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

ADDENDUM to the EAG assessment report

Produced by Aberdeen HTA Group

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REASON FOR ADDENDUM SUBMISSION

After submission of the EAG report, one of the DAP specialist committee members raised a concern that the two Onofriescu et al. studies included in the clinical effectiveness review (Onofriescu et al. 2012 and Onofriescu et al. 2014) may be reporting the same trial or may report outcomes from an overlapping patient population. We cannot confirm with certainty that this is the case. We have contacted the principal investigator of the two trials for further clarification but no reply has yet been received.

This Addendum presents the relevant clinical effectiveness analyses with inclusion of the Onofriescu et al. 2014 trial only, as well as the revised cost-effectiveness analyses. The 2014 trial provides more relevant outcome measures and is more recent.

In addition, it has come to light that there may be overlapping of participants in the non-randomised studies by O'Lone et al. 2014 and Oei et al. 2016. Enquires with the authors are ongoing, to establish the populations in these two studies. It is worth pointing out that only a narrative synthesis of non-randomised evidence was presented in the original EAG report and, therefore, there are no implications for "double counting". Moreover, only findings from the O'Lone et al 2014 study were used in certain scenarios in the economic model.

REVISED CLINICAL EFFECTIVENESS RESULTS

The following are the meta-analyses results without inclusion of the Onofriescu et al. 2012 study.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Huan-Sheng 2016	136	23	148	136	22	150	26.0%	0.00 [-5.11, 5.11]
Hur 2013	120	19	64	125	19	62	15.4%	-5.00 [-11.64, 1.64]
Luo 2011	132.99	19.47	78	139.07	22.4	82	16.1%	-6.08 [-12.57, 0.41]
Onofriescu 2014	138.9	14.7	62	140.5	11.4	69	32.9%	-1.60 [-6.14, 2.94]
Ponce 2014	134.6	31.13	101	136.5	28.16	88	9.5%	-1.90 [-10.35, 6.55]
Total (95% CI)			**453**			**451**	**100.0%**	**-2.46 [-5.07, 0.15]**

Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)

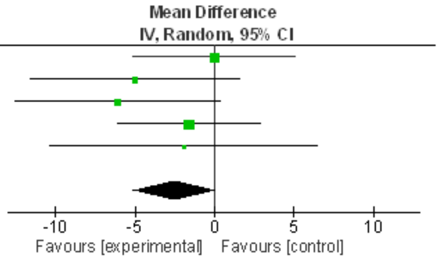

Figure 1 Meta-analysis of systolic blood pressure (Figure 6 in the original EAG report)

Figure 1 present the revised meta-analysis of systolic blood pressure. The effect size still suggests that participants who underwent bioimpedance measurements using the BCM device have lower systolic blood pressure but the effect is no longer significant. The confidence interval remains a similar width so the level of uncertainty is similar but the reduction in the effect size means that the lowering of blood pressure is no longer significant.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hur 2013	8.1	2.3	64	8.3	1.62	62	51.0%	-0.20 [-0.89, 0.49]
Onofriescu 2014	6.68	1.89	62	8.88	3.23	69	49.0%	-2.20 [-3.10, -1.30]
Total (95% CI)			**126**			**131**	**100.0%**	**-1.18 [-3.14, 0.78]**

Heterogeneity: Tau² = 1.83; Chi² = 11.98, df = 1 (P = 0.0005); I² = 92%
Test for overall effect: Z = 1.18 (P = 0.24)

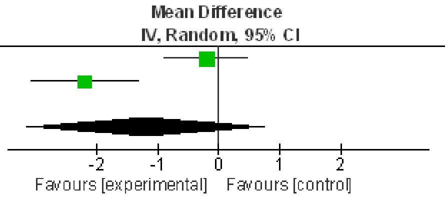

Figure 2 Meta-analysis of arterial stiffness (Figure 7 in the original EAG report)

With regards to the revised meta-analysis of arterial stiffness (Figure 2), there are now only two trials, with inconsistent results, that report arterial stiffness. The pooled effect of Hur et al. 2013 and Onofriescu et al. 2014 is no longer significant though the effect size still suggests lower arterial stiffness in the bioimpedance group. The effect size is lower and the confidence interval is wider indicating more uncertainty in the benefit of the BCM device.

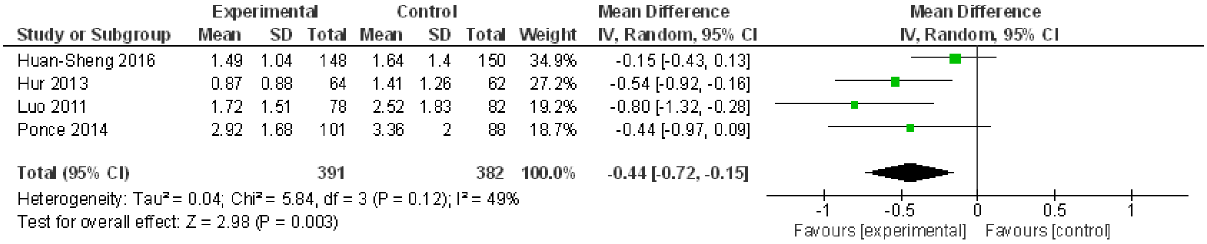

Figure 3 Meta-analysis of absolute overhydration (Figure 9 in the original EAG report)

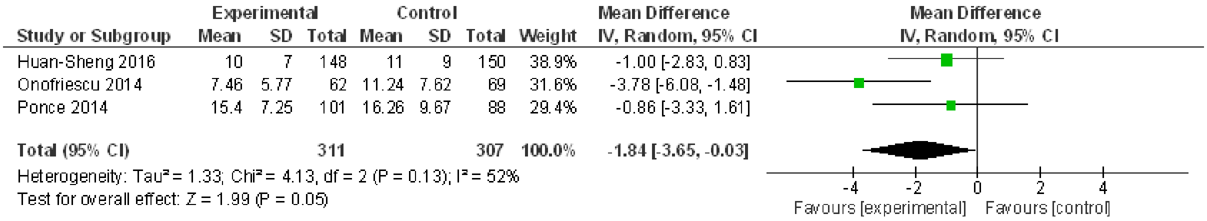

Figure 4 Meta-analysis of relative overhydration (Figure 10 in the original EAG report)

Excluding Onofriescu et al. 2012 from the meta-analysis of absolute overhydration makes little difference to the summary estimate of effect (Figure 3). The confidence interval is slightly wider but the effect size now suggests a greater benefit from using the BCM device. Similar observations can be made for the meta-analysis of relative overhydration (Figure 4). Excluding Onofriescu et al. 2012 makes the confidence interval slightly wider but also changes the effect size in favour of a greater benefit of bioimpedance measurement using the BCM device. In both meta-analyses (absolute overhydration and relative overhydration), the summary estimate of effect is significant, whether or not Onofriescu et al. 2012 is included.

