National Institute for Health and Care Excellence

Final

RRT and conservative management

Cost-effectiveness analysis: HDF versus high flux HD

NICE guideline NG107

Economic analysis report

October 2018

Final

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1 Cost-effectiveness analysis: HDF compared to high flux HD

1.1 Introduction

The committee considered the clinical evidence reviewed as part of the guideline to suggest that haemodiafiltration (HDF) may have a benefit in terms of mortality compared to standard haemodialysis (HD). However, it was noted that the cost of delivering HDF was likely to be higher than HD and so cost effectiveness was a relevant consideration. The economic evidence review identified three published economic analyses but having reviewed these. The committee considered there to be uncertainty about the cost effectiveness of HDF versus HD in the NHS setting. Full details of the published clinical and economic evidence and the committee's discussion are in evidence report B: Modalities of renal replacement therapy.

The committee noted at the time of prioritisation for new analysis that while HDF is used in some centres it is not widely used in the NHS in England and so a recommendation for its use would be a change in practice. Although it is noted that data obtained towards the later stages of development from selected centres via members of the Association of Renal Technologists suggested that HDF may now be more widely used in the NHS.

HDF versus HD was identified as the highest priority for new economic analysis by the committee due to it potentially being a significant change in practice that could have a substantial resource impact for the NHS; while cost differences might be fairly small per session, most people on HD (around 25,000) are potentially suitable for HDF. It was felt that new cost effectiveness analysis could reduce the uncertainty around the cost effectiveness of HDF in the current NHS setting.

1.2 Methods

1.2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance.[22] An incremental analysis was undertaken.

1.2.1.1 Comparators

The comparators selected for the model were:

1. High flux HD 3x per week in-centre
2. HDF 3x per week in-centre

In the clinical review comparisons of HDF with both low flux HD and high flux HD were combined under the heading of HD. However, the committee highlighted that high flux HD is the current standard of care for HD and so this was considered the appropriate comparator for the economic analysis given that the difference in costs between HD and HDF will vary depending on this.

The analysis was limited to in-centre use as the population is much larger (83% in-centre vs 4% at home; the remainder being PD), and so a higher priority for modelling, and no clinical evidence was identified for HDF in the home setting. There was also an additional complexity

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with the comparison in the home setting as some people currently have more than 3 session of HD when at home but evidence was not identified in the clinical review relating to this.

The analysis does not include peritoneal dialysis (PD) as an alternative - it essentially assumes that people have already made the decision that they do not want to do PD. No clinical evidence was identified that met the criteria for the clinical review for the guideline to differentiate between PD and HD and there are many practical considerations that will influence individual preferences.

1.2.1.2 Population

The population considered in the analysis was adults with CKD starting RRT that are naïve to RRT and have chosen dialysis using vascular access (over peritoneal dialysis – as discussed in the previous section).

The analysis was limited to adults as the population for children is much smaller, and so a lower priority for modelling, and no clinical evidence for HDF in children was identified.

1.2.2 Approach to modelling

A Markov model was constructed to calculate lifetime costs and QALYs for each comparator. In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

Following review of the clinical evidence and committee discussion, it was agreed that the key difference in clinical outcomes that needed to be captured in the model was a benefit in terms of mortality with HDF compared to HD. The committee did not consider there to be good evidence of other treatment effects. The committee noted that there was some evidence of clinical benefit in terms of hospitalisations in older patients however evidence in adults suggested no difference and this was from a larger evidence base and was more precise. It was agreed hospitalisation would therefore not be incorporated into the cost effectiveness model. Full details of the evidence and the committee's discussion are in evidence report B: Modalities of renal replacement therapy.

A model was constructed with three health states: alive on HD or HDF, transplant and dead. Figure 1 illustrates the model structure and the possible transitions between health states each cycle. A 1 year cycle length was used. The dead and transplant states are both absorbing states. Time- and treatment-dependent rates define how quickly people in the cohort move from the alive on HD/HDF state to the dead state. Time-dependent rates define how quickly people move from the alive on HD state to the transplant state; it is assumed that transplant numbers are the same on HDF as on HD. Given this, costs and outcomes incurred in this state can be excluded (the rationale for this is discussed further below). The state is included however so that the appropriate difference in number of people alive on treatment with HDF and HD is estimated by the model each cycle. People in the model cannot return to dialysis after transplant – this is a simplification of reality but was considered reasonable for modelling purposes. People in the model cannot switch to PD (data showed that a smaller number of people will make this switch and this was unlikely to vary between groups and so the committee agreed this was reasonable to exclude) or between HD and HDF.

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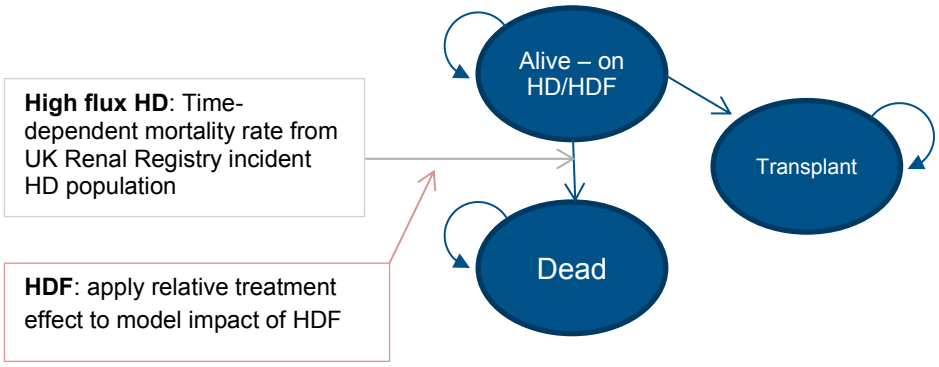
Figure 1: Model structure



The model is run for repeated cycles, and the time spent in the alive on HD/HDF health state is calculated. By attributing costs and quality of life weights to those alive on HD/HDF, total costs and QALYs can be calculated for the population. This model was run for 50 cycles/years in order to calculate lifetime costs and QALYs. Each comparator in the analysis (HD and HDF) had its own set of transition probabilities (mortality rates) therefore each will have different total costs and QALYs. Comparing these results allows us to identify which is the most cost-effective.

Summary of key model assumptions:

- Transplant numbers are not affected by the use of HDF and so transplant costs and outcomes can be excluded
- The HDF treatment effect observed in clinical trials can be applied while on treatment throughout the lifetime model
- People cannot switch between HD and HDF in the model
- People cannot switch to PD in the model
- People cannot return to dialysis after transplant in the model

Discussion about the transplant assumption

Whether, and how, to incorporate transplant into the analysis was carefully considered during development of the model as it was a decision that would impact the approach to modelling and data requirements.

One option would be to assume that the probability of transplant is constant whilst alive. In this case, even if the probability of having a transplant does not vary between HDF and HD, if mortality is lower with HDF this will also result in higher transplant rates. This will confer an additional mortality benefit to the HDF arm as people who have a transplant will benefit from a substantial mortality benefit. It would also result in improved quality of life and lower costs as these are associated with transplant. This type of approach is common in health economic models with people remaining at risk of clinical events whilst alive.

The committee felt that it wasn't implausible for greater survival with HDF to result in more transplants; however, it was not considered a given as the people who are eligible for a transplant are generally younger and more well therefore the committee noted that it may be that these people are less likely to be the people who live longer due to using HDF. In addition, given that the number of deceased donor kidneys available for transplant (and live donors as well to some extent) is a limited resource it may not be possible to increase kidney transplant rates; or, if transplant numbers in this population increase it could be that

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someone somewhere else in the system will not receive a kidney transplant so there may be an opportunity cost in a different population (69% of transplants were deceased donor and 31% live donor based on 2016-17 reference cost data). Taking these considerations into account an alternative assumption could be that the number of transplantations is not affected by the use of HDF or HD.

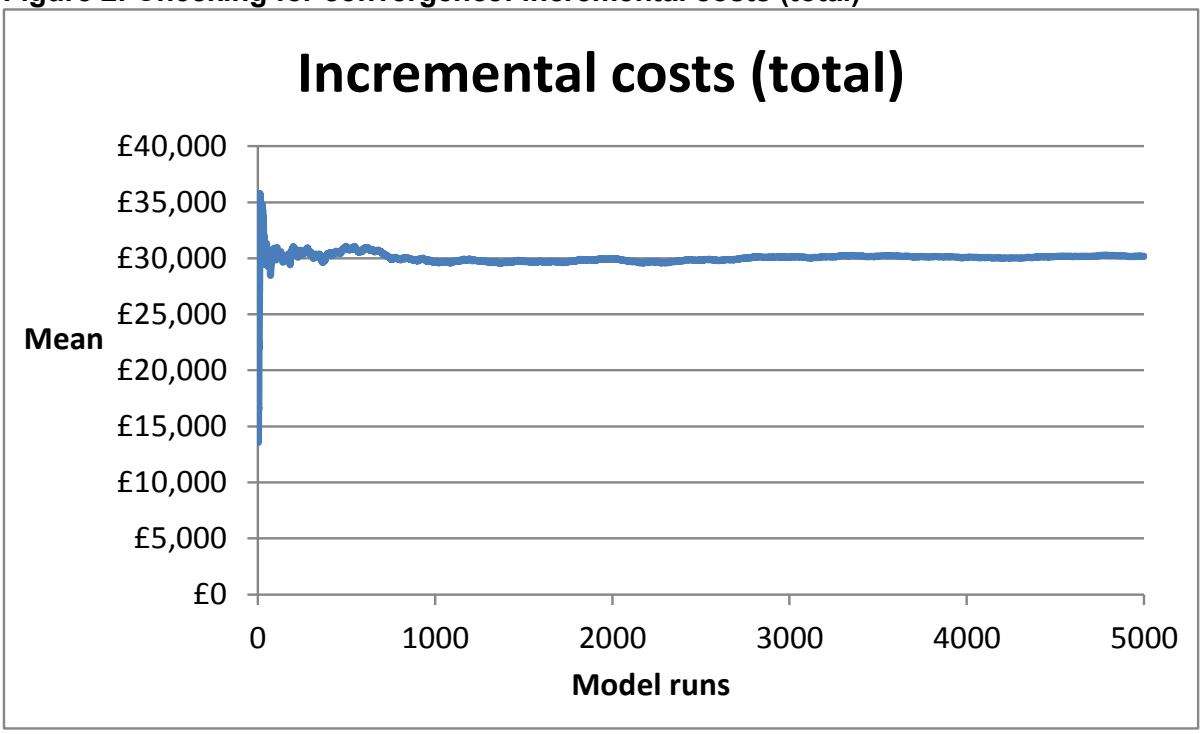
Given the above considerations the committee agreed that the most reasonable assumption for the model, albeit a potentially conservative one, was to assume constant numbers of transplants.

1.2.2.1 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5000 times for the base-case analysis and each sensitivity analysis – and results were summarised in terms of mean costs and QALYs, and the percentage of time HDF was the most cost-effective strategy at a threshold of £20,000/£30,000 per QALY gained. Probability distributions were selected to reflect the nature of the data and were parameterised using error estimates from data sources.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs (total and intervention only), QALYs and net monetary benefit (using both total and intervention only) at a threshold of £20,000 per QALY gained for HDF versus HD by plotting the number of runs against the mean outcome at that point (see example in Figure 2) for the base-case analysis. Convergence was assessed visually. All had converged before 5000 runs.

Figure 2: Checking for convergence: incremental costs (total)



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In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 1.2.4 Sensitivity analyses.

1.2.3 Model inputs

1.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 1 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 1: Summary of base-case model inputs

Input	Data	Source
Comparators	• High flux HD • HDF	
Population	Adults with CKD starting dialysis that are naïve to RRT	
Perspective	UK NHS & Personal Social Services	NICE reference case
Time horizon	Lifetime	NICE reference case
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case
Baseline event rates		
Mortality while on HD (annual)	Time-dependent (0.140 to 0.201)	UK Renal Registry novel analysis (years 1-10); assumption (years 11+)
Transplant rate on HD (annual)	Time-dependent (0.017 to 0.060 years 1-10; zero 11 years+)	UK Renal Registry novel analysis (years 1-10); assumption (years 11+)
Relative treatment effects		
Relative difference in mortality with HDF (HR)	0.82 (0.63 to 1.06)	Systematic review of RCTs undertaken as part of guideline development[7, 16-19, 29-31, 34]
Quality of life (utilities)		
HRQoL while alive on HD/HDF	0.56 (0.49 – 0.62)	Liem et al 2008[15]
Costs		
Difference in blood line cost with HDF	£2.82 per session / £439.92 per year	Resource used based on manufacturer information, renal technologists and the committee; unit costs based on the NHS supply chain catalogue[27]
Difference in water consumption cost with HDF	£0.04 per session /£6.24 per year	Additional 15 litres per session, expert opinion; average water and sewerage cost of NHS Trusts in England 2016/17[10]

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Input	Data	Source
Difference in ESA cost with HDF	-£98.93 per year based on dose reduction of 4.25 U/kg/week	Meta-analysis of dose data from RCTs included in clinical review[18, 29, 31]; UK average weight from HSE 2015[20], BNF epoetin alfa costs[11]
General dialysis-related costs	£32,259 per year	Dialysis (£23,362 – NHS Reference Costs 2016-17[6]), transport (£4058 – cost per journey based on 2016-17 data from a London Trust and working group estimate, combined with 2010 patient transport audit[26]), and 15% assumption for other costs (e.g. access related procedures, complications, health care visits, drugs)

Abbreviations: HD = haemodialysis; HDF = haemodiafiltration; ESA = erythropoietin stimulating agent; HR = hazard ratio; HRQOL = health-related quality of life

1.2.3.2 Baseline event rates on HD

1.2.3.2.1 Mortality

A time-dependent annual mortality probability was applied in the model to those who were alive on HD and had not had a transplant.

These probabilities were based on a novel analysis of data from the UK Renal Registry. We thank all the UK renal centres for providing data to the UK Renal Registry and Anna Casula from the UK Renal Registry for the statistical analysis she undertook. Note: the views and opinions expressed in this report are those of the guideline committee and do not reflect the views of the UK Renal Registry or UK Renal Association.

The analysis used a UK adult incident cohort starting RRT on HD between January 2005 and December 2014 with follow-up to the end of 2015 (except Cambridge patients who were followed to the end of 2014). As we required mortality probabilities for those who remained on HD a survival analysis was performed with censoring upon any switch away from HD (e.g. transplant). Data is shown in Figure 3 and Table 2.

