalisable to paediatric populations or across other multifrequency bioimpedance devices. With possible effects on mortality and hospitalisation rates modelled indirectly through estimated pooled reductions in surrogate end points (PWV or overhydration), it appears unlikely that the ICER for bioimpedance-guided fluid management will fall below standard thresholds for cost-effectiveness with dialysis costs included. If dialysis costs are excluded from the model, the ICER may feasibly fall below £20,000, with modest effects on mortality and/or hospitalisation rates. The economic modelling is subject to substantial uncertainty, given the limitations in the clinical evidence base.

### **Implications for service provision**

The current evidence suggests that BCM use, in addition to routine clinical assessment, may reduce overhydration and potentially improve intermediate outcomes such as SBP, but significant effects on mortality have not been demonstrated.

It would be useful if services that are currently, or subsequently, routinely using the BCM to augment routine clinical assessment could provide information on long-term outcomes before and after introduction of the bioimpedance device to extend the current evidence base.

Services that plan to introduce the routine use of the BCM to augment routine clinical assessment may consider adopting a protocol that is transparent and reproducible.

### **Suggested research priorities**

The ultimate aim of introducing multiple-frequency bioimpedance device measurement in addition to standard clinical assessment into clinical practice is to reduce clinically important events such as mortality, CV events and hospital admissions, whether this is through a reduction in overhydration- or underhydration-related events. However, clinical effectiveness has not been demonstrated yet for these important health outcomes. The effects of introducing multiple-frequency bioimpedance device measurement on intermediate outcomes, such as SBP control and hydration status, have been documented. The timeline from these intermediate end points to those end points that are clinically relevant, however, may not be captured within the identified clinical trials. The studies were generally short-lived and the sustainability of introducing a change in routine practice has yet to be established.

Those centres that have introduced routine multiple-frequency bioimpedance device measurement to augment clinical assessment of dialysis patients may consider conducting adjusted retrospective analyses to estimate effects on clinically relevant and intermediate outcomes both before and after the introduction of the device. It would also be useful to obtain further information on the sustainability of the measurement and its use in clinical practice over a sustained period.

It is important that currently ongoing and future clinical trials are adequately powered to identify any clinical benefit (not just intermediate benefits) and the likely timeline of how any benefit (e.g. through better blood pressure control) is factored in to allow such studies to truly demonstrate whether or not an important clinical effect exists.

Future trials should adopt protocols that are likely to be clinically applicable in multiple areas (e.g. 3-monthly testing to allow use at routine review appointments).

Future trials should also carefully match their included population to the outcomes of interest. For example, if the primary outcome is a reduction in blood pressure, an appropriate clinical population would be patients who had high blood pressure and were fluid overloaded post HD, as they would be likely to have overhydration-related hypertension. Removing fluid from patients with hypertension who are not overhydrated may result in harm to some participants.

Related to further key uncertainties identified in the economic modelling, we recommend that future studies:

- assess the impact of hydration status and bioimpedance-guided fluid management on health-related quality of life, preferably using a generic preference-based instrument suitable for the estimation of QALYs
- assess the impact of bioimpedance testing on the frequency and duration of dialysis, and associated costs
- further develop and strengthen the evidence base for linking changes in surrogate end points (e.g. fluid management-induced changes in blood pressure and PWV) to changes in health outcomes (mortality, CV events, hospitalisation rates). Ideally, data from relevant randomised studies should be used to quantify relationships between intervention-induced changes in the surrogate end points and longer-term changes in health outcomes
- quantify the risks and cost burdens of different types of hospitalisation event in people receiving dialysis, and better characterise the impact of hydration status on these risks.

## Study registration

This study is registered as PROSPERO CRD42016041785.

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