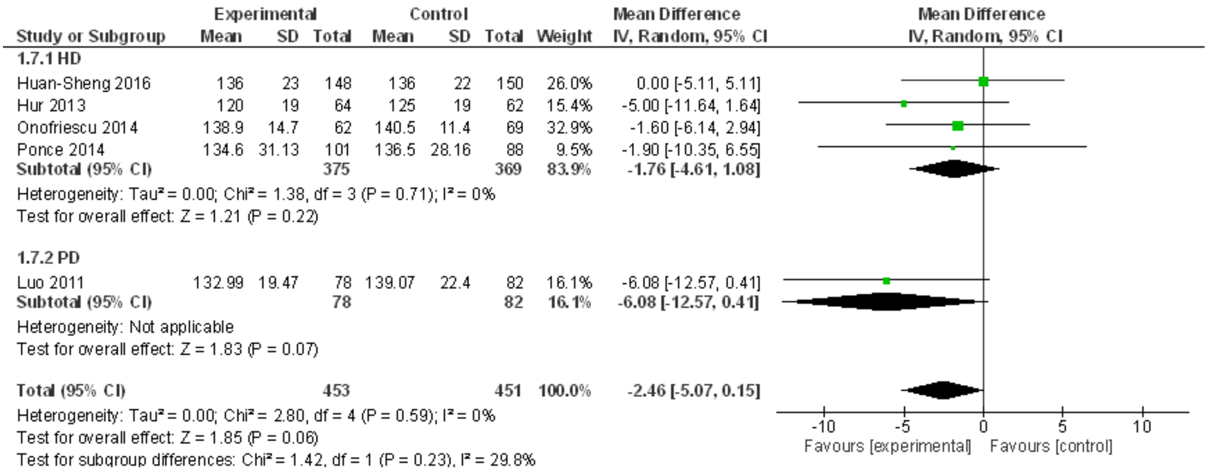

Figure 5 Subgroup analysis of systolic blood pressure according to type of dialysis (Figure 11 in original report)

With regards to the subgroup analysis of blood pressure, if Onofriescu et al. 2012 is not included (Figure 5), the effect in the HD subgroup is still in favour of BCM guided management but is now reduced in size, whilst the confidence interval remains similar in width as it was before. There is now a slight difference between the HD subgroup and the overall effect but it does not change the original conclusion that the type of dialysis does not make a difference in the effect of the BCM device.

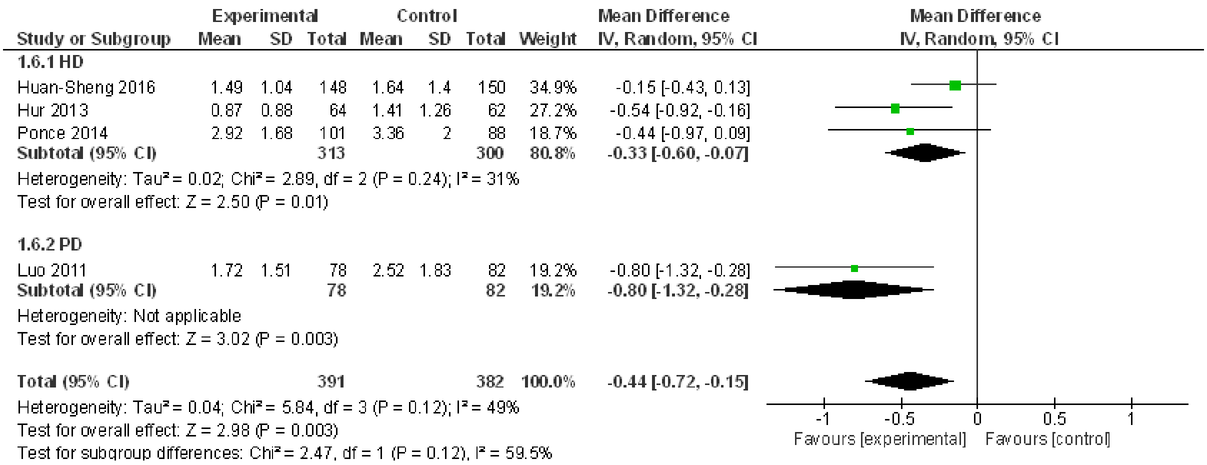

Figure 6 Subgroup analysis of absolute overhydration according to type of dialysis (Figure 12 in original report)

Exclusion of the Onofriescu et al. 2012 study from the absolute overhydration subgroup analysis (Figure 6) does not change our previous conclusion that, while there is a difference between the overall effect and the effect in the HD subgroup, this difference does not mean that there is a dialysis effect.

REVISED COST-EFFECTIVENESS ANALYSES

The following cost-effectiveness results reflect the exclusion of Onofriescu et al. 2012 from the relevant meta-analyses of clinical effectiveness. The exclusion of the Onofriescu et al. 2012 study impacts on the base cost-effectiveness scenarios 2,3 and 4, presented in Table 19 of the original EAG report. In these scenarios, effects on all-cause mortality and/or CV hospitalisation were modelled indirectly through the estimated pooled effect of bioimpedance monitoring on arterial stiffness (pulse wave velocity - PWV).

When both Onofriescu et al. 2012 and Onofriescu et al. 2014 were included in the PWV meta-analysis, the pooled effect was -1.53 m/s (-0.071, -2.995) in favour of bioimpedance guided fluid management. This was previously used to scale the effect (on all-cause mortality and CV hospitalisation) of a unit change in PWV (HR = 0.942 per m/s reduction (See Table 9 of original EAG report); Hazard ratio (HR) = 0.942^1.53 = 0.9123. With Onofriescu et al. 2012 excluded from the PWV meta-analysis, the pooled effect is smaller and more uncertain (-1.18 m/s, -3.14, 0.78). It should be noted that this meta-analysis now only includes two trials, showing inconsistent results (Figure 2).

Using this revised estimate to scale the effect of a unit change in PWV, gives a hazard ratio for the effect of bioimpedance testing on all-cause mortality/CV hospitalisation of 0.9318 (=0.942^1.18). This value is applied in the revised scenarios that follow. The greater uncertainty surrounding the pooled reduction in PWV is also propagated through the probabilistic analyses for clinical effectiveness scenarios 3 and 4.

Revised versions of all relevant tables and figures from the original EAG report are reproduced below. All results in red represent those affected by the changes.

Tables 1 and 2 provide the revised base scenarios including and excluding dialysis costs. With the smaller effect on CV hospitalisation/mortality (HR = 0.9318), the point estimates of the ICERs for scenarios 2, 3 and 4 have all increased by only a small amount.