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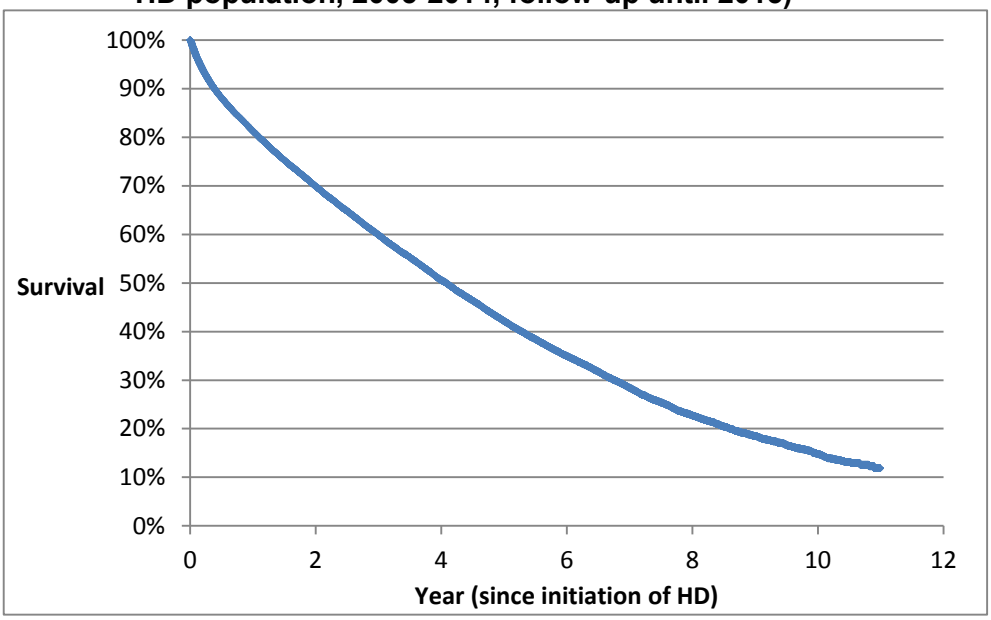
Figure 3: Kaplan Meier survival curve of incident HD population 2005-2014 (follow-up until 2015) censored at transplant and any switch away from HD (incident HD population, 2005-2014, follow-up until 2015)



Source: UK Renal Registry novel analysis.

Table 2: Summary data per year from survival analysis of incident HD population 2005-2014 (follow-up until 2015) censored at transplant and any switch away from HD

	Survival (%)	N at risk	N died	N tx	N PD	N rec	N lost[a]	N stop[a]	N end-follow-up on HD
start	100.00	49732							
1 year	81.26	34879	8687	1957	2778	408	317	630	76[b]
2 years	69.89	24723	13142	3695	3013	516	428	834	3381
3 years	59.86	17140	16356	5137	3135	561	477	998	5928
4 years	50.54	11594	18754	6165	3188	574	512	1105	7840
5 years	42.16	7641	20474	6842	3209	584	527	1196	9259
6 years	34.98	4913	21629	7230	3224	591	538	1240	10367
7 years	28.41	2901	22426	7469	3240	596	545	1262	11293
8 years	22.70	1599	22924	7557	3248	596	549	1277	11982
9 years	18.46	776	23165	7605	3251	596	555	1288	12496
10 years	14.77	288	23276	7618	3251	596	558	1295	12850

Source: UK Renal Registry novel analysis.

Abbreviations: HD = haemodialysis; lost = lost/transfer-out from renal unit; PD = peritoneal dialysis; rec = recovered; stop = stopped treatment (patient considered as needing dialysis but have taken the decision not to proceed with RRT); tx = transplant

(a) In the analysis, if the patient dies within one week from date of treatment being stopped the date of death (and therefore event) has been used, otherwise it has been censored.

(b) All from Cambridge, starting during 2014 and follow-up to December 2014

Using the survival each year we calculated the time-dependent probability of death each year (cycle) for those alive in the model on HD at years 1 to 10 after initiating dialysis as described below.

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First the cumulative hazard each year, *H(t),* was calculated from the survivor function, *S(t)*, for the corresponding time period:

$$H(t) = -ln\{S(t)\}$$

The transition probabilities for each year were then calculated as follows where u is the cycle length (1 year) and t is the time point of interest:

$$tp(t_u) = 1 - exp\{H(t-u) - H(t)\}$$

The annual probability of death after year 10 was assumed to be the same as in year 10.

The resulting probabilities are summarised in Table 3 and presented graphically in Figure 5. There is generally a trend for increasing mortality over time with the exception of year one which is higher than in the years immediately following; this can be explained as mortality risk is generally higher in the period immediately after starting dialysis. These probabilities were incorporated into the probabilistic analysis using a beta distribution as this is bounded by 0 and 1 like probabilities. This was parameterised using the N at risk at the start of the year – details are in Table 3.

Table 3: Model inputs: probability of death each year post initiation of HD, for those alive

Year/cycle	Probability of death	Probabilistic analysis: beta distribution parameters		
		N	Alpha	Beta
1	0.187	49732	9321	40411
2	0.140	34879	4880	29999
3	0.144	24723	3548	21175
4	0.156	17140	2668	14472
5	0.166	11594	1923	9671
6	0.170	7641	1301	6340
7	0.188	4913	922	3991
8	0.201	2901	583	2318
9	0.187	1599	299	1300
10	0.200	776	155	621
11+[(a)]	*0.200*	*288*	*58*	*230*

Source: Calculated based on data from UK Renal Registry novel analysis
Abbreviations: HD = haemodialysis; N = number at risk at the beginning of the year
(a) Extrapolation; annual probability in year 11 onwards assumed to be the same as in year 10. The probability distribution was parameterised using the N at risk at the end of year 10.This was considered more appropriate than simply using the same probabilistic input at for year 10 as it will result in a higher level of uncertainty which is appropriate given this is an extrapolation.

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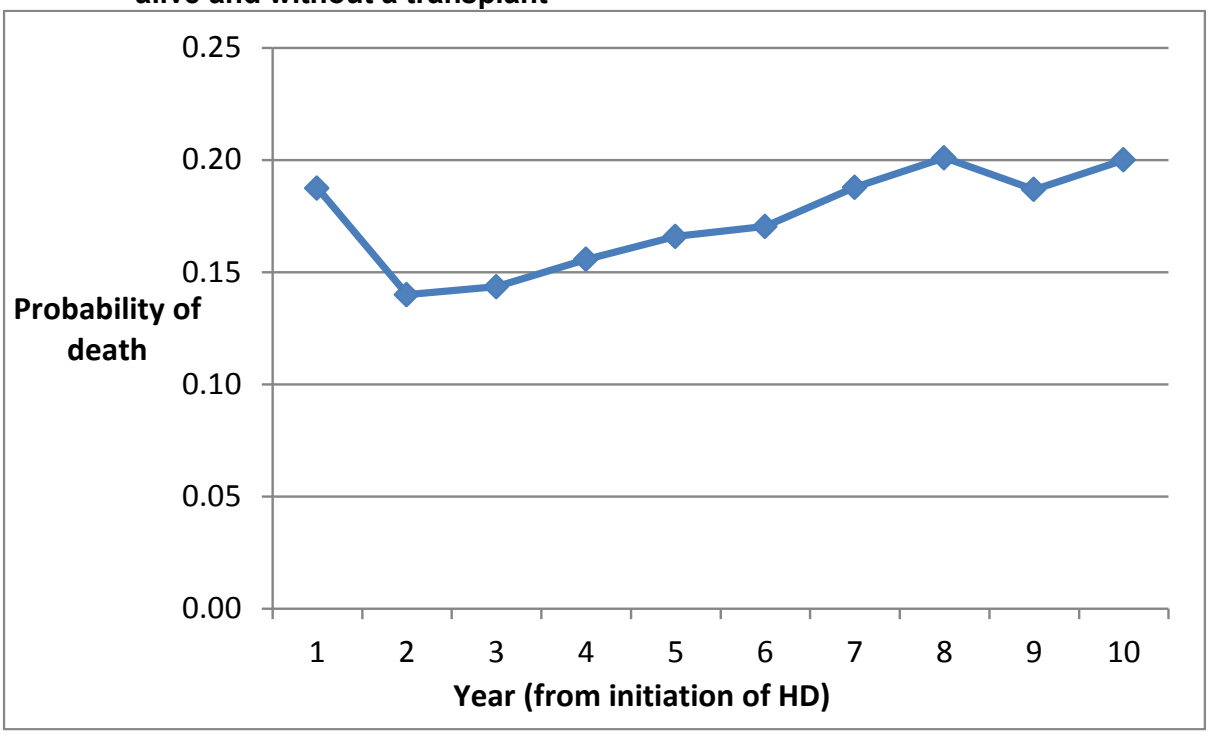
Figure 4: Model inputs: probability of death each year post initiation of HD, for those alive and without a transplant



Source: Calculated based on data from UK Renal Registry novel analysis

Abbreviations: HD = haemodialysis

1.2.3.2.2 Transplant

A time-dependent annual transplant probability was applied in the model to those who were alive on HD. These are summarised in Table 4 and Figure 5.

These probabilities were estimated based on the same analysis of data from the UK Renal Registry used for mortality data. The analysis used a UK adult incident cohort starting RRT on HD between January 2005 and December 2014 with follow-up to the end of 2015 (except Cambridge patients who followed to the end of 2014). The probability of transplant each year was calculated by dividing the number of new transplants in each year by the number at risk at the end of the previous year (data in Table 2).

The data shows that the probability of transplant initially increases over time up to a peak at 4 years post-initiation of dialysis and then decreases over time. The committee considered this to reflect their expectations of how the probability of transplant might vary over time. Kidneys are allocated according to match of tissue type, with "tie breakers" for equally matched kidneys. In the first couple of years, you may be lucky and be the only one matching that well for that kidney. However, for each kidney that comes up, more usually there may be 4-5 equally matched patients. In that case, those waiting longer are more likely to receive it and this peaks at the 3-5 year time point. Thereafter, there will be other reasons (patients with rare tissue types or previously formed antibodies making it more difficult to match, or medical/surgical conditions putting additional restrictions on the organs that can be used for them) why the rates drop off – essentially as time progresses those who can have a kidney transplant will have had one.

In the model, after 10 years there was assumed to be a zero rate of transplant. This was based on the trend for a decreasing rate of transplant over time observed in the later years of the analysis (see Table 4 and Figure 1 below), the low probability of transplant observed in

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year 10 and expert clinical opinion that transplant rates were likely to be very low after 10 years. These probabilities were incorporated into the probabilistic analysis using a beta distribution as this is bounded by 0 and 1 like probabilities. This was parameterised using the N at risk at the start of the year – details are in Table 4.

Table 4: Model inputs: probability of transplant each year post initiation of HD

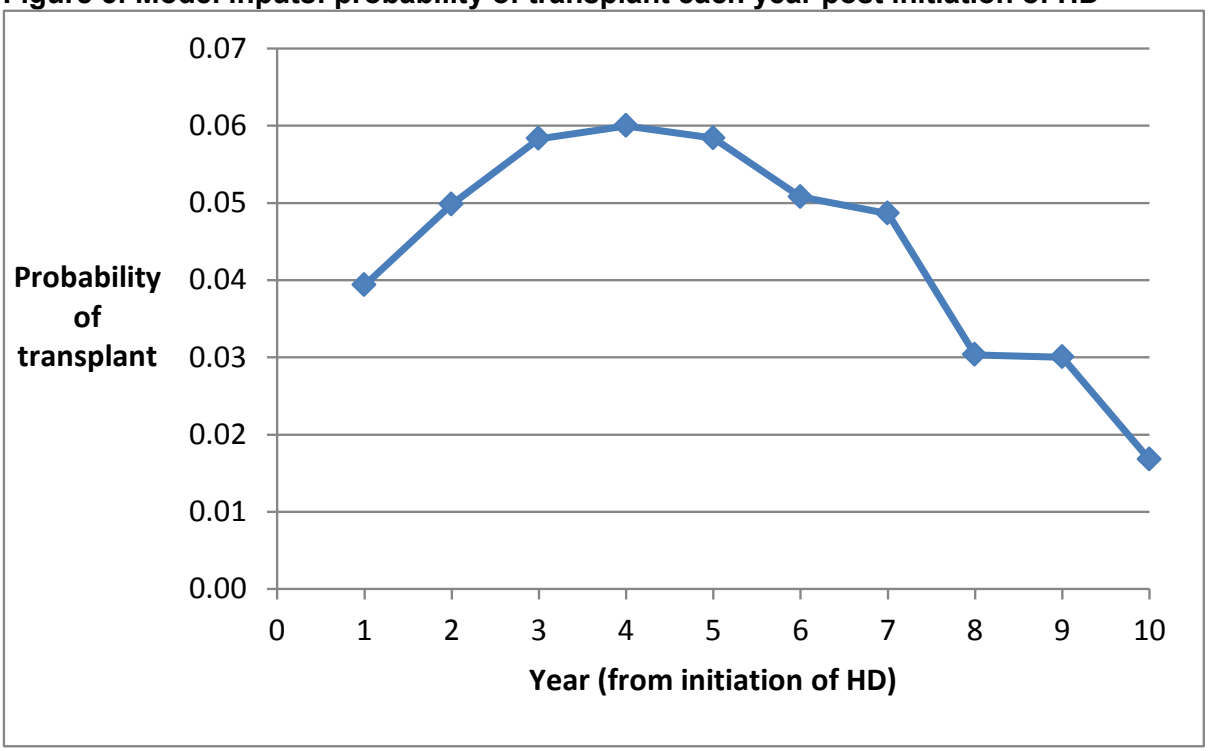
Year/cycle	Probability of transplant	Probabilistic analysis: beta distribution parameters		
		N	Alpha	Beta
1	0.039	49732	1957	47775
2	0.050	34879	1738	33141
3	0.058	24723	1442	23281
4	0.060	17140	1028	16112
5	0.058	11594	677	10917
6	0.051	7641	388	7253
7	0.049	4913	239	4674
8	0.030	2901	88	2813
9	0.030	1599	48	1551
10	0.017	776	13	763
11+[(a)]	0			

Source: Calculated based on data from UK Renal Registry novel analysis

Abbreviations: HD = haemodialysis N = number at risk at the beginning of the year

(a) Probability of transplant is assumed to be zero after 10 years

Figure 5: Model inputs: probability of transplant each year post initiation of HD



Source: Calculated based on data from UK Renal Registry novel analysis

Abbreviations: HD = haemodialysis

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The number of people who have a transplant is assumed to be constant in the model. That is the same numbers of people have a transplant in the analysis with HD and HDF. See Section 1.2.2 for further discussion about this assumption.

1.2.3.3 Relative treatment effects

In the base-case analysis a hazard ratio of 0.82 (95% CI 0.63 to 1.06) was used to model the relative treatment effect of HDF compared to HD on mortality.

This was based on the systematic review of the clinical evidence for HDF compared to HD undertaken as part of guideline development (full details of the evidence and the committee's discussion are in evidence report B: Modalities of renal replacement therapy). This identified nine randomised controlled trials compared HDF and HD.[7, 17-19, 29-31, 34] A summary of the mortality data from report B is included below in Table 5. Note that the evidence review was conducted combining all comparisons of HDF with HD (low flux and high flux) with subgroup analysis planned if there was heterogeneity in the analysis. As there was some degree of heterogeneity in the meta-analysis of mortality this subgroup analysis was undertaken but this did not explain the heterogeneity and data was kept combined. Given this the overall effect size in the base-case analysis of the model also uses all studies . Alternative estimates were tested in sensitivity analyses, including using only high flux HD studies.

Table 5: Clinical evidence summary: HD – HDF vs HD, RCT (adults age 18-70 years)

Outcomes	N (studies) Follow-up	Relative effect (95% CI)
Mortality, TTE, general population	1620 (2 studies) 2-3 years	HR 0.82 (0.61 to 1.11)
Mortality, RR, general population	2964 (9 studies) 2-3 years	RR 0.82 (0.64 to 1.05)

Abbreviations: N = total number of participants in studies; 95% CI = 95% confidence interval; TTE = time-to-event; HR = hazard ratio; RCT = randomised clinical trial; RR = relative risk; DM = diabetes mellitus
*(a) HR = ln(-RR*CER+1) ÷ ln(1-CER), where CER = control event rate (number of people with event in control groups ÷ total number of people in control groups)*

As can be seen above, the clinical review reported mortality data in the form of hazard ratios (2 studies) and relative risk (9 studies including those reporting hazard ratios). The most appropriate way to analyse time-to-event data is using survival analysis and reporting hazard ratios as this takes account of censoring (for example, due to drop-outs) during follow-up (both are reported in the clinical review however as not all studies will undertake survival analysis and report hazard ratios). In addition, a relative risk relates to the probability during a specific time period (if followed up for long enough the relative risk of mortality will eventually be 1 as everyone will ultimately die, whereas this will not be the case with a hazard ratio which considers the rate of mortality) and in the model we wish to assume that the relative treatment effect observed during the study periods can be applied over a longer time period. Computationally using hazard ratios in a model will also mean that probabilities will not exceed 1 as hazard ratios are applied to the underlying hazard and then converted back to a probability (as described in Section 1.2.5.Computations).

To maximise the data used but retain reported hazard ratios where available an additional meta-analysis was undertaken for the model that included hazard ratio data, where available, and where it was not used hazard ratios calculated from relative risks. A random effects meta-analysis was undertaken consistent with the method and rationale used for the meta-analysis undertaken for relative risk data for the guideline (see Chapter B). Hazard ratios were calculated from relative risks using the formula below:

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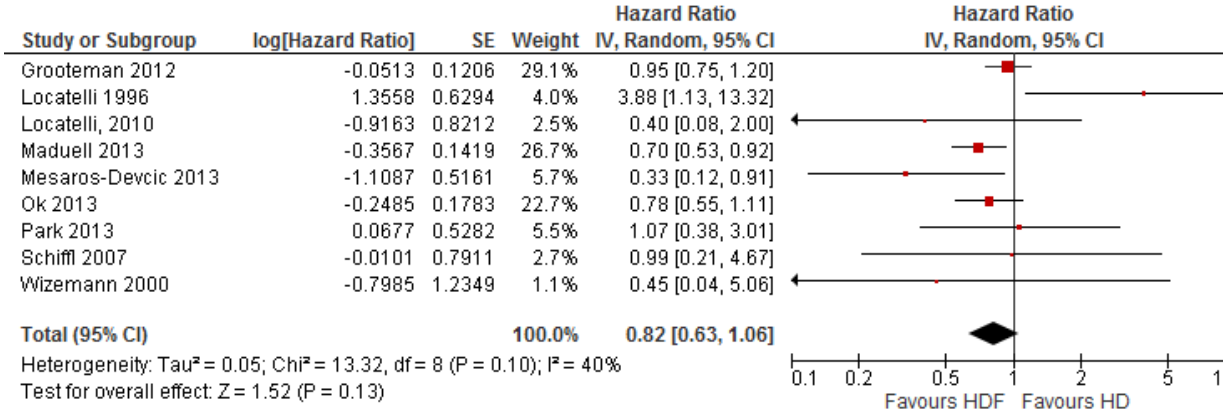
$$\mathrm{HR} = \frac{\ln(-\mathrm{RR} * \mathrm{CER} + 1)}{\ln(1 - \mathrm{CER})}$$

- HR = hazard ratio
- RR = relative risk
- CER = control event rate (number of people with event in control group ÷ total number of people in control group)

Figure 6: Model inputs: Relative treatment effect on mortality with HDF compared to HD - meta-analysis of reported and estimated[(a)] hazard ratios



Hazard ratio data available from study: Grootman 2012[7]; Maduell 2013[18]. Hazard ratio calculated from relative risk: Mesaros-Devcic 2013[19]; Wizemann 2000[34]; Locatelli 1996[17]; Locatelli 2010[16]; Ok 2013[29]; Park 2013[30]; Schifl 2007[31].

*(a) HR = ln(-RR*CER+1) ÷ ln(1-CER), where CER = control event rate (number of people with event in control groups ÷ total number of people in control groups)*

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The hazard ratio was incorporated into the probabilistic analysis using a log normal distribution. This was parameterised using the summary hazard ratio estimate from the meta-analysis and the standard error calculated from the confidence interval.

1.2.3.4 Quality of life (utilities)

A utility of 0.56 (SE 0.03) was used in the base-case analysis for people in the alive state. This did not vary by treatment in the base-case analysis as the committee concluded the clinical evidence did not support there being a difference (full details of the evidence and the committee's discussion are in evidence report B: Modalities of renal replacement therapy).

This is based on an estimate of EQ-5D utility for people on HD from a published systematic review and meta-analysis.[15] The pooled estimate of EQ-5D utility was based on 7 studies and a total of 1384 people. The authors did not state the EQ5D tariff used by each study but note that the tariff based on UK population sample values is most commonly used. They also did not state that all values are measured directly in patients but it is considered likely that most if not all will be. The authors describe EQ-5D as having 3 levels and so based on this, and study dates, it is assumed that all studies included used EQ-5D-3L.

A more recent systematic review and meta-analysis of utility data was also identified. This reported a higher utility estimate of 0.69 (95% CI 0.59 to 0.80). This was however based on a meta-analysis that included all measures of utility (not just EQ-5D) and also mapped SF36 and SF12 data to EQ-5D.[35] The Liem et al data was therefore considered more in line with the NICE reference case (direct EQ-5D data is considered preferable to EQ-5D estimates derived from mapping other measures[24]) and so was used in preference to this. Using data from this study was explored in sensitivity analysis.

Utility was incorporated into the probabilistic analysis using a beta distribution as this is bounded by 0 and 1 as utilities are generally between these values (where 0 is death and full health is 1). It is possible that utility values can be less than 1 (states considered worse than death) however given the mean estimate is far from zero this was considered reasonable. This was parameterised using the method of moments approach that uses the mean and SE to calculate alpha and beta for the distribution.

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1.2.3.5 Resource use and costs: intervention-related, delivery costs

In the model an intervention cost difference of £445.11 per person per year with HDF compared to high flux HD was applied based on the estimated increase in bloodline costs (£2.82 per session) and water consumption (£0.04 per session). No difference in cost was applied in the base-case analysis related to changes in machine purchasing.

Detail about how this cost was estimated and a full discussion about consideration of the possible differences in intervention costs between HDF and high flux HD is included in the sections below.

Note that estimating the cost difference between HDF and high flux HD is complex for a number of reasons including the availability of different machines requiring different consumables, the evolution of machines performing HDF over time, limited information about usage and how things might change in the future and the lack of public list prices. Given this, the use of higher and lower differences in intervention costs with HDF compared to high flux HD in the model was explored in sensitivity analyses.

Uncertainty around these costs were not incorporated into the probabilistic analysis but were explored in sensitivity analyses.

1.2.3.5.1 Approach to estimating difference in intervention costs

Many dialysis machines currently available to buy in the UK can perform both HDF and high flux HD, however machines are also available that can do high flux HD but not HDF – see Table 6 for details. Older models are also currently in use in the NHS (for example: Gambro AK200/AK96, Fresenius 4008, Nikkiso DBB05, Surdial 55). Some of these can be used to do HDF and some cannot. Machines are replaced periodically; a 7 to 10 year replacement cycle was considered typical by the committee.

Table 6: Dialysis machines (models currently available to purchase in UK)

HDF-capable machines	Non-HDF-capable machines
B Braun Dialog+	Baxter/Gambro AK98
B Braun Dialog IQ	Nikkiso DBB-06
Baxter/Gambro Artis 230v Physio	Nipro Surdial X Type A/B
Fresenius 5008 series	
Nipro Surdial X Type C	
Nikkiso DBB-07	
Nikkiso DBB-EXA	

Note: These are models currently available to purchase in the UK (as indicated by the manufacturers, or if they did not reply to correspondence based on their website information); other older models are also still currently in use in the NHS for example Gambro AK200/AK96, Fresenius 4008, Nikkiso DBB05, Surdial 55. A committee member noted that a newer Fresenius 6008 was being used in a few centres but no information was provided regarding this from the manufacturer and no NHS costs relating to this were identified and so this is not considered here.

For the model, costs were considered based on the dialysis machine models listed in Table 6 above that are currently available to purchase. Some older models will be in use in the NHS however these will be phased out over time. It was felt that the cost difference based on current models was more representative to use to estimate lifetime costs; older models may have greater cost differences between HDF and high flux HD as they may not have been built to undertake HDF originally and so require modification or additional consumables.

In our approach to costing the potential difference in intervention costs between HDF and high flux HD we considered the following in the sections that follow:

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1. Will cost difference occur when using HDF-capable machines to deliver HDF or high flux HD?
2. Will additional cost differences occur due to differences in machine purchasing?:
   a. Due to more purchasing of non-HDF-capable machines in a scenario where HDF isn't recommended
   b. Due to faster replacement of non-HDF-capable machines in a scenario where HDF is recommended

1.2.3.5.2 1. Will cost difference occur when using HDF-capable machines to deliver HDF or high flux HD?

In the model, an intervention cost difference of £445.11 per year with HDF compared to high flux HD was applied based on the estimated increase in bloodline costs (£2.82 per session) and water consumption (£0.04 per session) in HDF-capable machines.

This section includes a full discussion regarding which costs will vary when delivering HDF and high flux HD in HDF-capable machines. It also details the basis for estimating the cost difference, where they are considered to vary. Note that this discussion relates to models currently available to purchase as detailed in Table 6 in the previous section.

Information about how consumables vary with HDF and high flux HD was sought from published cost analyses[13, 28], manufacturers (by email and online), renal technologists, the committee and other experts in the field.

Machines

HDF-capable machines can undertake HDF and high flux HD and there is no difference in machine costs.

Dialysers

A high flux dialyser is required for both HDF and high flux HD and the same dialysers can be used for both therefore the cost of the dialyser is not included in the costing.

Bloodlines

For most HDF-capable machines there is a difference in the lines required for HDF compared with high flux HD. Some machines require different bloodline sets to be purchased, others require a bloodline set and a separate reinfusion line to be purchased.

Information about differences in bloodlines was sought from manufacturers and supplemented by information from renal technologists and the guideline committee. NHS unit costs were taken from the NHS supply chain catalogue (accessed February 2017).[27] Double needle costs were used over single needle, as this was considered to be most commonly used. Where more than one relevant cost was available (for example if a consumable was available with different features or from different suppliers) an average was used. Where a cost was not available for the specified consumable or labelling in the supply chain catalogue was unclear, an assumption regarding which cost to use was agreed with clinical input. The costs used in the model are summarised in Table 7 with details about consumables and any assumptions given in the footnotes. An unweighted average cost difference was calculated.

Based on this, an additional cost of £2.82 for bloodlines with HDF compared to high flux HD in HDF-capable machines was used in the base-case analysis. The range for the estimated difference was £0.00 to £5.75.

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Table 7: Model inputs: Bloodline costs for HDF and high flux HD

HDF-capable machines	Modality	Bloodline set	Separate HDF reinfusion line	Total cost	Difference with HDF
Baxter/Gambro Artis 230v Physio[a]	High flux HD	£3.96	£0.00	£3.96	
	HDF	£6.80	£0.00	£6.80	£2.85
B. Braun Dialog+[b]	High flux HD	£2.82	£0.00	£2.82	
	HDF	£4.02	£0.00	£4.02	£1.20
Fresenius 5008 series[c]	High flux HD	£6.60	£0.00	£6.60	
	HDF	£6.60	£0.00	£6.60	£0.00
Nikkiso DBB07[d]	High flux HD	£2.60	£0.00	£2.60	
	HDF	£2.60	£5.75	£8.35	£5.75
Nikkiso DBB-EXA[d]	High flux HD	£2.60	£0.00	£2.60	
	HDF	£2.60	£5.75	£8.35	£5.75
Nipro Surdial X Type C[e]	High flux HD	£3.34	£0.00	£3.34	
	HDF	£4.70	£0.00	£4.70	£1.36
Unweighted average high flux HD				**£3.65**	
Unweighted average HDF				**£6.47**	**£2.82**

(a) The manufacturer specified different bloodlines (High flux HD: HD DNL HC bloodlines. HDF: Artiset pre-post line) plus a separate HDF infusion line (Ultra HD line). The separate infusion line was not listed in the NHS Supply Chain Catalogue; a Kimal 'Online HDF Set for Gambro' cost was therefore used for the overall HDF cost (the HDF bloodline alone was £5.07).

(b) The manufacturer did not specify bloodlines. A renal technician specified a Kimal AV837/838PS for HD and Kimal AV837/838/HDF/1 for HDF which includes the infusion line. An average of three blood lines described as for B. Braun dialog (and not specified as for HDF) in the NHS supply chain catalogue has been used for high flux HD (this includes the Kimal line and two other manufacturers). The NHS supply chain listed the Kimal HDF bloodline set including reinfusion line and so this cost has been used for HDF.

(c) The manufacturer specified that the same bloodline set would be used whether doing high flux HD or HDF. The average of any bloodlines for Fresenius 5008 in NHS supply chain catalogue excluding those specified as single needle has been used.

(d) Manufacturer specified that the difference with HDF was the need for an additional reinfusion line (DBB07, C07J-P; DBBEXA, C18 AFA-P); the bloodlines were not specified although did not vary between HDF and high flux HD, a renal technologist specified Kimal AV855/856 for DBB07 and AV18AFA-P for DBB-EXA. No bloodline in NHS supply chain catalogue is labelled specifically for these machines or with these codes - one labelled as for Nikkiso and not specified as for a different machine has been used (will not impact difference between HDF and HD as only difference is reinfusion line). Substitution line codes provided by manufacturer were not in the NHS supply chain catalogue – the only item that appears to be the infusion line only (labelled 'Re-infusion lines for Nikkiso dialysis machine') has been used for both machines. One other HDF set for Nikkiso (machine not specified) was also in the catalogue - this had a cost of £9.84 and is assumed to include both the bloodline and reinfusion line.

(e) Manufacturer specified different bloodlines for HD (A372R/V858R bloodline for HD DIF, A365R/V851R bloodline for HD DIF single needle lines) and HDF (A364R/V850R bloodline for HDF). Specific bloodline codes provided by manufacturer for HD and HDF bloodlines were not in supply chain catalogue; lines labelled 'Bloodline set for Nipro Surdial X AV set HD' and 'Bloodline set for Nipro Surdial X HDF' used.

Substitution fluid

HDF requires the use of substitution fluid and high flux HD does not. However, HDF-capable machines currently available to purchase can provide online HDF that does not require substitution fluid bags and so no difference in cost related to this is included in the costing.

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Saline

Published studies included a cost for saline bags with high flux HD that was not required with HDF.[13, 28] However, HDF-capable machines currently available to purchase have the option to utilise the online function to produce solution suitable for priming etc even in HD mode and therefore a difference in cost of saline bags is not included in the costing for the model.