Table 1 Deterministic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (including dialysis costs) – updates Table 20 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. Applying the point estimate for the pooled effect of BCM on mortality only (HR = 0.689)						
Standard care	£158,104		2.7014			-£104,077
BCM	£193,780	£35,676	3.272	0.5706	£62,524	-£128,341
2. Applying the point estimate for the pooled effect of BCM on mortality (HR = 0.689), and a linked effect on non-fatal CV events through the pooled reduction in PWV (HR=0.9318)						
Standard care	£158,104		2.7014			-£104,077
BCM	£193,474	£35,370	3.2791	0.5777	£61,222	-£127,892
3. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318)						
Standard care	£158,104		2.7014			-£104,077
BCM	£165,057	£6,952	2.8171	0.1157	£60,097	-£108,715
4. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR=0.9318), and a 10% reduction in BP medications use						
Standard care	£158,104		2.7014			-£104,077
BCM	£164,994	£6,890	2.8171	0.1157	£59,554	-£108,653
5. Modelling effects of bioimpedance testing through associations between severe OH and mortality and all cause-hospitalisation (assumes a 28% reduction in severe OH)						
Standard care	£162,039		2.77			-£162,039
BCM	£166,557	£4,518	2.84	0.07	£66,007	-£166,557

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

Table 2 Deterministic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (excluding dialysis costs) - updates Table 21 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. Applying the point estimate for the pooled effect of BCM on mortality only (HR = 0.689)						
Standard care	£46,214		2.7014			£7,813
BCM	£55,555	£9,341	3.272	0.5706	£16,370	£9,884
2. Applying the point estimate for the pooled effect of BCM on mortality (HR = 0.689), and a linked effect on non-fatal CV events through the pooled reduction in PWV (HR=0.9318)						
Standard care	£46,214		2.7014			£7,813
BCM	£54,951	£8,737	3.2598	0.5584	£15,646	£10,244
3. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318)						
Standard care	£46,214		2.7014			£7,813
BCM	£48,133	£1,919	2.8171	0.1157	£16,590	£8,208
4. Applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR=0.9318), and a 10% reduction in BP medications use						

Standard care	£46,214		2.7014			£7,813
BCM	£48,071	£1,856	2.8171	0.1157	£16,046	£8,271
5. Modelling effects of bioimpedance testing through associations between severe OH and mortality and all cause-hospitalisation (assumes a 28% reduction in severe OH)						
Standard care	£47,046		2.77			-£47,046
BCM	£48,497	£1,451	2.84	0.07	£21,201	-£48,497
6. Modelling effects of bioimpedance guided fluid management through associations between severe OH and mortality and all cause-hospitalisation (assumes a 38% reduction in severe OH)						
Standard care	£47,046		2.77			-£47,046
BCM	£48,843	£1,797	2.86	0.09	£19,345	-£48,843

Markov Traces

Figures 7 and 8 below show the Markov traces for the standard care arm and the bioimpedance arm under the revised clinical effectiveness scenario 3. In the standard care arm, the ten year mortality for the 66 year old cohort is 78.8%. Assuming a constant proportional effect of bioimpedance guided fluid management on mortality, over ten years, the ten year mortality in the bioimpedance arm comes to 76.6%. Over the lifetime of the modelled cohort, the gain in undiscounted life expectancy is 0.29 years (6.29 versus 6.0). The modelled life-time cumulative incidence of any CV hospitalisation event is 46.9% in the bioimpedance arm of the model, and 47.1% in the standard care arm. 7.8 % of patients in the bioimpedance arm receive a transplant during their lifetime, whilst the corresponding figure is 7.6% in the standard care arm.

Table 3 provides a breakdown of the cumulative costs for the standard care and bioimpedance arms respectively – under the revised clinical effectiveness scenario 3. The costs are higher across all categories in the bioimpedance arm, due to the increase in survival. However, it can be noted that it is the additional dialysis costs in extra years that makes up 74% of the total incremental cost of the bioimpedance guided strategy. This same pattern is consistent across all the main clinical effectiveness scenarios (1-6). The actual increase in lifetime costs due to bioimpedance testing is small (£491 per patient in the revised effectiveness scenario 3).

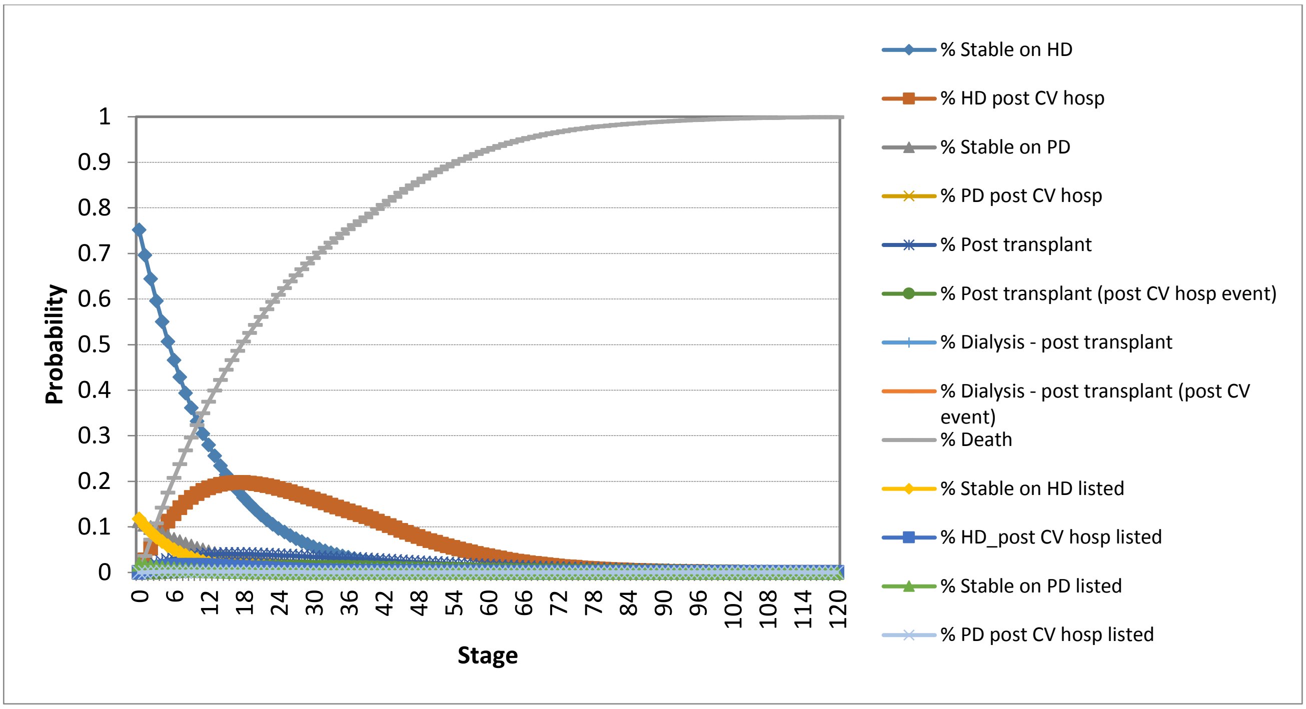

Figure 7 Markov cohort trace, Standard care (1 stage equals three months) – replicates Figure 14 of the original EAG report

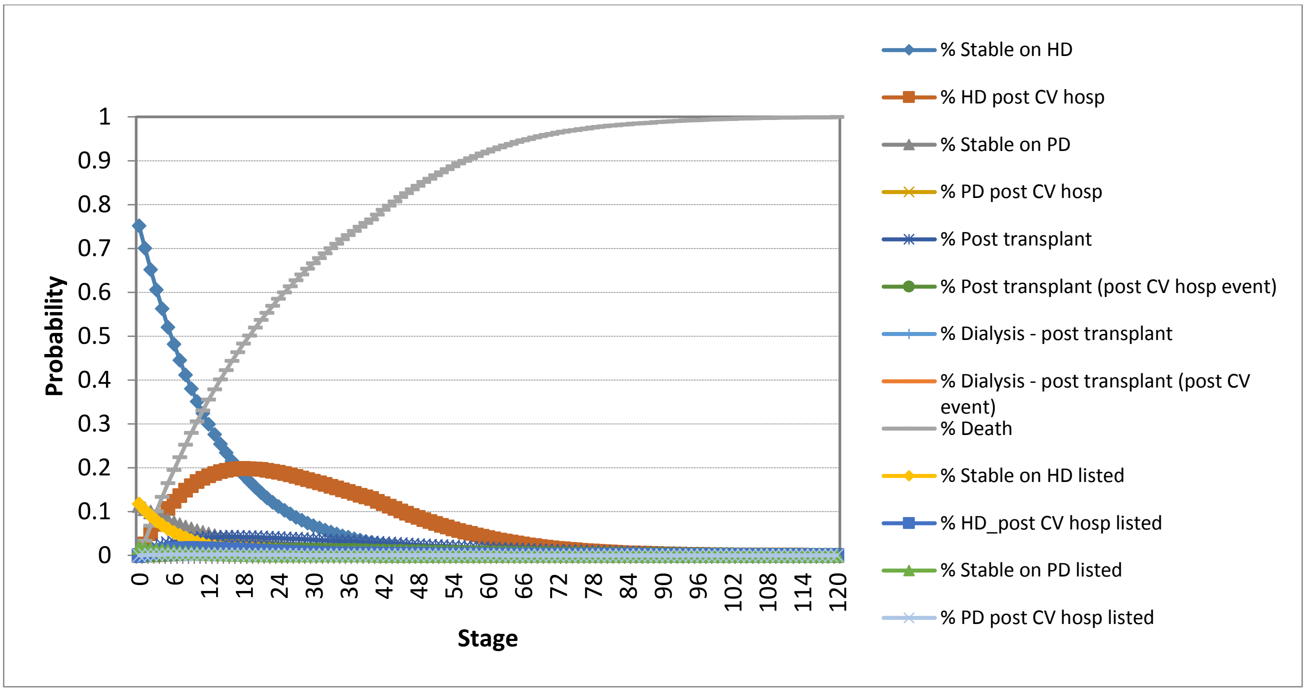

Figure 8 Markov cohort trace, BCM - Body Composition Monitor, under clinical effectiveness scenario 3 (1 stage equals three months) -updates Figure 14 of the original EAG report

Table 3 Breakdown of cumulative costs by categories under clinical effectiveness scenario 3 -updates Table 22 of the original EAG report

	Standard Care	Body Composition Monitor-BCM	Difference BCM versus standard care
Cumulative in-patient hospital costs	£21,775	£22,260	£485
Cumulative dialysis costs	£111,890	£116,923	£5,033
Cumulative medication costs	£10,792	£11,277	£485
Cumulative outpatient costs	£6,076	£6,349	£273
Cumulative acute transplant cost	£1,066	£1,093	£27
Cumulative post-transplant follow-up costs	£6,505	£6,663	£158
Bioimpedance testing costs	NA	£491	£491
Cumulative cost	£158,104	£165,057	£6,952

Deterministic sensitivity analysis

Figures 10 and 11 illustrate the effects of one way sensitivity analysis on key model input parameters, with dialysis costs included (Figure 16) and excluded (Figure 17). These reference ICERs for both these tornado diagrams reflect the revised clinical effectiveness scenario 3 (i.e. a hazard ratio of 0.9318, inferred through the pooled reduction in pulse wave velocity, applied to both all-cause mortality and CV hospitalisation).

When dialysis costs are included, the ICER for bioimpedance guided fluid management is most sensitive to changes in the hazard ratio for the effect on all-cause mortality. The most favourable ICER occurs when the hazard ratio on all-cause mortality is equal to one, as this equalises survival and eliminates the excess dialysis costs incurred in added years. However, under the revised clinical effectiveness scenario 3, the ICER only drops to £40,480 when no effect on mortality is applied (previously it dropped to £21,519). This is due to the smaller effect on CV hospitalisation now being applied.

When dialysis costs are excluded, the ICER remains most sensitive to the hazard ratio on all-cause mortality, but the in this case the least favourable ICER occurs when the hazard ratio is equal to 1.

Results are also moderately sensitive to the hazard ratio for CV hospitalisation, the utility multiplier for haemodialysis, and the cost of haemodialysis. However, when dialysis costs are included, the ICER for bioimpedance guided management now remains well above £30,000 when all parameters are varied within their ranges.

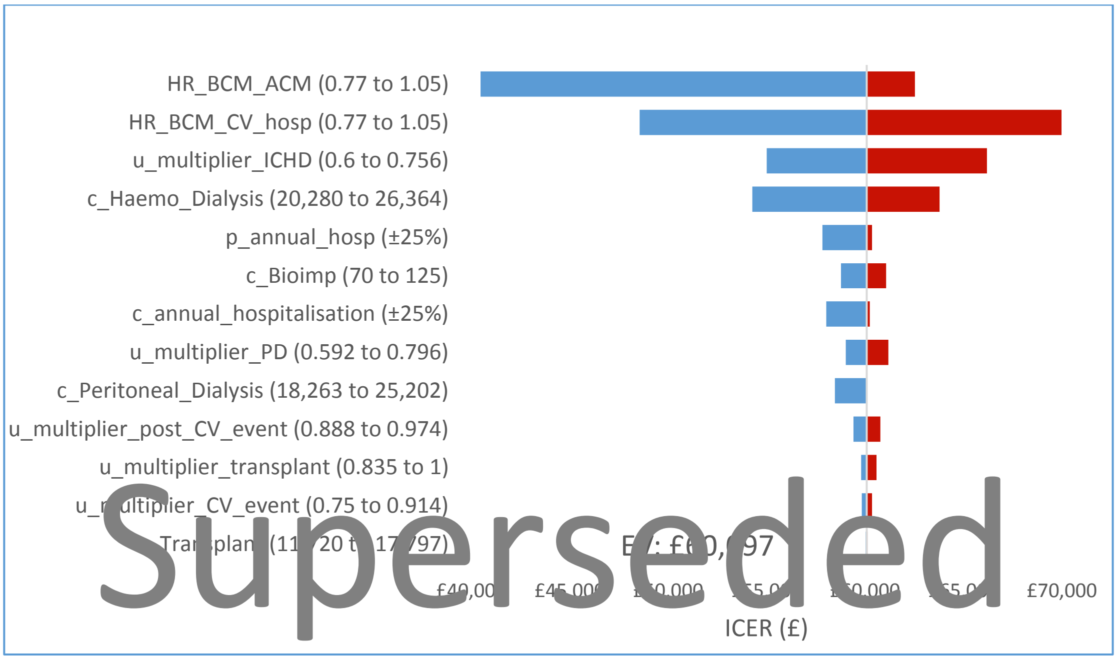

Figure 10 One-way sensitivity analysis: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs) – updates Figure 16 of original EAG report