Endotoxin filters

In HDF-capable machines currently available to purchase two filters are generally permanently fitted (see Table 8) and this would not differ when used for HDF or high flux HD so no difference in cost related to this is included in the costing.

Table 8: Endotoxin filters in HDF-capable machines

HDF-capable machines	Endotoxin filters	Source
Baxter/Gambro Artis 230v Physio	2	Manufacturer email
B. Braun Dialog+	2	Renal technologist
Fresenius 5008 series	2	Online search
Nikkiso DBB07	2	Manufacturer info / renal technologist
Nikkiso DBB-EXA	2	Renal technologist
Nipro Surdial X Type C	?	Information not identified

Water testing

No difference in water testing costs with HDF versus high flux HD was applied in the model on the basis that the requirements do not vary between the two.

Lebourg 2013 (France) estimated a higher cost for water testing with HDF compared to high flux HD in their cost analysis.[13] Oates 2012 (UK) noted that once high quality water is established no difference in water testing costs in their cost analysis.[28] However, the committee agreed that current UK guidelines state that while a minimum standard is required for water for dialysis there is no requirement for a difference in testing between HDF and high flux HD.[9] These guidelines also state that the production of ultrapure dialysis fluid or for online infusion fluid used in HDF is generally achieved by the use of additional filters which form part of the dialysis machine hydraulic pathway and there is no additional requirement to test for bacterial growth or endotoxins when operated according to the manufacturers instruction, unless the manufacturer requires such tests to be performed.[9] They noted that if water in a renal unit does not meet these recommended standards there would be costs of setting up and testing of the water plant however this is not a cost that would vary between high flux HD and HDF and so was not incorporated into the costing.

Water consumption

Lebourg 2013 (France) estimated higher water consumption with HDF compared to high flux HD, although they note that it is difficult to estimate precisely and was based on calculated theoretical water consumption.[13] Oates 2012 (UK) did not comment on this.[28]

The committee agreed that water consumption was likely to be higher with HDF and estimated that this would typically be around 15 litres (0.015m^3) difference. Using a cost of £2.35 per m^3 based on the weighted average (by volume used) water and sewerage cost of NHS Trusts in England 2016/17 (latest data at time of analysis) this would be an additional cost of £5.50 per patient per year (£0.04 per session).[10]

The committee recognised that there is a range of convection volumes used in HDF and that the amount of extra water that would need to be generated for HDF compared to HD

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depends on the equipment used to deliver the treatment. In some systems the reduced dialysate flow rate required for optimal filter performance for HDF vs HD would equate to the water required to generate the replacement fluid and no additional water would be required. The committee thought that current high flux haemodialysis would deliver approximately 9L of convective treatment, and therefore 15L was selected as the additional fluid required to deliver replacement fluid for convective treatments where target convection volumes are higher than this.

Acid and bicarbonate concentrates

No difference in cost due to a difference in acid or bicarbonate concentrates was applied in the model.

Lebourg 2013 (France) estimated higher acid concentrate usage with HDF compared to high flux HD; 4.7 to 5.5 litres with HDF compared to 3.5 to 4.3 litres with high flux HD. Bicarbonate usage was higher; 720-950g with HDF compared to 650g to 750g with high flux HD. Oates 2012 (UK) included the same cost for bicarbonate solution (700g) for both HDF and high flux HD.[28]

The committee agreed that while there may be additional acid or bicarbonate concentrate use it was not clear if this would always result in an additional cost. For example, bicarbonate bags or cartridges are used and any unused product is thrown away at the end of treatment, therefore there would only be an additional cost if an additional or larger unit is required. Practices will also vary between machines and centres. Given this, an additional cost relating to acid or bicarbonate concentrates has not been incorporated into the analysis. However, note that the impact of variations in the cost difference between HDF and high flux HD were explored in sensitivity analysis.

1.2.3.5.3 2. Will cost differences occur due to differences in machine purchasing?

No difference in cost was applied in the base-case analysis related to changes in machine purchasing.

This section includes a full discussion considering whether costs may vary due to changes in machine purchasing patterns in a scenario where HDF is recommended compared to one where it is not and the rationale for excluding any costs related to this in the base-case analysis. There were considered to be two potential sources of additional cost differences related to machine purchasing:

a. More purchasing of non-HDF-capable machines in a scenario where HDF isn't recommended
b. Faster replacement of non-HDF-capable machines in a scenario where HDF is recommended

Note that this discussion relates to models currently available to purchase as detailed in Table 6 in the previous section.

a) More purchasing of non-HDF-capable machines in a scenario where HDF isn't recommended

If either machine costs or high flux HD consumable costs vary between HDF-capable and non-HDF capable machines it is relevant to consider whether an additional difference in costs to the NHS may arise due to differences in machine purchasing patterns in a scenario where HDF is recommended or where it is not. If non-HDF-capable machines are lower cost or have lower consumable costs than HDF capable machine, it would seem possible that more non-HDF-capable machines may be purchased overall in a scenario where HDF is not recommended than one where HDF is recommended and this could result in a difference in

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costs. Although it is important to note that many people may continue to purchase HDF-capable machines even in this scenario as this is not the only difference between them. Therefore we considered what the potential additional differences in machine and consumable costs due to this might be in. This is discussed below.

Machine costs

Published list prices are not available for dialysis machines and prices are subject to individual negotiations. However, the committee agreed that costs for machines that can do HDF may be higher than those that cannot. It is noted that this will not be the only difference between machines however, and machines that can do HDF may be higher specification with additional features unrelated to HDF. As such, even if people do not wish to do HDF they may still purchase an HDF capable machine.

Assuming a difference between non-HDF capable and HDF-capable machines of £3000 for illustrative purposes, the difference in machine costs per high flux HD session in a non-HDF-capable machine compared to an HDF-capable machine is estimated on the following basis:

- Difference in cost per 10 years: difference between midpoints of cost ranges for HDF-capable and non-HDF-capable machines: -£3,000
- Difference in cost per year = -£300
- Difference in cost per session (divide by 2.5 sessions per day [2 or 3 depending on centre] x 6 days per week x 52 weeks per year) = -£0.38

High flux HD consumable costs in HDF-capable and non-HDF capable machines

The cost of high flux HD bloodlines with non-HDF-capable machines compared to HDF-capable machines was also estimated. Relevant costs were sought from the NHS supply chain catalogue. An unweighted average cost was the calculated and compared to the average high flux HD bloodline costs in HD-capable machines. This suggested that costs may be lower as the average cost was £0.64 lower in non-HD-capable machines (see Table 9) although there was uncertainty in the unit costs used.

Table 9: Cost of bloodlines for high flux HD in non-HDF-capable machines

Non-HDF-capable machines	Bloodline	Difference with HDF-capable machine HD
Baxter/Gambro AK98[(a)]	£3.03	
B. Braun Dialog a1 - single pump[(b)]	£2.82	
Nikkiso DBB-06[(c)]	£2.85	
Nipro Surdial X Type B (single pump)[(b)]	£3.34	
Average high flux HD	£3.01	**-£0.64**

(a) The manufacturer specified the Novaline (BL245) bloodline. This was not listed in the NHS supply chain and other bloodlines were not labelled as specifically for AK98. A Kimal 'Gambro bloodline' cost was therefore used.
(b) It is assumed that the high flux HD bloodline is the same as for the HDF-capable configuration of this machine
(c) It is assumed that the high flux HD bloodline is the same as for the HDF-capable Nikkiso machine's no bloodline was listed labelled as specifically for the DBB-06.

Bagged saline would generally be required in non-HDF capable machines whereas it may not be in HDF-capable machines (as described above) as the online function can be used to produce suitable fluid. Although some models may also offer this function (for example the manufacturer noted that Nipro Surdial X non-HDF configurations still have this function). This was likely to be 1 or 2 bags. The cost of bagged saline was estimated as £0.74 based on the cost for 0.9% sodium chloride 1000ml reported in the NICE IV fluids guideline of £0.70 inflated to current costs.[4, 21] However, conversely only one endotoxin filter will generally be required rather than two resulting in a cost saving. Based on costs from the NHS Supply

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Chain Catalogue this was estimated to be in the region of £0.75 per session (assuming filters are changed every 100 sessions).[27]

Other consumables were considered unlikely to vary between the HDF-capable and HD-capable machines performing high flux HD.

Summary

Non-HDF-capable machines are judged likely to be lower cost. Some high flux HD consumables costs were also considered to potentially be lower (filters, bloodlines) but some were considered potentially likely to be higher (bagged saline) in non-HDF capable machines. This may vary by machine.

Estimating the cost difference precisely was considered difficult due to uncertainties in the unit costs, the differences between non-HDF-capable and HDF-capable machines, and most importantly whether purchasing would differ and if so by how much. An illustrative cost estimate is provided in Table 10assuming costs and resource differences apply. Given an example average cost difference of £3000 between non-HDF capable and HDF capable machines, and differences in blood lines, filters and saline requirements the cost additional difference per HDF session would be -£1.03. However, this assumes that all machines used to do HD are non-HDF capable. However, if you assume that some people would still use HDF-capable machines for HD then this this cost will reduce – for example if 30% of people use non-HDF capable machines for HD it will reduce to -£0.31.

Given that the machines vary in other ways the committee did not consider it likely that machine purchasing would vary between a scenario where HD and HDF were recommend. Given this and the relatively small cost per session it was agreed that an additional cost difference due to potential differences in machine purchasing patterns in a scenario where HDF was recommended compared to one where it was not would not be incorporated into the base-case analysis. However, sensitivity analysis was undertaken where this cost was incorporated.

Table 10: Illustrative calculation of potential difference in high flux HD costs in non-HDF-capable machine compared to HDF capable machine

Resource use	Cost difference
Saving in machine costs every 10 years[(a)]	-£3,000
Saving per year	-£300
Machine cost saving per session[(b)]	-£0.38
1 additional saline bag (1l)[(c)]	£0.74
1 less endotoxin filter[(d)]	-£0.75
Saving in blood line[(e)]	-£0.64
Total cost difference for high flux HD in non-HDF-capable machine compared with HDF-capable machine	**-£1.03**
Example difference in non-HDF-capable machine purchasing[(f)]	30%
Overall per person per session cost of difference in machine purchasing	**-£0.31**

(a) The committee agreed costs were likely to be lower; no list prices are available however so an estimate has been used.
(b) 2.5 sessions per day (2 or 3 depending on centre) x 6 days per week x 52 weeks per year = 780 session per machine per year.
(c) Cost for 0.9% sodium chloride 1000ml reported in the NICE IV fluids guideline of £0.70 inflated to 2015/16 costs (latest year available in inflation indices).[4, 21]
(d) Based on average of filters listed in the NHS Supply Chain Catalogue (Diacap ultra df-online filter by B. Braun and Diasafe plus filter from Fresenius) and an assumption that filters are changed every 100 sessions.[27]
(e) Estimated based on the cost of high flux HD bloodlines in non-HDF-capable machines compared to in HDF-capable machines using unit costs from the NHS supply chain catalogue. See Table 9 for full details.
(f) An assumption for illustration of potential difference in costs per person per session in this scenario.

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b) Faster replacement of non-HDF-capable machines in a scenario where HDF is recommended

In addition, another potential source of cost difference could be that in a scenario where HDF is recommended, current machines that do not do HDF may be replaced sooner than usual in order to offer people HDF (this would be a one off initial cost). However, as it appears that most centres already have a mixture of HDF-capable and non-HDF capable machines it is considered unlikely to happen as many patients already stable on HD will choose to remain on this treatment and so initial demand for HDF can be accommodated by existing machines and provision can be expanded as demand increases within the usual replacement cycles.

An email survey of renal technologists found that amongst those that replied (9 centres, 972 machines) 68% of machines were HDF capable (ranging from 30% to 100%) and these machines were used for HDF 86% of the time (ranging from 14% to 100%). Assuming the HDF and non-HDF capable machines are used equally frequently by patients that would mean 59% of the time HDF is used currently. This is only a limited selection of renal units and so it is unknown if this is representative for the whole country. Some committee members thought that the number would be lower overall.

1.2.3.6 Resource use and costs: intervention-related, drug usage

An annual cost saving with HDF of £98.93 due to a reduction in erythropoietin-stimulating agent (ESA) use is applied in the model while people were on HDF.

This is based on a reduction in ESA dose of 332 U/week (SE 2.32) with HDF, calculated from an estimated mean reduction of 4.25 U/kg/week from meta analysed RCT dose data and an average weight for adults in England of 78.1kg (SE 0.26).[20] The dose difference was incorporated into the probabilistic analysis using a normal distribution parameterised by the summary estimate of mean difference from the meta-analysis and standard error calculated from the confidence interval. The average weight was incorporated into the probabilistic analysis using a normal distribution parameterised by the reported mean and standard error.

The unit cost of ESA used in the model is £5.73 per 1000 units based on the average cost of epoetin alfa. Costs are from the British National Formulary.[11] BNF (02/08/2017). The ESAs currently available in England are epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa and methoxy polyethylene glycol-epoetin beta. However, the committee considered epoetin alfa the most widely used in in-centre HD where there is less use of long acting agents as patients are seen so frequently. The public list price is used in the base-case analysis as per NICE methodological guidance[24] however the committee highlighted that substantial discounts are often given on drug prices in practice. The cost of ESA remained fixed in the probabilistic analysis as it is based on the national list price.

Uncertainty relating to cost savings from a reduction in ESA use was explored in sensitivity analyses (see Section 1.3.2).

No other cost differences due to changes in drug usage were applied in the model. The basis for this and the ESA dose reduction estimate are described in detail below.

Investigation into difference in drug usage from clinical trials

The committee noted that in one of the published within-trial economic analyses of HDF a difference in medication costs was seen that offset increased intervention costs with HDF.[14] Therefore data regarding drug use was sought from the 6 RCTs included in the clinical review that compared HDF with high flux HD. Three studies included data on drug use

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(Maduell 2013[18], OK 2013[29] and Schiffl 2007[31]); one made a narrative statement only (Ward 2000[33]); and two did not discuss drug use (Locatelli 1996[17] and Park 2013[30]).

Three RCTs included data on ESA dose[18, 29, 31], two included data on iv iron dose[18, 29] and one included data on antihypertensive drug use[18]. One RCT stated that phosphate binder use was examined and did not differ between treatment groups but the numerical data was not reported.[18] Evidence was not identified for a difference in any other drugs. The data is discussed in the sections that follow.

The committee noted that anticoagulation requirements may be higher with HDF however none of the studies reported this. A difference in anticoagulation costs was not incorporated in the model due to this and that it was judged unlikely to result in a difference in costs as dose increases would not require an additional vial. This is supported by the analysis of HDF costs reported by Oates 2012[28] where the cost of anticoagulation is reported to be the same for HDF and high flux HD.

ESA dose data

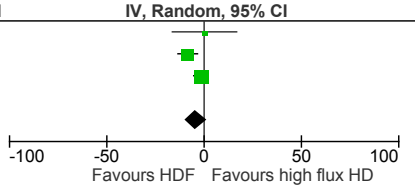
ESA dose data was available from three studies and so was meta-analysed; this is presented in Figure 7 below. Further details about the data and analysis follow this. In summary, the average dose over the whole study was considered the best estimate of dose as it used all available data. Where this was not reported it was calculated. As the fixed effects analysis had substantial heterogeneity a random effects analysis was considered more appropriate.

The committee agreed that a reduction in ESA dose should be incorporated into the model. It was noted that the effect size is quite small, however small differences could be quite important in the analysis as the cost difference between HDF and HD are also quite small.

Figure 7: HDF vs high flux HD - ESA dose (U/kg/week; average across study)

	HDF			High flux HD				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Maduell 2013	114.6	127.2	456	114.4	126.4	449	9.6%	0.20 [-16.32, 16.72]	
Ok 2013	33.6	31.2	391	42	39.9	391	41.5%	-8.40 [-13.42, -3.38]	
Schiffl 2007	66.4	11.56	76	68	11.9	76	48.9%	-1.60 [-5.33, 2.13]	
Total (95% CI)			**923**			**916**	**100.0%**	**-4.25 [-9.81, 1.31]**	

Heterogeneity: Tau² = 12.80; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 1.50 (P = 0.13)



Source: Maduell 2013[18]: Doses for those receiving ESA reported separately for epoetin, darbepoetin and methoxy polyethylene glycol-epoetin beta at 6 month time points up to 36 months. Data here was combined with darbepoetin and methoxy polyethylene glycol-epoetin beta dose converted using a conversion factor of 200. An average across all time points (weighted by numbers receiving ESA at each time point) and all patients (incorporating a zero ESA dose for those not receiving ESA).

OK 2013[29]: ESA time averaged dose over study for all patients including those who did not receive ESA (at baseline 57% were using an ESA); mean follow-up 22.8 months, max 39 months. Of those receiving ESA 92.2% received epoetin and the rest darbepoetin, and darbopoeitin alfa dose was converted to epoetin dose by multiplying by 200. Data reported here as U/kg/week calculated by dividing U/week reported by study by average body weight in study.

Schiffl 2007[31]: Doses for those receiving ESA reported at 12 and 24 month time points for each intervention on both arms (cross over study design). Data here is an average across all time points. All patients received erythropoietin alpha or beta.

The mean drug dose and standard deviation reported for each arm of the study was obtained. Different studies reported dose data differently. Where necessary data was combined or converted to estimate the mean epoetin units/kg/week across the whole population; that is combining dose data from different types of ESA and including those who did not receive ESA:

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- Schiffl 2007 reported the average ESA dose in units/kg/week and all patients received an ESA (epoeitin).
- OK 2013 reported the average ESA dose for all patients including those who did not receive ESA (at baseline 57% were using an ESA). Of those receiving ESA 92.2% received epoetin and the rest darbepoetin; darbopoeitin alfa dose was converted in the study to epoetin dose by multiplying by 200. Data was reported as U/week and so was converted to U/kg per week by dividing by the average body weight in the study.
- Maduell 2013 reported mean dose per kg/week for epoeitin, darbepoetin and methoxy polyethylene glycol-epoetin beta separately and the proportion receiving each drug. All data were converted to epoetin and a weighted average ESA dose was calculated incorporating all dose data and those not receiving ESA. Darbepoetin dose was converted using a darbepoetin:epoetin ratio of 1:200. This is the adult conversion ratio currently stated in the UK summary of product characteristics for calculating initial dose and was used in the OK trial when combining ESA doses. Methoxy polyethylene glycol-epoetin beta dose was also converted using a ratio of 1:200 based on local analysis by a committee member in the absence of a widely recognised conversion ratio. It is acknowledged that the exact conversion rates are the subject of debate however it was considered preferable to make the conversions and include all the data available over using just the epoetin data. It is considered unlikely that the conversion rate used would make a big difference to the results.

The studies also varied in terms of how the dose was reported over the study period:

- OK 2013 reported a time average over the study (mean follow-up 22.8 months; maximum 39 months).
- Maduell 2013 reported data at 6 month time points up to 36 months.
- Schiffl 2007, which was a crossover study, reported data at 6 months and 12 months for each intervention in each study group; it also reported dose at end of therapy for each intervention.

Where average dose across the study was not reported it was calculated as a weighted mean based on the dose and number of people at each time point; the standard deviation of this mean was also calculated from the data. Data at different time points will be correlated and this correlation should be accounted for when combining this type of data otherwise the results will appear to be more precise that they actually are. As information was not available about this correlation it was assumed to be 0.9. This is considered a conservative assumption as the higher the correlation the greater the imprecision.

IV iron dose data

IV iron dose data was available from two studies and so was meta-analysed; this is presented in Figure 8 below. The average dose over the whole study was considered the best estimate of dose as it used all available data. Where this was not reported it was calculated as described for ESAs. As the fixed effects analysis had substantial heterogeneity a random effects analysis was considered more appropriate.

The committee agreed that the evidence did not support a difference in iv iron dose and so did not need to be incorporated into the analysis.

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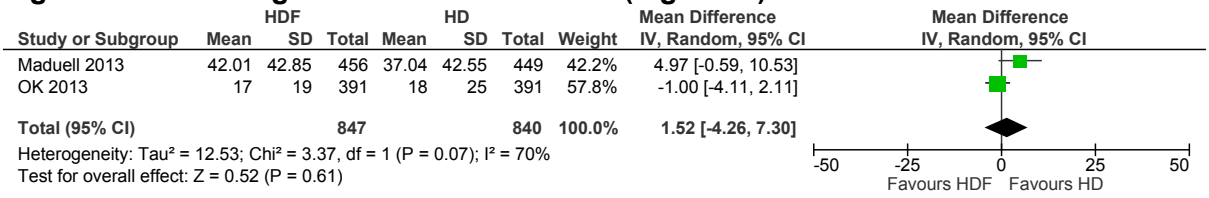
Figure 8: HDF vs high flux HD – iv iron dose (mg/week)



Source: Maduell 2013[18]: Doses reported at 6 month time points up to 36 months. An average across all time points was calculated (weighted by numbers at each time point).

OK 2013[29]: time averaged dose over study; mean follow-up 22.8 months, max 39 months.

Antihypertensive drug use data

Number of people receiving antihypertensive drugs was reported in Maduell 2013 but the committee concluded it did not suggest this varied between HDF and HD (average use in each arm across the study was the same) and so was not incorporated into the model.

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1.2.3.7 Resource use and costs: general dialysis-related

Intervention costs are relevant in the model for two reasons. Firstly we need to capture the difference in intervention costs with HDF and high flux HD. In addition, in line with standard NICE methodological guidance, we also need to capture in the model costs related to the condition of interest incurred in additional years of life (because the model includes a mortality difference between HDF and high flux HD).

In the previous section we have described the differences in costs that occur with HDF compared to high flux HD. In addition, whilst patients are alive on HD or HDF they also incur general dialysis related-costs. These do not vary between HDF and HD in terms of unit costs, but as the number of people alive each cycle varies this cost will also vary overall between comparators.

In the model a general dialysis-related cost of £32,259 per year is applied whilst people are alive on HD or HDF. This is calculated based on a cost of dialysis of £23,362, a cost of transport for dialysis of £4058 and a cost for other dialysis-related resource use of £4,839. The bases for these costs are described below.

Dialysis costs

A cost of in-centre dialysis per year of £23,362 was applied in the model based on an average cost per session of £149.76 and assuming 3 sessions per week for 52 weeks.

This cost per session is based on a weighted average cost of all in-centre categories in England from the NHS reference costs 2016-17 as shown in Table 11.[6]

The NHS Reference costs are the average unit cost to the NHS and are based on data submitted by all Trusts in England. Providers cost reference costs on a full absorption basis, which means that all the running costs of providing these services are included within the submission including overheads. This includes the full range of staffing inputs, equipment and building costs and the cost of all ESAs and drugs for bone mineral disorders. Transport costs are not included. Costs such as access procedures, out-patient appointments and management of complications are not included. These other costs are considered below.

The committee highlighted that there are some concerns regarding the accuracy of NHS reference cost data for renal dialysis however this was the best available data identified at this time and so was used in the model.

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Table 11: NHS reference costs for HD

Currency code	Renal dialysis[a]	Currency description	No. of sessions	Unit cost per session			*Cost per year[b]*
				National average	Lower quartile	Upper quartile	
LD01A	At base	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	412,415	£150	£123	£165	*£23,371*
LD02A	At base	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	701,601	£161	£136	£172	*£25,123*
LD03A	At base	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	16,202	£177	£143	£218	*£27,543*
LD04A	At base	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	28,125	£184	£136	£236	*£28,667*
LD01A	Away from base	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	404	£148	£118	£190	*£23,095*
LD02A	Away from base	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	356	£232	£146	£251	*£36,236*
LD05A	At base	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	539,870	£137	£124	£157	*£21,375*
LD06A	At base	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	1,155,230	£148	£127	£165	*£23,030*
LD07A	At base	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	28,020	£148	£124	£171	*£23,037*
LD08A	At base	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	49,872	£150	£125	£161	*£23,457*
LD05A	Away from base	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	142	£168	£177	£187	*£26,206*
LD06A	Away from base	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	692	£153	£133	£163	*£23,817*
LD08A	Away from base	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	2	£160	£160	£160	*£24,955*
Weighted average[c]				**£149.76**			***£23,362***

Source: NHS Reference costs 2016/17[6]

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(a) NHS reference costs submission data separately identifies the costs and activity associated with providing haemodialysis to patients aged 19 years and over while they are away from their normal base. The aim is to help ensure that national prices differentiate appropriately between the costs of dialysis away from base and at the patient's normal base. Costs are provided on the same basis as for regular dialysis at the base unit.
(b) Calculated assuming 3 sessions per week for 52 weeks
(c) Weighted average weighted by number of sessions

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Dialysis transport costs

An average transport cost per person of £4058 per year was used in the model.

Transport costs are not included in the NHS reference costs for dialysis (or in the NHS reference costs as a separate item) but they are an important source of costs to the NHS as people receiving dialysis in-centre will need to come three times a week indefinitely. Data on average transport costs for dialysis patients was sought via committee members from their Trusts. In addition, estimates identified from published UK studies were considered and ad hoc internet searching was undertaken to look for other relevant data.

Data on transport costs for dialysis patients were only available from one London trust. From this an average cost of a journey was estimated to be £21.70 in 2016/17. This was only for those using patient transport. Some people may use their own method of transportation but have the cost reimbursed.

An alternative estimate of £45 per journey was also suggested by a committee member. This was based on work undertaken by a dialysis transport working group a member of the committee was part of that involved the Renal Association and Kidney Care UK and included representation from two individuals with experience of commissioning or providing patient transport services. This estimate is a consensus informed by data from some members of the group. The data related to all patient transport (of which dialysis was estimated to be around 50%).

An average of these two costs (£33.35) has been used to estimate average transport costs for the guideline. It is noted this is based on limited data and so is somewhat uncertain.

An Audit from 2010 about dialysis patient transport reported that 78% of people do not pay for transport; that is they either use patient transport services or their transport costs are reimbursed.[26] In order to estimate an average cost per year we assumed that the cost of patient transport for those that have transport costs reimbursed is the same as the average cost using patient transport services and that people have dialysis 3 times a week. This results in an average cost per person per year of £4058 for in-centre dialysis. See also Table 12.

Table 12: Estimated transport costs for in-centre dialysis

Item	Data	Source
Average cost of journey	£33.35	Average of:[(a)] • £21.70: average cost per renal patient transport journey from a London Trust 2016/17 • £45: estimated average cost of a patient transport journey from a dialysis transport working group
% not paying for transport	78%	2010 audit on patient transport[26]
Sessions per year	156	Assumption based on 3 session per week
Average cost per person on in-centre dialysis	**£4058**	*Using lower estimate only = £2640* *Using higher estimate only = £5476*

(a) In the absence of other data, it is assumed that the cost of a journey where the patient pays and is reimbursed is same as a patient transport journey

Some other estimates were identified and these were generally similar to the calculated value used. Kerr 2012 used a value of £2792 per HD patient in their analysis of the cost of CKD in England.[12] This was based on average transport cost (not specifically renal) and an estimate that NHS-funded transport was provided for 61% of patient journeys in England for hospital and satellite HD (data could not be accessed). Baboolal 2008 reported an estimated

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transport cost of £2438 and £1905 per year for hospital and satellite HD respectively as part of their dialysis cost analysis.[1] A report from Health Watch Coventry report that the average annual cost per patient nationally is £6000 but the source was not clear and it was unclear if this is cost in those that have transport paid only or averaged across all patients (as for the other estimates reported here).[3]

Other costs

Costs such as access procedures, out-patient appointments and management of complications are not included in the NHS reference cost for dialysis above. This will mean that the costs in additional years of life accrued may be an underestimate, if this is not accounted for.

In the model base-case analysis it was assumed that 15% of the total costs were due to costs other than dialysis itself and transport. In a study about the costs of dialysis for older people in the UK 30% of costs were found to be allocated to resource use other than dialysis and transport.[8] However, it was considered that these costs are likely to be higher in an older population (for example, it was thought to be likely they would require more in-patient admissions and other health care contact) and so the committee agreed a lower estimate should be used. This assumption was explored in sensitivity analyses.

1.2.4 Sensitivity analyses

1.2.4.1 Baseline mortality with HD (SA1-4)

In the base-case analysis the mortality rate for people while on HD is modelled using data from an incident cohort. In sensitivity analyses, baseline mortality with HD was varied from a 50% decrease to a 200% increase to explore whether this impacted conclusions.

This was undertaken to take account of the fact that particular subgroups of the overall cohort will have different mortality rates (older vs younger, with and without diabetes). Based on the clinical evidence review undertaken, the committee concluded there was not good evidence of a difference in relative treatment effect for different population strata. However, even if relative effects are constant, absolute differences will vary if baseline risk varies and this could impact cost effectiveness.