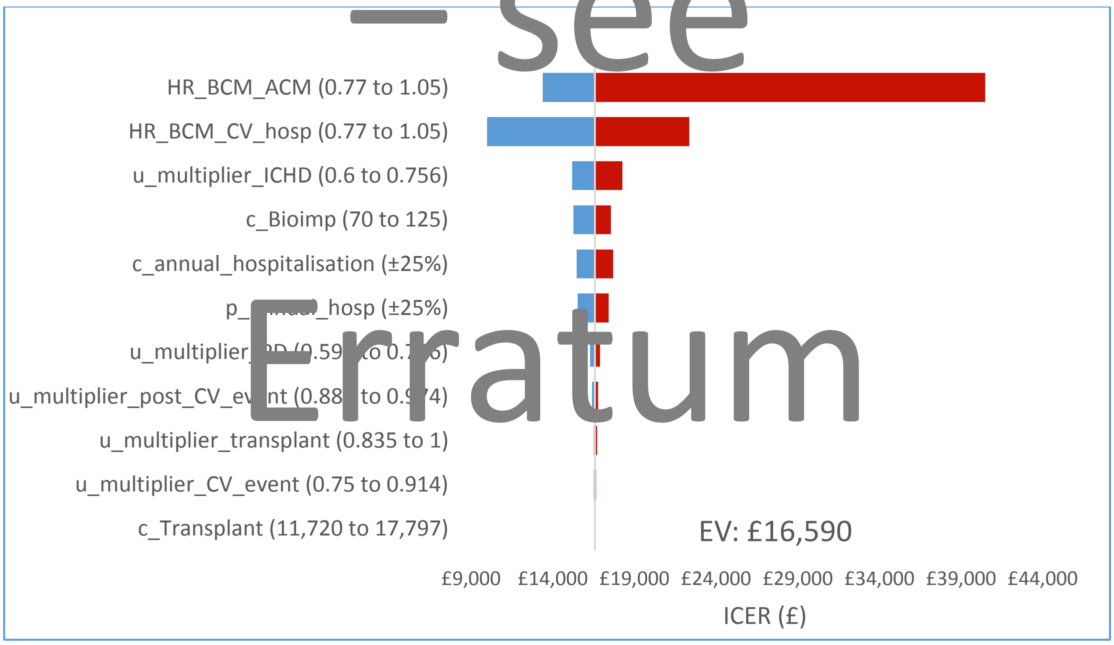

Figure 11 One-way sensitivity analysis: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs) - updates Figure 17 of original EAG report

Scenarios analyses

Table 4 below presents the revised results of the further scenario analyses, referent to the revised clinical effectiveness scenario 3 (HR of 0.9318 applied to all-cause mortality and CV hospitalisation). Unless otherwise stated, these additional scenarios exclude dialysis costs, to better illustrate sensitivity around the cost-effectiveness threshold should the exclusion of dialysis costs be considered appropriate for the purpose of decision making. Under most of the scenarios with dialysis costs excluded, the ICER for bioimpedance monitoring remains below £30,000, and in many cases is below £20,000.

Under only a few scenarios does the ICER for bioimpedance monitoring fall below £30,000 when dialysis costs are included: When assuming bioimpedance testing results in a 5% or 10% reduction in dialysis costs (Scenarios 15 and 16) over the lifetime of patients; and when it is assumed that bioimpedance guided fluid management results in a 5% increase in health state utility, maintained over the lifetime of all dialysis patients (Scenario 13). However, there is very little data available to justify these possible scenarios.

As mentioned above, when the effect of bioimpedance testing on mortality is set to zero (i.e. a hazard ratio of 1 is applied to all-cause mortality) and an effect on non-fatal CV hospitalisation is maintained, the ICER now no longer drops below £30,000 with dialysis costs included (Scenario 17). This is due to the smaller accompanying effect on CV hospitalisation now being applied in this revised analysis.

Table 4 Scenario analyses referent to base clinical effectiveness scenario 3 (all analyses exclude dialysis costs unless stated otherwise) – updates Table 23 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
Base case scenario 3: applying linked effects on mortality and non-fatal CV events, estimated through the pooled reduction in PWV (HR of 0.9318 applied to both all-cause mortality and CV hospitalisation)						
Standard care	£46,214		2.7014			£7,813
Bioimpedance guided	£48,133	£1,919	2.8171	0.1157	£16,590	£8,208
1. Applying an increased cost of monitoring in adults by increasing the number of tests per patient to 12 annually						
Standard care	£46,214		2.7014			£7,813
BCM	£48,754	£2,540	2.8171	0.1157	£21,955	£7,587
2. Applying the estimated costs of bioimpedance monitoring in paediatric centres with lower throughput (assuming 4 tests annually)*						
Standard care	£46,214		2.7014			£7,813
BCM	£48,830	£2,616	2.8171	0.1157	£22,611	£7,511
3. Applying the estimated costs of bioimpedance monitoring in paediatric centres with lower throughput (assuming 12 tests annually)*						
Standard care	£46,214		2.7014			£7,813
BCM	£49,323	£3,108	2.8171	0.1157	£26,868	£7,019
4. Applying the cost of BioScan for bioimpedance monitoring						
Standard care	£46,214		2.7014			£7,813
BioScan	£48,052	£1,837	2.8171	0.1157	£15,882	£8,290
5. Applying the cost of Inbody S10 for bioimpedance monitoring						

Standard care	£46,214		2.7014			£7,813
Inbody S10	£48,080	£1,866	2.8171	0.1157	£16,127	£8,261
6. Applying the cost of MultiScan 5000 for bioimpedance monitoring						
Standard care	£46,214		2.7014			£7,813
MultiScan 5000	£48,084	£1,870	2.8171	0.1157	£16,163	£8,257
7. Applying the lowest estimated annual bioimpedance monitoring from Table 15 (£70)						
Standard care	£46,214		2.7014			£7,813
BCM	£47,981	£1,767	2.8171	0.1157	£15,275	£8,360
8. Applying the highest estimated annual bioimpedance monitoring cost from 15 (£125)						
Standard care	£46,214		2.7014			£7,813
BCM	£48,248	£2,033	2.8171	0.1157	£17,577	£8,094
9. Applying an alternative lower cost per CV hospitalization event (£1386 per CV event)						
Standard care	£44,116		2.7014			£9,912
BCM	£46,090	£1,974	2.8171	0.1157	£17,065	£10,251
10. Applying alternative age adjusted utility multipliers for dialysis and post-transplant[123]						
Standard care	£46,214		2.9814			£13,414
BCM	£48,133	£1,919	3.1109	0.1295	£14,824	£14,084
11. Assume bioimpedance guided management results in a 2% improvement in the health state utility over the lifetime of dialysis patients (including dialysis costs)						
Standard care	£158,104		2.7014			-£104,077
BCM	£165,057	£6,952	2.866	0.1646	£42,231	-£107,737
12. Assume bioimpedance guided management results in a 2% improvement in the health state utility over the lifetime of dialysis patients (excluding dialysis costs)						

Standard care	£46,214		2.7014			£7,813
BCM	£48,133	£1,919	2.866	0.1646	£11,658	£9,187
13. Assume bioimpedance guided management results in a 5% improvement in the health state utility over the lifetime of dialysis patients (including dialysis costs)						
Standard care	£158,104		2.7014			-£104,077
BCM	£165,057	£6,952	2.9394	0.238	£29,207	-£106,268
14. Assume bioimpedance guided management results in a 5% improvement in the health state utility over the lifetime of dialysis patients (excluding dialysis costs)						
Standard care	£46,214		2.7014			£7,813
BCM	£48,133	£1,919	2.9394	0.238	£8,063	£10,655
15. Assume bioimpedance guided management results in a 10% reduction in dialysis costs over the lifetime of patients						
BCM	£153,364		2.8171			-£97,023
Standard care	£158,104	£4,740	2.7014	-0.1157	Dominated	-£104,077
16. Assume bioimpedance guided management results in a 5% reduction in dialysis costs over the lifetime of patients						
Standard care	£158,104		2.7014			-£104,077
BCM	£159,211	£1,106	2.8171	0.1157	£9,563	-£102,869
17. Applying only an effect on non-fatal CV events (HR= 0.9318), excluding any effect on mortality (including dialysis costs)						
Standard care	£158,104		2.7014			-£104,077
BCM	£158,329	£225	2.7069	0.0056	£40,480	-£104,191
18. Applying a smaller effect on mortality and non-fatal CV events (HR = 0.95 for both)						
Standard care	£46,214		2.701			£7,813
BCM	£47,737	£1,523	2.785	0.084	£18,137	£7,970
19. Applying a larger effect of bioimpedance monitoring on both CV events and mortality (0.844); consistent with the cross sectional main effect of a unit change in PWV reported by Verbeke et al[106].						

Standard care	£46,214		2.7014			£7,813
BCM	£50,144	£3,929	2.9791	0.2777	£14,148	£9,439
20. Applying differential effects on mortality (HR = 0.95) and non-fatal CV events (HR = 0.844) – including dialysis costs						
Standard care	£158,104		2.7014			-£104,077
BCM	£162,885	£4,780	2.7947	0.0933	£51,243	-£106,991
21. Applying differential effects on mortality (HR = 0.95) and non-fatal CV events (HR = 0.844) – excluding dialysis costs						
Standard care	£46,214		2.7014			£7,813
BCM	£47,341	£1,126	2.7947	0.0933	£12,075	£8,553
22. Excluding all non-CV causes of hospitalisation form the analysis – including dialysis costs						
Standard care	£144,931		2.7138			-£90,655
BCM	£151,295	£6,364	2.8301	0.1163	£54,729	-£94,693
23. Applying no effects of bioimpedance monitoring beyond 3 years; HR for all-cause mortality and CV hospitalisation = 0.9318 up to three years						
Standard care	£46,214		2.7014			£7,813
BCM	£47,511	£1,297	2.7663	0.065	£19,968	£7,815
24. Applying no effects of bioimpedance monitoring beyond 3 years; HR for all-cause mortality and CV hospitalisation = 0.95 up to three years						
Standard care	£46,214		2.7014			£46,214
BCM	£47,288	£1,074	2.7488	0.0474	£22,647	£47,288

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

Subgroup analysis

Table 4 presents the results considering key subgroups of the dialysis population.

Separate analyses were considered by comorbidity status (none; at least one), dialysis modality (haemodialysis, peritoneal dialysis), starting age of the cohort (55 years), and transplant listing (yes/no). For comparability, all of these analyses were conducted with the revised clinical effectiveness scenario 3 (HR = 0.9318 for the effect of bioimpedance monitoring on mortality and CV hospitalisation).

The subgroup analyses using the overhydration states in the model (clinical effectiveness scenarios 6, analyses 8 and 9 in Table 5) remain unchanged from the original EAG report.

These analyses do not reveal any large changes in the estimated ICERs compared with those in Table 24 of the original EAG report, with the differences in cost-effectiveness between subgroups remaining small. The ICER remains slightly higher in the subgroup waitlisted for transplant, as they spend less time on dialysis and so benefit less from the modelled reduction in all-cause mortality and CV hospitalisation conferred by bioimpedance guided fluid management.

Table 5 Subgroup analysis (using clinical effectiveness scenario 3 unless otherwise stated) - updates Table 24 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
1. People on dialysis who have comorbidities and higher hospitalisation rate*						
Standard care	£47,011		2.6974			£6,937
BCM	£48,951	£1,940	2.813	0.1156	£16,781	£7,309
2. People on dialysis with no comorbidities and lower hospitalisation rate*						
Standard care	£43,102		2.7166			£11,230
BCM	£44,941	£1,839	2.8326	0.116	£15,852	£11,711
3. People on haemodialysis (start age: 67; years on dialysis: 3)						
Standard care	£45,821		2.5803			£5,785
BCM	£47,751	£1,930	2.6933	0.113	£17,079	£6,115
4. People on peritoneal dialysis (start age: 64; years on dialysis: 2)						
Standard care	£53,033		3.3993			£14,954
BCM	£54,819	£1,786	3.5186	0.1192	£14,982	£15,552
5. Mixed haemodialysis/peritoneal dialysis cohort aged 55						
Standard care	£79,985		4.7225			£14,466
BCM	£82,157	£2,173	4.8503	0.1278	£17,001	£14,849
6. Patients listed for a transplant*						
Standard care	£87,221		4.1846			-£3,530
BCM	£89,416	£2,195	4.2892	0.1047	£20,968	-£3,631