1.2.4.2 Relative treatment effect on mortality with HDF (SA5-8)

In the base-case analysis a hazard ratio of 0.82 (95% CI 0.63 to 1.06) was used to model the relative treatment effect of HDF compared to HD on mortality. This was based on a meta-analysis of hazard ratios from RCTs that compared HDF with HD where hazard ratios were calculated from relative risks if not reported by a study to maximise the data incorporated. In addition data from studies comparing HDF to low or high flux HD was used. The full rationale for this is explained in Section 1.2.3.3. Alternative bases for the estimate of the hazard ratio were explored in sensitivity analysis:

- SA5 Only studies that reported hazard ratios (i.e. studies that only reported relative risk were excluded): 0.82 (0.61 to 1.11)
- SA6 High flux data only hazard ratio (including studies where the hazard ratio is calculated from the relative risk): 0.76 (0.62 to 0.94)

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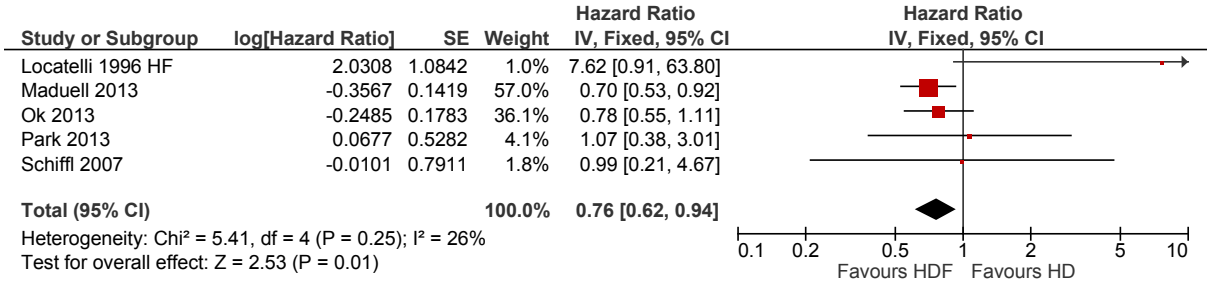
Figure 9: Sensitivity analysis inputs: relative treatment effect on mortality with HDF compared to HD meta analysis of reported and estimated[(a)] hazard ratios (high flux HD studies only)



Hazard ratio data available from study: Maduell 2013[18]. Hazard ratio calculated from relative risk: Locatelli 1996[17] (high flux HD data only); Ok 2013[29]; Park 2013[30]; Schifl 2007[31].
*(a) HR = ln(-RR*CER+1) ÷ ln(1-CER), where CER = control event rate (number of people with event in control groups ÷ total number of people in control groups)*

Based on the clinical evidence review undertaken, the committee concluded there was not good evidence of a difference in relative treatment effect for different population strata. However, the limited evidence available for the diabetes population strata showed a greater effect size, although with more imprecision. Given this, a sensitivity analysis using this effect size was also undertaken:

- SA7 Diabetes population study data: 0.75 (0.46 to 1.22)

The only other evidence available for a population stratum was for people over 70 years of age. The relative treatment effect point estimate in this population was virtually the same

In the base-case analysis it is assumed that the treatment effect applies whilst people remain on HDF over the lifetime analysis. This assumption is explored in sensitivity analysis where in SA8 the duration of treatment effect is limited to 3 years (based on the average follow-up in the RCTs comparing HDF and HD). In this analysis, after 3 years intervention costs continue to be applied but the mortality benefit is no longer applied. This analysis aimed to explore whether conclusions were sensitive to the assumption that the treatment effect from clinical trials can be applied over the lifetime analysis.

1.2.4.3 Intervention costs (SA9-13, SA32-33)

In the base-case analysis an additional cost of £2.86 per session was applied to reflect the additional consumable costs due to differences in lines (£2.82) and water (£0.04) required with HDF compared to high flux HD. In addition a reduction of ESA dose was applied to those on HDF. However, there was uncertainty in this estimate due to a lack of unit cost data for some consumables, variation between dialysis machines and potential additional costs with HDF (for example due to differences in machine purchasing patterns as discussed in the costs section above). Therefore sensitivity analysis was undertaken with higher and lower cost differences based on the estimated range of bloodline costs, potential differences due to changes in machine purchasing patterns and inclusion or removal of cost difference due to water consumption and ESA use. These were (costs shown are per session; see Section 1.2.3.5. for details of how costs used are derived):

- SA9 Lower intervention costs: minimum difference in bloodline costs (£0) and no water consumption difference (£0); ESA savings remain.
- SA10 Lower intervention costs: minimum difference in bloodline costs (£0); water consumption difference remains (£0.04); ESA savings remain.
- SA11 Higher intervention costs: maximum bloodline cost difference (£5.75) plus 30% difference in machine purchasing (£0.31); ESA savings remain.

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- SA12 Higher intervention costs: maximum bloodline cost difference (£5.75) plus 100% difference in machine purchasing (£1.03); ESA savings remain.
- SA13 Higher intervention costs: maximum bloodline cost difference (£5.75) plus 100% difference in machine purchasing (£1.03) ; no ESA savings

In addition threshold analyses (SA32-33) were also undertaken to explore the difference in intervention costs required for a change in conclusion regarding cost effectiveness (based on an ICER of £20,000) in both analyses 1 (NICE reference case) and 2 (intervention cost differences only).

1.2.4.4 Drug use (SA14-18)

ESA dose

It was noted that the ESA doses in two of the three studies used for this input were low compared to current UK practice. The mean difference in dose was used in the base case analysis. It was noted that potentially a bigger difference would be seen with higher doses and so a sensitivity analysis was undertaken where the percentage difference in dose was calculated and the mean difference in dose estimated using this and the mean ESA dose in England from the Renal Registry data.

The percentage difference in mean dose with HDF compared to HD was calculated for each study and a weighted average was calculated using the weighting from the mean difference meta-analysis. This results in an estimated reduction of 9% with HDF.

In the model an average ESA dose of 6600 U/week was used for the high flux group. This was based on the UK Renal Registry 19th report that reported the average use of ESA on HD of 88% and the median dose for those receiving ESA of 7500 u/week in England (mean dose was not reported).[2]

This resulted in an alternative estimate of the reduction in ESA dose of 579 units/week.

Using a unit cost of £5.73 per 1000 units epoetin alfa this is an annual saving of £172.70.

Cost of ESA

The list price for epoetin alfa was used in the base-case analysis as per NICE methodological guidance. The committee noted that substantial discounts are often available in practice and so a series of sensitivity analysis were undertaken where these costs were reduced by 25%, 50% and 75%.

The list prices for some ESAs are higher than for epoetin alfa, however given that in practice substantial discounts are common, it was not considered necessary or useful to undertake sensitivity analysis with these higher list prices.

A reduction in ESA use

A reduction in ESA use with HDF was incorporated in the base case analysis. A sensitivity analysis was undertaken where this benefit was removed.

1.2.4.5 General dialysis-related costs (SA19-24)

The cost of general dialysis-related costs that are applied in the model while people are alive on HD or HDF was based on the NHS reference cost for dialysis, an estimate of transport costs and an assumption that this reflected 85% of the total costs and there is additional 15% of other costs (reflecting things such as access procedures, infection management and outpatient reviews). In sensitivity analysis the assumption was varied to explore the impact

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on results. Additional costs were varied from 0% to 30% in 5% increments; cost of general dialysis-related costs varied between £27,420 and £39,171 as a result.

It is noted that transport costs are also somewhat uncertain due to a lack of data to inform them. Two estimates were averaged in the base case analysis. Using the lower of these would result in an annual transport cost of £2,640 and using the higher would result in an annual transport cost of £5,476. This would result in the cost of general dialysis-related costs being £30,591 and £33,927 respectively, keeping everything else the same as in the base case analysis. Given these are within the range tested in the sensitivity analysis above a separate analysis was not run with these figures.

1.2.4.6 Quality of life (SA25-29)

Quality of life in the alive state

A more recent systematic review and meta-analysis of utility data was also identified. This reported a higher utility estimate of 0.69 (95% CI 0.59 to 0.80). This was however based on a meta-analysis that included all measures of utility (not just EQ-5D) and also mapped SF36 and SF12 data.[35] The Liem et al data was therefore considered more in line with the NICE reference case and so was used in preference to this in the base-case analysis. Using data from this study was explored in sensitivity analysis.

In addition a sensitivity analysis was undertaken where quality of life was set to 1 as this represents the maximum QALY gain from the additional years of life.

A quality of life difference between HDF and high flux HD

A quality of life difference was not incorporated into the base-case analysis as the committee concluded that the clinical evidence was not supportive of a difference. However, the committee highlighted that anecdotally patients report improved quality of life and so this was considered a plausible scenario that should be explored in sensitivity analysis.

A sensitivity analysis was undertaken using the data identified in the clinical review where one study reported a mean difference of 0.01 (95% CI: -0.03 to 0.05). The committee agreed that greater increases may be plausible and so additional sensitivity analyses were undertaken applying a greater increase – values of 0.05 and 0.1 were selected. This difference in quality of life between groups was incorporated into the probabilistic analysis using a normal distribution. This was parameterised using the mean difference and standard error calculated from the reported confidence interval.

1.2.4.7 Discount rate (SA30)

In-line with NICE methodological guidance a sensitivity analyses was undertaken where the discount rate was set to 1.5% for costs and outcomes instead of 3.5% to explore whether results are sensitive to the discount rate used.[22]

1.2.5 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation.

The cohort entered the model at cycle 0 in the alive on HD or HDF health state. Each cycle people could transition to either the transplant or dead state (both absorbing states). The transplant probability was time dependent (but not treatment dependent) conditional on the number of years after entry to the model, which is the time since initiation of dialysis. The mortality probability was time in the same way. The mortality probability was also treatment dependent; the mortality probability on HD was converted to an instantaneous hazard and

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the hazard ratio with HDF applied; this was then converted back to a probability. In order for transplant numbers to be kept constant in the model, and so the mortality data is applied appropriately, the transplant probability was applied first each cycle in the HD model. In the HDF model the number of people who transition to the transplant state was based on the number transitioning in the HD model each cycle. Subsequently (in both the HD and HDF model) the mortality probability was applied to those alive who have not had a transplant each cycle.

Life years for the cohort were computed each cycle based on the number of people in the alive on HD/HDF state each cycle. To calculate QALYs for each cycle life years were weighted by a utility value (this was not time or treatment dependent). A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle were calculated on the same basis as QALYs. Costs per cycle were calculated in terms of: general dialysis related costs (non-treatment dependent annual unit cost applied in the alive on HD/HDF state) and intervention-related cost differences with HDF compared to HD (only applied in the HDF model). Intervention-related cost differences were the sum of consumable cost differences (blood lines and water consumption) and ESA use differences. Total costs were the sum of the general dialysis-related costs and, in the HDF model, the intervention-related cost differences. Costs were also discounted to reflect time preference (discount rate 3.5%).

Discount formula for costs and QALYs:

$$Discounted\ total = \frac{\text{total}}{(1+r)^{n-1}}$$	Where: *r* = discount rate per annum *n* = time (year)

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

In this analysis, as well as calculating the ICER using total costs, it was calculated using only the intervention-related costs difference calculated in the HDF model.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost effective if: • Highest net benefit

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Both methods of determining cost effectiveness will identify exactly the same optimal strategy. Results are not presented in this format in this report but for ease of computation NMB is used in the probabilistic analysis to identify the optimal strategy at a particular threshold when calculating the percentage of times HDF is cost effective.

The probabilistic analysis was run for 5000 simulations. Each simulation, discounted costs and discounted QALYs were calculated for HDF and high flux HD. Net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 and £30,000 per QALY gained. The results of the probabilistic analysis were summarised in terms of the difference in mean costs and mean QALYs, where each was the average of the 5000 simulated estimates. An ICER was calculated from this and the percentage of simulations where HDF was the most cost-effective option was reported. Results from all the simulations are also presented graphically where incremental costs and incremental QALYs for HDF compared to high flux HD are shown using a scatter plot.

1.2.6 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[23] sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

1.2.6.1 Additional considerations for this analysis

RRT sustains life when the kidneys can no longer function sufficiently. Based on current NHS reference costs, at a minimum, in-centre dialysis costs around £25000 per patient per year for adults (higher for children), not including costs such as access creation and management, complications and other health care contacts. Once the kidneys cannot sustain life, no treatment would result in death and therefore zero costs and QALYs. Hence at this point dialysis cannot have a cost effectiveness ratio within the range typically considered cost effective by NICE – the ICER cannot be less than the intervention costs in this circumstance, even if life extension is at full health (which will not be the case). For example, even just taking intervention costs alone of £25000 (in reality there will be additional costs of care) and assuming life extension with a quality of life weight of 0.7 this would result in an ICER of around £36,000. While in modern practice, the 'no dialysis' option is conservative management and dialysis may be started earlier and so immediate death may not be inevitable, this may mean that the difference in costs during this period are reduced, however the magnitude of health benefit during this period will also be reduced as whilst the patient is alive the QALY difference with dialysis will only be driven by the difference in quality of life alone and so will be much reduced. It is therefore highly unlikely that dialysis would be considered cost effective by usual NICE criteria. However, dialysis has been the standard of care for people with kidney failure for many years despite the clear high costs for the NHS and so it is considered that this can be interpreted as evidence that society consider dialysis worthwhile despite this high cost. In the guideline we therefore started from the assumption that the current standard of care is considered acceptable in knowledge of this issue.

This also however results in an issue where new treatments in a dialysis population extend life. Because dialysis treatment is so costly, treatments that are effective in sustaining life may not be cost effective even if similar or less costly to deliver due to the additional costs of

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dialysis in the additional years of life. Whilst the opportunity cost to the NHS of these additional costs during the additional years of life are real, whether it is appropriate not to recommend such treatments is less straightforward given that the costs are arising from the continuation of a treatment that is accepted.

In this analysis we therefore present, alongside the base-case analysis using the standard NICE reference case for health care interventions, results where costs incurred in additional years of life not specifically due to differences between the cost of HDF and HD are excluded.

1.2.7 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations.

1.3 Results

1.3.1 Base case

Base-case analysis results are presented in Table 13 and graphically in Figure 10 and Figure 11. As described in the methods (see Section 1.2.6.1), results are presented where costs included are as per the NICE reference case (that is including costs related to the condition of interest and incurred in additional years of life gained as a result of treatment as well as intervention-related cost differences) and also where only intervention-related cost difference are included (that is costs incurred during additional years of life are excluded) due to the high cost of dialysis.

HDF was associated with higher costs and higher QALYs in both base-case analyses. In analysis 1, using standard NICE reference case methods, the incremental cost-effectiveness ratio was £61,903 per QALY gained. This would not generally be considered cost-effective using standard NICE decision making criteria and there was little uncertainty in this conclusion in the probabilistic analysis. In analysis 2, where only intervention cost differences are included (that is, general dialysis-related costs incurred whilst people are alive in the model are excluded), the incremental cost-effectiveness ratio was £4,348 per QALY gained. This would be considered cost-effective using standard NICE decision making criteria and there was little uncertainty in this conclusion in the probabilistic analysis. Note that uncertainty in costs was explored in sensitivity analyses – these are presented in the next section.

Table 13: Results: base-case analysis (probabilistic analysis)

	Mean lifetime cost per person		Difference (HDF – HD)	*95% LCI*	*95% UCI*
	HD	HDF			
Analysis 1: NICE reference case[a]					
Costs that vary with HDF vs HD	£0	£1,814	£1,814	£1,422	£2,277
Change in dialysis consumables	£0	£2,332	£2,332	£1,830	£2,934
Change in ESA use	£0	-£518	-£518	-£651	-£405

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General dialysis-related costs[b]	£140,525	£168,995	£28,471	-£7,856	£71,394
Total cost	£140,525	£170,809	£30,284	-£6,458	£73,666
Total cost (discounted)	£124,299	£146,435	£22,136	-£4,807	£51,533
Life years	4.36	5.24	0.88	-0.24	2.21
QALYs	2.44	2.94	0.49	-0.14	1.25
QALYs (discounted)	2.16	2.52	0.36	-0.10	0.87
ICER (HDF versus HD)			£61,903	per QALY gained	
% simulations HDF cost-effective (£20K/QALY)			5%		
% simulations HDF cost-effective (£30K/QALY)			4%		
Analysis 2: Intervention cost differences only[c]					
Intervention cost differences only (discounted)	£0	£1,555	£1,555	£1,269	£1,872
ICER (HDF versus HD)			£4,348	per QALY gained	
% simulations HDF cost-effective (£20K/QALY)			87%		
% simulations HDF cost-effective (£30K/QALY)			90%		

Abbreviations: ESA = erythropoietin-stimulating agent; HD = haemodialysis; HDF = haemodiafiltration; ICER = incremental cost-effectiveness ratio; 95% LCI = 95% confidence interval lower bound; UCI = 95% confidence interval lower bound; QALY = quality-adjusted life year

(a) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use) and costs related to the condition of interest and incurred in additional years of life gained as a result of treatment.

(b) These costs vary with HDF and HD because life years vary.

(c) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use). Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment are excluded.

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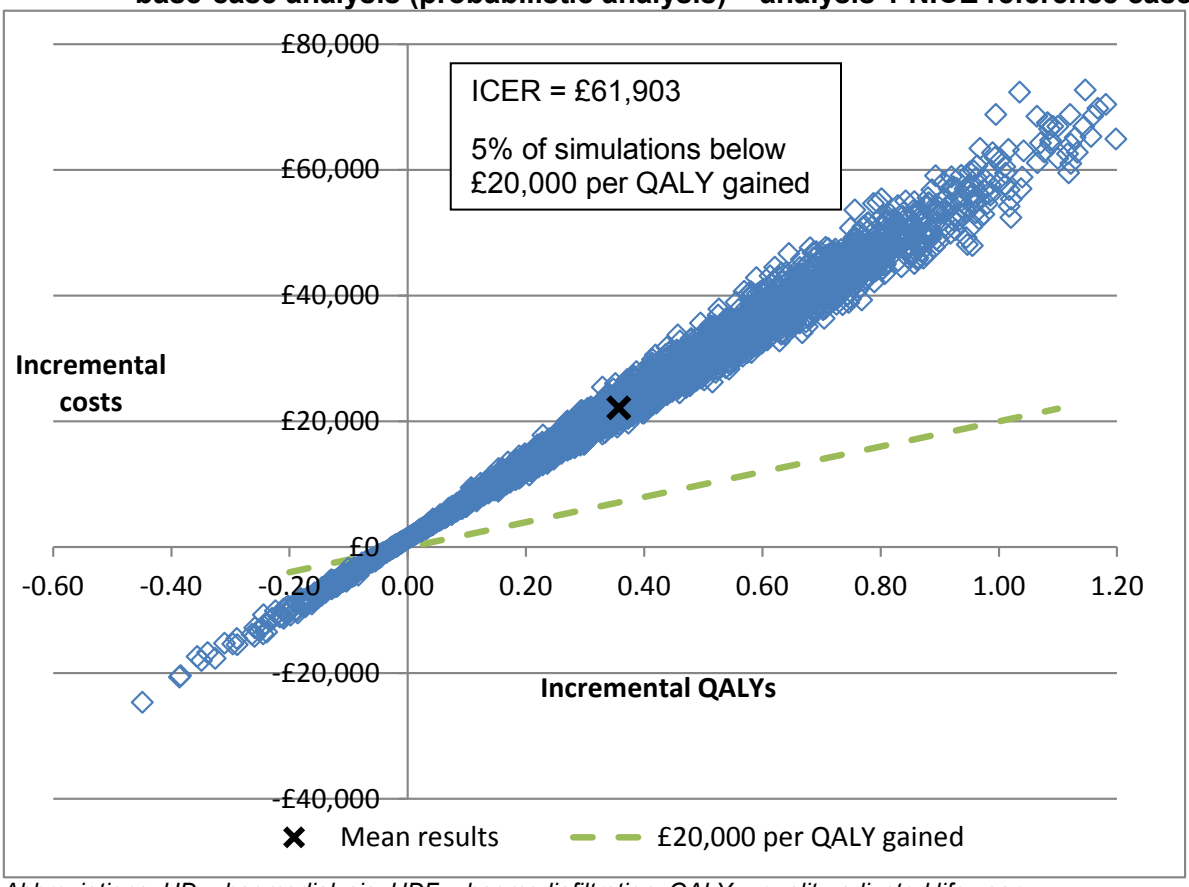
Figure 10: Results: incremental (HDF – HD) cost and QALY pairs scatter plot for base-case analysis (probabilistic analysis) – analysis 1 NICE reference case



Abbreviations: HD = haemodialysis; HDF = haemodiafiltration; QALY = quality-adjusted life year

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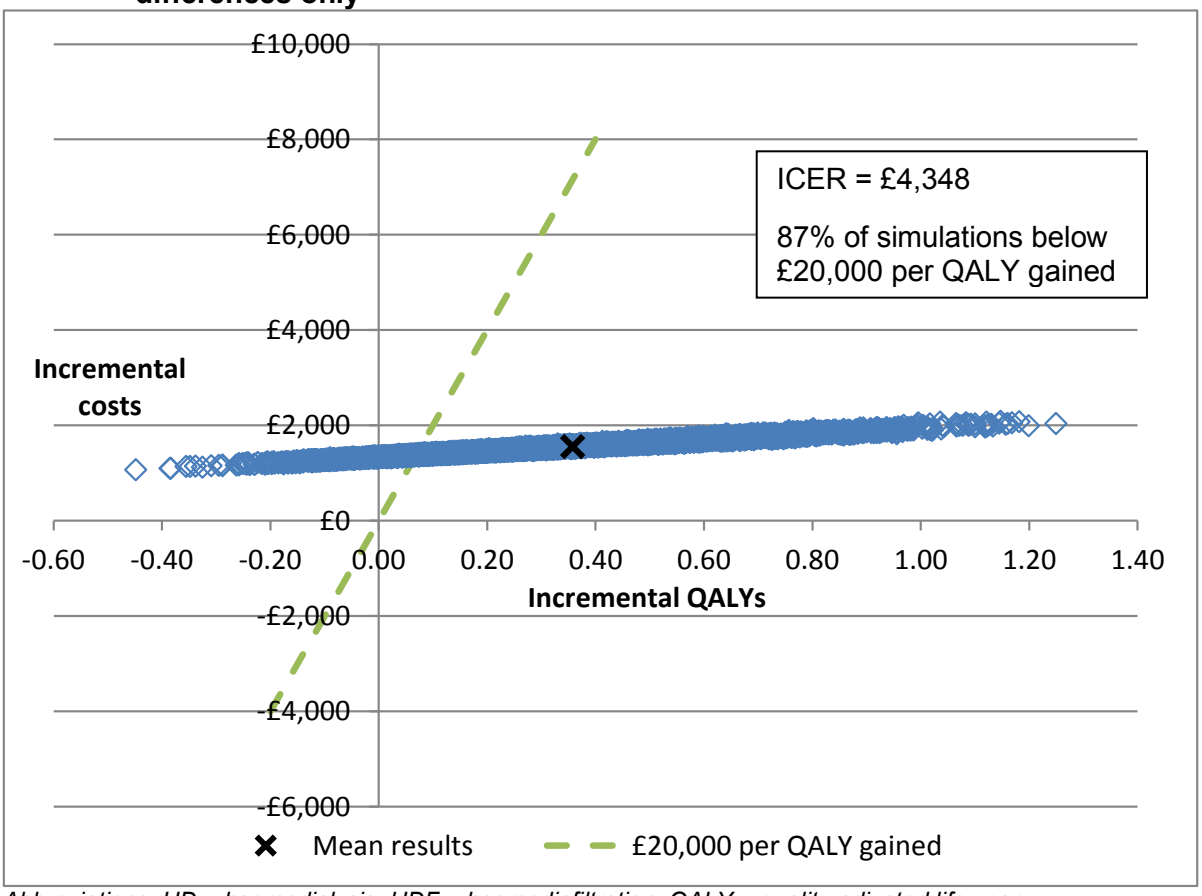
Figure 11: Results: incremental (HDF – HD) cost and QALY pairs scatter plot for base-case analysis (probabilistic analysis) – analysis 2 intervention cost differences only



Abbreviations: HD = haemodialysis; HDF = haemodiafiltration; QALY = quality-adjusted life year

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1.3.2 Sensitivity analyses

The results of the sensitivity analyses undertaken (described in full in Section 1.2.4 above) are presented in Table 14 and Table 15. Overall conclusions were not changed by sensitivity analyses.

There were a number of uncertainties in the estimation of differences in costs with HDF compared to HD (see methods section) however the sensitivity analyses exploring the implications of potentially lower and higher costs did not find that conclusions were changed. This included sensitivity analyses to account for the variation in differences in bloodlines between dialysis machines and the incorporation of potential cost differences due to differences in machine costs. In the base-case analysis an additional cost of £2.82 per session (£440 per year) was applied with HDF relating to bloodlines. This was based on the unweighted average of the estimated cost differences for bloodlines in current models of HDF-capable machines. An additional cost of £0.04 per session (£5.50 per year) was also applied relating to additional water consumption. A saving of £98 per year was also applied relating to reduction in ESA use with HDF. In sensitivity analyses 9 to 14 different assumptions regarding these costs were tested. This included using the maximum estimated cost difference for bloodlines rather than the average, adding in a cost relating to potential changes in machine purchasing patterns between an HDF and HD scenario and removing the ESA cost saving. HDF remained cost effective in the intervention cost only analysis even when high estimates were used for both bloodline cost differences (£5.75 per session) and machine purchasing differences (£1.03 per session – estimated assuming in the HD scenario 100% of machines are non-HDF capable and in the HDF scenario 100% of machines are HDF-capable), and all ESA savings were removed (SA14); the ICER was £13,251 per QALY gained).

A threshold analysis found that a saving of around £18 per session (-£2,829 per year) with HDF compared to HD was required to reduce the ICER to £20,000 per QALY gained in analysis 1 (NICE reference case where disease-related costs incurred in additional years of life are included) and so for HDF to be considered cost effective. An additional intervention-related cost of around £11 per session (£1,726 per year) with HDF compared to HD would result in the ICER increasing to £20,000 per QALY gained in analysis 2 (intervention cost differences only).

Table 14: Results: sensitivity analyses (probabilistic analysis)

Analysis	Analysis 1: NICE reference case[a]					Analysis 2: Intervention cost differences only[b]			
	Mean difference (HDF - HD)		ICER (Cost per QALY gained)	% CE 20K	% CE 30K	Mean diff (HDF - HD)	ICER (Cost per QALY gained)	% CE 20K	% CE 30K
	Cost	QALY				Cost			
Base-case analysis results	£22,136	0.36	£61,903	5%	4%	£1,555	£4,348	87%	90%
Mortality risk with HD									
SA1 Mortality risk -50%	£29,946	0.48	£62,761	4%	4%	£2,437	£5,108	87%	89%

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SA2 Mortality risk +50%	£17,337	0.28	£61,596	5%	5%	£1,135	£4,032	88%	90%
SA3 Mortality risk +100%	£14,138	0.23	£61,414	5%	4%	£878	£3,814	89%	90%
SA4 Mortality risk +200%	£9,551	0.16	£61,193	5%	4%	£563	£3,606	89%	91%
Relative treatment effect with HDF									
SA5 Alternative treatment effect data (MA HRs only)	£21,761	0.35	£62,151	8%	8%	£1,551	£4,430	84%	86%
SA6 Alternative treatment effect data (MA HRs and RRs converted to HR - high flux only)	£30,680	0.50	£60,821	0%	0%	£1,645	£3,262	99%	99%
SA7 Alternative treatment effect data (HR in diabetes population)	£33,924	0.56	£60,523	11%	10%	£1,680	£2,997	84%	86%
SA8 Mortality treatment effect duration reduced to 3 years	£11,145	0.17	£66,137	4%	3%	£1,438	£8,534	83%	87%
Intervention cost (consumables difference per session with HDF)									
SA9 Lower intervention costs (minimum bloodline cost difference and no water consumption difference)	£19,980	0.35	£56,309	8%	8%	-£443	HDF dominant	94%	94%
SA10 Lower intervention costs (minimum bloodline cost difference)	£20,020	0.36	£56,391	8%	8%	-£419	HDF dominant	94%	94%
SA11 Higher intervention costs (maximum bloodline cost difference)	£24,446	0.36	£67,662	3%	2%	£3,616	£10,009	78%	84%
SA12 Higher intervention costs (maximum bloodline cost difference plus 30% difference in machine purchasing)	£24,400	0.36	£68,362	3%	2%	£3,827	£10,721	75%	83%
SA13 Higher intervention costs (maximum bloodline cost difference plus 100% difference in machine purchasing)	£24,801	0.35	£69,931	3%	2%	£4,329	£12,207	72%	81%
SA14 Higher intervention costs (maximum bloodline cost difference plus 100% difference in machine purchasing; no ESA savings)	£25,554	0.36	£70,807	2%	2%	£4,782	£13,251	69%	80%
ESA costs									
SA15 ESA dose % change	£21,793	0.36	£60,881	5%	5%	£1,204	£3,363	89%	91%
SA16 ESA cost discount (25%)	£22,582	0.36	£62,167	5%	4%	£1,670	£4,596	88%	90%
SA17 ESA cost discount (50%)	£22,388	0.36	£62,520	4%	4%	£1,777	£4,963	87%	89%
SA18 ESA cost discount (75%)	£22,556	0.36	£62,953	5%	4%	£1,889	£5,272	86%	89%
SA19 ESA dose - no change	£22,665	0.36	£63,084	4%	3%	£2,000	£5,567	87%	89%
General dialysis-related costs									
SA20 General dialysis related costs - other costs 0%	£19,006	0.36	£53,211	4%	3%	£1,554	£4,352	88%	90%

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SA21 General dialysis related costs - other costs 5%	£19,827	0.36	£55,822	5%	4%	£1,553	£4,373	88%	90%
SA22 General dialysis related costs - other costs 10%	£21,421	0.36	£58,731	4%	4%	£1,560	£4,277	88%	90%
SA23 General dialysis related costs - other costs 20%	£23,398	0.36	£65,568	5%	5%	£1,555	£4,356	88%	89%
SA24 General dialysis related costs - other costs 25%	£24,667	0.35	£69,691	5%	4%	£1,552	£4,386	88%	90%
SA25 General dialysis related costs - other costs 30%	£26,245	0.35	£74,318	5%	5%	£1,552	£4,396	88%	91%
Quality of life									
SA26 Baseline quality of life with HD - alternative data	£22,301	0.44	£50,259	5%	4%	£1,557	£3,508	90%	91%
SA27 Baseline quality of life with HD - set to 1	£22,530	0.65	£34,659	4%	0%	£1,559	£2,398	91%	92%
SA28 Adding in a quality of life benefit with HDF - from clinical review, 0.01	£22,031	0.40	£55,046	7%	8%	£1,554	£3,882	90%	91%
SA29 Adding in a quality of life benefit with HDF - 0.05	£21,947	0.58	£37,918	13%	24%	£1,553	£2,683	98%	98%
SA30 Adding in a quality of life benefit with HDF - 0.1	£22,439	0.81	£27,620	24%	64%	£1,558	£1,918	100%	100%
Discount rate									
SA31 Discount rate 1.5% for costs and outcomes	£26,255	0.43	£61,417	5%	5%	£1,690	£3,954	88%	90%

Abbreviations: ESA = erythropoietin-stimulating agent; HD = haemodialysis; HDF = haemodiafiltration; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MA = meta-analysis; QALY = quality-adjusted life year; SA = sensitivity analysis; % CE £20K/£30K = % of simulations where HDF is cost effective at a £20,000/£30,000 threshold. Grey numbers indicate values that are not impacted by sensitivity analysis – minor differences with the base-case analysis values are due to random variation in the probabilistic analysis when the analysis is re-run.