7. Patients not listed for transplant*						
Standard care	£39,807		2.4696			£9,586
BCM	£41,683	£1,876	2.587	0.1174	£15,980	£10,058
8. Chronically overhydrated patients only, at increased risk of mortality and all-cause hospitalisation; using modelling structure and assumptions of clinical effectiveness scenario 6 (38% reduction of chronic overhydration with bioimpedance monitoring relative to standard practice) – dialysis costs included						
Standard care	£157,985		2.7			-£157,985
BCM	£179,576	£21,591	3.06	0.36	£59,701	-£179,576
9. Chronically overhydrated patients only, at increased risk of mortality and all-cause hospitalisation; using modelling structure and assumptions of clinical effectiveness scenario 6 (38% reduction of chronic overhydration with bioimpedance monitoring relative to standard practice) – dialysis costs excluded						
Standard care	£46,095		2.7			-£46,095
BCM	£51,306	£5,211	3.06	0.36	£14,409	-£51,306

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

Probabilistic cost-effectiveness results

For comparison with the deterministic results in Table 1 and 2, Tables 6 and 7 presents the results for the revised clinical effectiveness scenarios 3 and 4 based on 1000 probabilistic iterations of the model, with dialysis costs included (Table 6) and excluded (Table 7). The effects in scenario 1 remain unchanged from the original EAG report, but are included for comparison.

The point estimates for the ICERs remain very similar to the deterministic ICERs. However, with the greater uncertainty surrounding the pooled effect of bioimpedance monitoring on PWV, there is greater uncertainty surrounding the cost-effectiveness results.

With dialysis costs included, the probability of bioimpedance testing being cost-effective is ~10%-14% in the revised effectiveness scenarios 3 and 4 (previously < 6%).

With the dialysis costs excluded, the probability of bioimpedance testing being cost-effective is now ~62%-63% in the revised effectiveness scenarios 3 and 4 (Table 7). This is substantially lower than the previous probabilities of 70%-73% respectively, reflecting the greater uncertainty surrounding the pooled effect in PWV, and consequently the linked effects on all-cause mortality and CV hospitalisation.

The revised incremental cost-effectiveness scatter-plots for bioimpedance testing versus standard practice, and the corresponding cost effectiveness acceptability curves, are presented in Figures 12 and 13 below, for the revised effectiveness scenario 3 (including dialysis costs). The corresponding revised figures with dialysis costs excluded are presented in Figures 14 and 15.

Table 6 Probabilistic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (including dialysis costs) – updates Table 25 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	Probability cost-effective at £20,000 threshold
1. Clinical effectiveness scenario 1; applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£157,313		2.692			0.752
BCM	£190,130	£32,817	3.217	0.525	£62,563	0.248
2. Clinical effectiveness scenario 3; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318 on both CV events and mortality)						
Standard care	£158,450		2.6923			0.896
BCM	£165,877	£7,427	2.8159	0.1236	£60,114	0.104
3. Clinical effectiveness scenario 4; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318 on both CV events and mortality), and a 10% reduction in BP medications use						
Standard care	£157,167		2.69			0.86
BCM	£163,623	£6,456	2.799	0.1089	£59,258	0.14

Table 7 Probabilistic cost-effectiveness scenarios for bioimpedance guided fluid management versus standard practice (excluding dialysis costs) - updates Table 26 of the original EAG report

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	Probability cost-effective at £20,000 threshold
1. Clinical effectiveness scenario 1; applying the point estimate for the pooled effect of BCM on mortality only						
Standard care	£45,975		2.691			0.313
BCM	£54,786	£8,811	3.238	0.547	£16,100	0.687
2. Clinical effectiveness scenario 3; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318 on both CV events and mortality)						
Standard care	£46,221		2.6973			0.378
BCM	£48,161	£1,939	2.8169	0.1196	£16,208	0.622
3. Clinical effectiveness scenario 4; applying linked effects on mortality and non-fatal CV events through the pooled reduction in PWV (HR = 0.9318 on both CV events and mortality), and a 10% reduction in BP medications use						
Standard care	£45,919		2.6947			0.367
BCM	£47,722	£1,803	2.8098	0.1151	£15,657	0.633

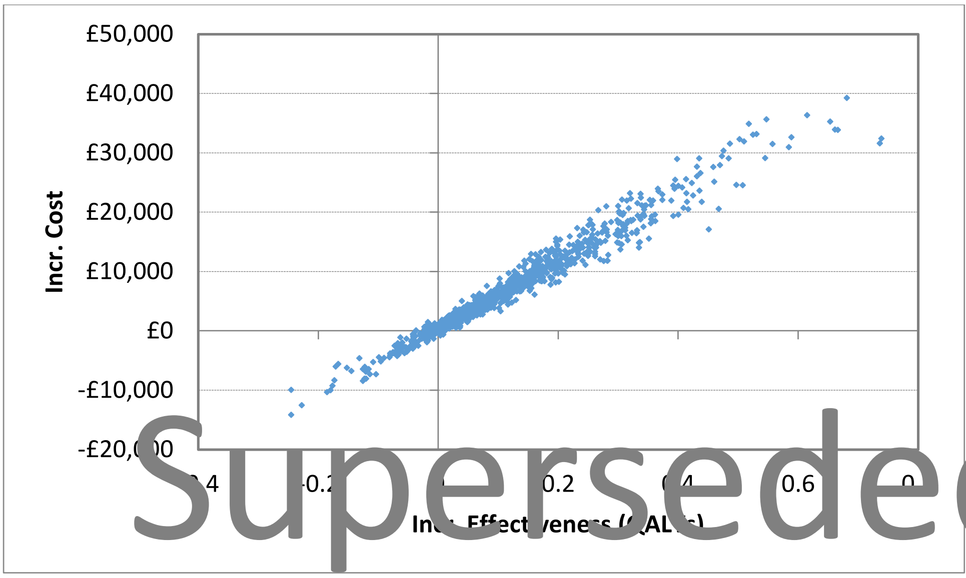

Figure 12 Incremental cost-effectiveness scatter plot: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs) - updates Figure 20 of the original EAG report

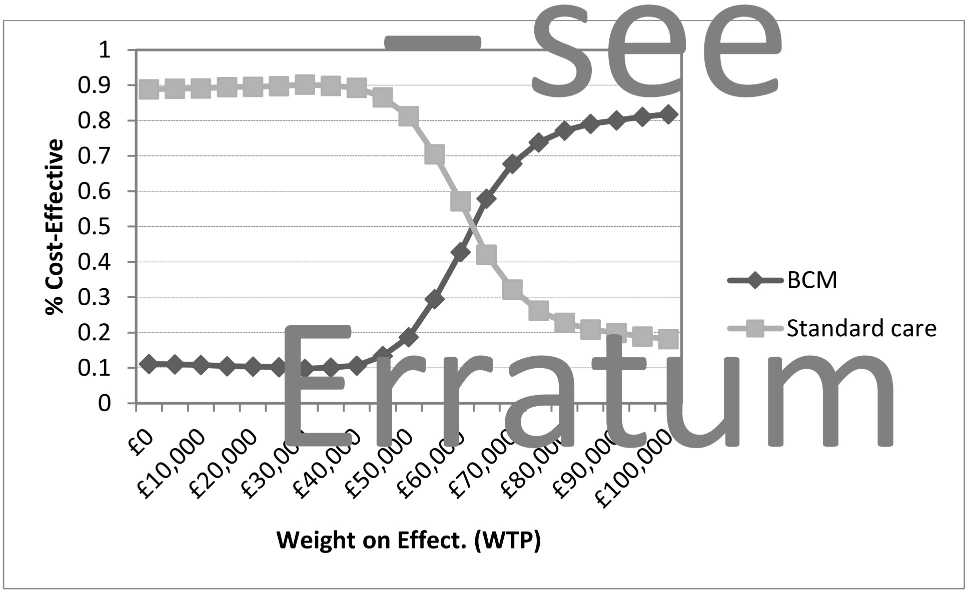

Figure 13 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – including dialysis costs) - updates Figure 21 of the original EAG report

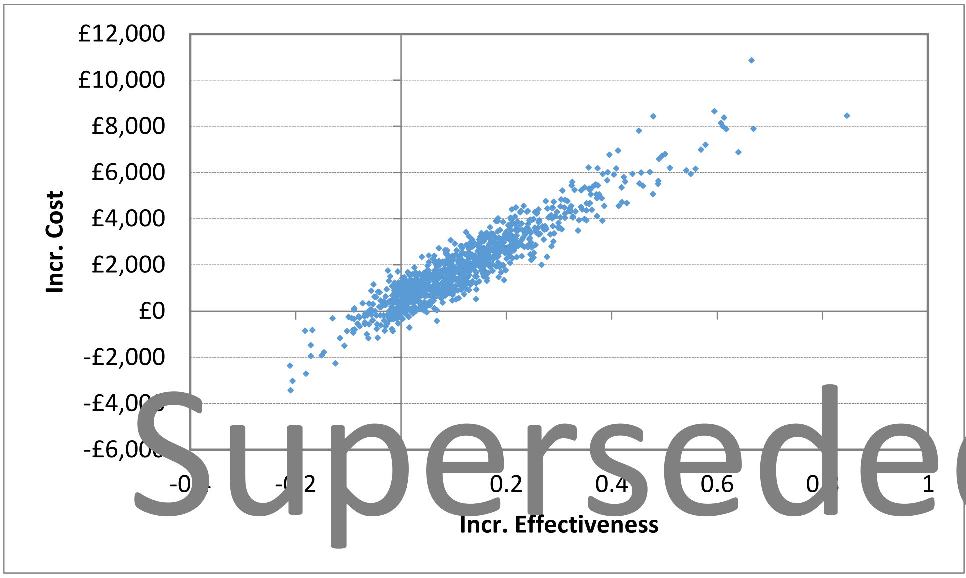

Figure 14 Incremental cost-effectiveness scatter plot: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs) - updates Figure 24 of the original EAG report

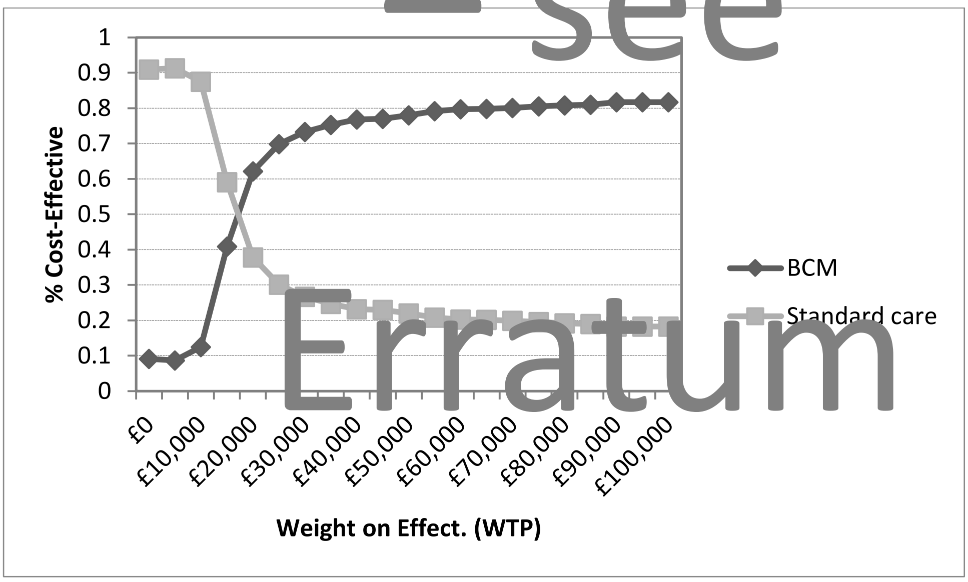

Figure 15 Cost-effectiveness acceptability curves: BCM – Body Composition Monitor versus standard care (Clinical effectiveness scenario 3 – excluding dialysis costs) - updates Figure 25 of the original EAG report

Interpretation of the revised cost-effectiveness results

The revised cost-effectiveness results in the tables above, reflect a slightly smaller and more uncertain effect of bioimpedance monitoring on arterial stiffness, and consequently a smaller linked effect on CV hospitalisation and/or all-cause mortality. This is the consequence of the exclusion of Onofriescu et al. 2012 from the meta-analysis on arterial stiffness (PWV).

The impact of this change on the point estimates of the ICERs for bioimpedance guided management is fairly limited. The ICER point estimates for all the main clinical effectiveness scenarios remain well above £30,000 when dialysis costs are included, and mostly below £20,000 when dialysis costs are excluded from the economic model.

They key impact of the revised effect of bioimpedance testing on PWV, is the increased uncertainty surrounding the cost-effectiveness estimates. With dialysis costs included, the probability of bioimpedance monitoring being cost-effective at standard thresholds remains low. With the dialysis costs excluded, the probability of bioimpedance testing being cost-effective drops to ~62%-63% with the revised effectiveness scenarios 3 and 4 (Table 7). This is substantially lower than the previous probabilities of 70%-73% respectively (Table 26 of the original EAG report).

The revised cost-effectiveness results remain dependent on very limited evidence for the effect of bioimpedance guided fluid management on PWV. With the exclusion of Onofriescu et al. 2012, only two trials, with inconsistent findings, were included in the PWV meta-analysis. This further increases the uncertainty surrounding the validity and robustness of the cost-effectiveness findings based on this surrogate endpoint. Added to this uncertainty is the lack of available evidence by which to link the intervention induced changes in this surrogate endpoint to changes in health outcomes. Therefore, the indirect/linked modelling scenarios rely on observational associations to estimate possible effects of bioimpedance guided fluid management on final health outcomes.

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