(a) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use) and costs related to the condition of interest and incurred in additional years of life gained as a result of treatment.

(b) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use). Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment are excluded.

Table 15: Results: threshold analyses, cost difference with HDF that results in ICER of £20,000 per QALY gained

Threshold analyses	Threshold cost difference with HDF[a]	
	Per session	Per year
SA32 Intervention cost difference threshold for analysis 1 (NICE reference case[b])	-£18	-£2,829
SA33 Intervention cost difference threshold for analysis 2 (intervention cost differences only[c])	£11	£4,726

Abbreviations: HDF = haemodiafiltration; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SA = sensitivity analysis.

(a) Base-case analysis uses an additional intervention cost with HDF of £2.85 per session (£445 per year).

(b) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use) and costs related to the condition of interest and incurred in additional years of life gained as a result of treatment.

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(c) Includes costs intervention-related cost differences (bloodlines, water consumption and ESA use). Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment are excluded.

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1.4 Discussion

1.4.1 Summary of results

The analysis found that HDF was associated with higher costs and higher QALYs than high flux HD. In analysis 1, using standard NICE reference case methods, the incremental cost-effectiveness ratio was £61,903 per QALY gained. This would not generally be considered cost-effective using standard NICE decision making criteria and there was little uncertainty in this conclusion in the probabilistic analysis. In analysis 2, where only intervention-related cost differences are included (that is, general dialysis-related costs incurred whilst people are alive in the model are excluded), the incremental cost-effectiveness ratio was £4,348 per QALY gained. This would be considered cost-effective using standard NICE decision making criteria and there was little uncertainty in this conclusion in the probabilistic analysis.

Overall conclusions were not changed by sensitivity analyses. This included exploration around baseline mortality rate, treatment effects, quality of life weights and intervention costs differences. There were a number of uncertainties in the estimation of differences in costs with HDF compared to HD however the sensitivity analyses exploring the implications of potentially lower and higher costs did not find that conclusions were changed. This included sensitivity analyses to account for the variation in differences in bloodlines between dialysis machines and the incorporation of potential cost differences due to differences in machine costs. In the base-case analysis a difference in intervention costs of £2.85 per session (£445 per year) was applied. A threshold analysis found that a saving of around £18 per session (-£2,829 per year) with HDF compared to HD was required to reduce the ICER to £20,000 per QALY gained in analysis 1 (NICE reference case where disease-related costs incurred in additional years of life are included) and so for HDF to be considered cost effective. An additional intervention-related cost of around £11 per session (£1,656 per year) with HDF compared to HD would result in the ICER increasing to £20,000 per QALY gained in analysis 2 (intervention cost differences only) and HDF no longer being considered cost effective.

1.4.2 Limitations and interpretation

Baseline mortality risk data

In the analysis mortality risk on HD is based on a novel analysis from the UK Renal Registry. In reality this data will include people on HDF as well as people on HD as they are not currently distinguished in the registry. This could result in mortality risks from the analysis being an underestimate, given that the clinical evidence suggested a mortality reduction with HDF. However, the analysis used a UK adult incident cohort starting RRT on HD between January 2005 and December 2014 with follow-up to the end of 2015 and HDF use will be lower in earlier years that will contribute more years of follow-up to the analysis. In addition HD mortality has generally fallen during this time period and so data from earlier years may overestimate mortality compared to more recent years and this could conversely result in mortality rates from the analysis being an overestimate. Overall these effects will balance each other out at least to some extent. Sensitivity analyses were also undertaken with higher and lower mortality rates and these did not change conclusions.

Treatment effects with HDF

The mortality treatment effect with HDF compared with HD was based on the systematic review and meta-analysis undertaken as part of guideline development (see Evidence report B: modalities of RRT).

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The RCTs included were mostly in the general adult population. The populations in the four largest studies were considered relatively representative on the general HD population. However, it was noted that overall the populations in the included studies appeared to be slightly younger (based on the average age). However, one RCT was identified in older people that had a very similar effect size to the other studies and so this was not considered likely to impact interpretation of the analysis.

The committee noted that the populations within the trials considered for HDF vs HD were predominantly previously stable on HD and not RRT naïve, and therefore the findings may not represent the best evidence on how to start new patients. However, the committee's consensus was that if anything, HDF would be expected to be more effective in naïve patients as they would not have been exposed to potential downsides of less "efficient" forms of dialysis.

The reporting of treatment effects also varied between studies. Many studies did not report a hazard ratio and only reported relative risk – for the model, estimated hazard ratios were calculated from the available data for studies that reported relative risk only. However, given that the treatment effect did not vary based on this this is not considered likely to impact conclusions. This is supported by sensitivity analyses where alternative hazard ratio estimates are used and conclusions are not changed.

It was assumed in the model that the treatment effect observed in the RCTs could be applied over a lifetime whilst on HDF but RCT follow-up was less than this with average follow-up typically 2-3 years. Whilst it is unknown how treatment effect might vary beyond the time observed in trials the committee agreed that assuming constant effect was not an implausible assumption. In addition, a sensitivity analysis was undertaken for a worst case scenario where the treatment effect was only applied for the first 3 years of treatment and costs differences were applied for a lifetime. This found that whilst the ICER increased, overall conclusions did not change from the base-case analysis. This therefore did not impact interpretation of results.

In the model the absolute number of transplants that occurs with HDF and HD is kept constant. This assumption was made rather than assuming that the probability of transplant was constant because if mortality is lower with HDF, even if a constant probability is applied, the number of transplants that occur will be higher as more people will be alive each cycle. This would result in an additional mortality benefit with HDF because people who have a transplant have a much lower mortality risk that those who are on HD. The committee agreed that whilst this effect was not necessarily implausible it was a reasonable assumption for the model. However, they noted that it may be a conservative one.

There was very little quality of life data reported in studies of HDF versus HD. The committee concluded that the evidence that was available did not support a difference between treatments however they also agreed that it was plausible from their experience that people may experience a benefit in terms of quality of life. More research on the impact of HDF on quality of life would therefore clarify this. Sensitivity analyses where a quality of life benefit was included for HDF compared to HD showed that QALYs increased and so the ICER for HDF reduced; however, overall conclusions were not changed.

The committee noted that an additional benefit of HDF over high flux HD that may not be captured by the model is the potential reduction in dialysis-related amyloidosis in people on long term dialysis (for example more than 10 years). Although most people will not be on dialysis this long where it occurs it can cause significant joint problems. It occurs due to accumulation of amyloid proteins in the body and may be improved by HDF as middle molecule clearance is greater.

The committee noted that the convection volume with HDF varied between studies and post-hoc analyses of some of the included studies [7, 18, 29] had reported greater mortality benefits

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for HDF compared to HD in segments of their populations that achieved higher convection volumes. This issue is discussed in more detail in Evidence report B. In brief the committee agree that people may be more likely to see a benefit of HDF over HD at higher convection volumes but that the evidence is not strong enough to support definitive thresholds at which the benefit does or does not exist. Intervention costs are unlikely to be substantially different between higher and convection volumes with the main difference being a higher water consumption which is low cost. If higher volume HDF results in a greater mortality benefit over HD, this would result in more QALY gains and more costs incurred in the additional years of life. This would mean that HDF is likely to be more cost effective in analysis 2, where only intervention-related cost differences are included (that is, general dialysis-related costs incurred whilst people are alive in the model are excluded).

Utility data

Quality of life (utility) weights for the alive (on HDF or HD) state in the model were based on a meta-analysis of direct EQ-5D data. This included studies published before September 2007 and so it is possible that more recent estimates may have been published since. A more recent meta-analysis was identified although this was not used in the base-case analysis as the data used in the earlier report was more in-line with the NICE reference case – the more recent report include EQ-5D estimates obtained from mapping from other measures. However, this was used in sensitivity analysis and while the QALY gain with HDF increased overall conclusions were not impacted and so this did not impact interpretation of the analysis.

HDF-related cost differences

There were a number of uncertainties around the costs differences with HDF compared to HD. There were sometimes difficulties matching the reported differences in consumables to appropriate NHS unit costs. Cost differences varied between machines and an unweighted average costs was used in the absence of information to inform a weighted average. The potential differences in cost associated with HDF-capable and non-capable machines were difficult to quantify due to a lack of cost data and difficulty in predicting how machine purchasing patterns might vary. However, sensitivity analyses explored the implications of potentially lower and higher costs. This included using the smallest and largest difference in machine costs rather than an average and also adding in estimates for potential differences in costs if machine purchasing patterned differed in a scenario where HD or HDF was recommended. These sensitivity analyses did not impact conclusions and so the committee agreed that despite these uncertainties in was reasonable to conclude that HDF was likely to be cost effective (when general dialysis costs are excluded).

It should be noted that this analysis has not been designed to assess the relative costs and benefits of different HDF-capable machines and it should not be used to imply that HDF is more cost-effective using machines where there is a smaller difference in consumable costs between HDF and HD. Machine costs are also likely to vary between HDF-capable machines. Decisions about which HDF-capable machine to purchase will be based on many different factors including machine and consumable costs and functions of the machine. It is assumed that the decision about which HDF-capable machine to buy is not impacted by the decision to recommend HDF or HD and so it not relevant to include in this analysis.

A difference in ESA dose was applied in the model based on the mean difference from RCTs comparing HDF and high flux HD included in the clinical evidence review. The committee noted that ESA doses in two of the three studies where data was available were lower than typical in the UK. The committee noted that you might expect the difference to be greater if doses were more in line with current practice and this would result in a greater ESA saving that would further offset additional intervention costs with HDF. However, conversely ESA list prices were used in the analysis and the committee noted that in reality these are heavily

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discounted which would reduce the saving due to ESA dose reduction. These issues were however explored in sensitivity analysis and did not impact conclusions.

Only one of the RCTs looked at phosphate binder use and it reported there was no difference; the same was the case for blood pressure medication. The committee perception was that these may also be reduced with HDF; however, given the lack of evidence for a difference from the RCTs the committee agreed it was appropriate not to include a difference in the model. If other drugs are also reduced this would result in additional cost savings with HDF that could further offset the additional intervention costs with HDF.

Other dialysis-related costs

The majority of other dialysis-related costs were due to the cost of dialysis itself which was based on the NHS reference costs. The committee acknowledged that there had been some concerns about these costs and work had been done with the aim of improving cost collection, however overall they accepted these as the best available estimate of current NHS costs. However, these exclude transport costs which is a substantial additional cost to the NHS related to dialysis. In the model transport costs were estimated however no national data was available for this and while we attempted to obtain data from a number of trusts in the end our estimate was based on information from a single Trust regarding 2016/17 cost per patient transport journey combined with a cost estimate from a working group, and data from 2010 regarding the proportion of patients who did not pay for transport. No information was available about the cost of transport paid for by the patient but reimbursed and so this was assumed to be the same as for a patient transport journey. In addition the additional costs related to dialysis (e.g. related to access procedures, outpatient appointments etc) were based on an assumption. However, while there was some uncertainty in these costs, sensitivity analysis using higher and lower costs did not change conclusions overall and so this uncertainty was considered unlikely to impact interpretation of the analysis.

The bigger issue regarding interpretation is whether or not it is appropriate to include these costs in the analysis at all. The NICE reference case requires costs related to the condition of interest and incurred in additional years of life gained as a result of treatment to be included.[24] However, as detailed in the methods section above, an issue arises where the costs in additional years of life are high as in this case. In this case even if HDF could be provided at zero additional cost over HD, it would not be cost effective due to the general dialysis related costs incurred in additional years of life conferred by HDF use. This is a complex issue for which there is no specific methodological guidance however it has been acknowledged as a methodological issue.[5, 32] The committee discussed interpretation of the analysis with regard to this issue and concluded that it was appropriate to consider the ICER where these costs are excluded when judging cost effectiveness on the basis that it did not make sense to deny an intervention due to costs incurred in additional years of life from a treatment that is widely accepted for use in the NHS, despite its high costs. This approach has been taken before, for example in NICE guideline CG157 Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia.[25]

1.4.3 Generalisability to other populations or settings

The clinical review looked for evidence for difference strata related to age and diabetes status. Where evidence was available it found that relative treatment effects did not vary greatly in different subgroups. Absolute event rates will however vary by baseline risk as well as by relative treatment effect, that is, even if relative treatment effect is the same, absolute benefits may be higher in a population at higher baseline risk and lower in a population with lower baseline risk and this may impact costs and QALY. In sensitivity analyses where baseline mortality risk was increased and decreased this did not change conclusions regarding cost effectiveness and so the committee considered it reasonable to conclude that conclusions were generalizable across different subpopulations.

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Around 80% of dialysis is in-centre and the clinical evidence identified related to in-centre dialysis only, hence the model used costs related to in-centre HD. The committee discussed whether conclusions from the clinical evidence and cost effectiveness model could be extrapolated to the home setting. The committee noted that it was possible that HD at home may be done more frequently. The benefits of more frequent HD are unknown but it is possible that if HD is done more than 3 times a week at home, HDF may provide less additional benefit compared with in-centre 3 times a week HD. Evidence regarding the frequency of dialysis was inconclusive and there was no evidence assessing the efficacy of HDF at home. In general costs differences between delivering HDF and HD at home were considered likely to be similar to in-centre although general dialysis costs are lower based on NHS reference cost data. On this basis HDF at home was considered likely to be cost effective when compared to home HD at the same frequency. The committee was aware that some centres do offer home HDF, although in some circumstance, for example where people opt for transportable dialysis machines (which cannot do HDF currently), these centres continue to provide home HD. The committee agreed that more research was required in this area.

The committee discussed whether conclusions could be extrapolated to children. The number of children on dialysis is much lower than adults with only around 100 people recorded as on HD in the UK Renal Registry latest report (this will include both HD and HDF).[2] None of the RCTs comparing HDF with HD were in children. The committee considered that in general costs differences between delivering HDF and HD in children were likely to be similar to in adults although general dialysis costs are higher based on NHS reference cost data. On this basis HDF was considered likely to be cost effective when considering intervention-related cost difference only and so the committee concluded it was reasonable to extrapolate this evidence to children when making recommendations.

1.4.4 Comparisons with published studies

The economic literature review results are detailed in full in Evidence report B: modalities of RRT. Three published economic evaluations were included that compared HDF with HD.

One published economic evaluation (Ramponi 2016) compared HDF with high flux HD using a decision model. The new analysis undertaken for the guideline takes a similar approach but uses UK data sources and current UK costs so it is more applicable to the current NHS context, uses the systematic clinical evidence review and meta-analyses undertaken for this guideline to inform clinical outcomes in the model and uses NICE reference case methods. Cost differences in terms of delivering HDF compared to HD were included in the analysis (general dialysis-related costs incurred in additional years of life were not included). It found that HDF was more expensive with higher QALYs and was cost effective. This is consistent with the results in this analysis when only intervention-related cost differences are included (that is, general dialysis-related costs incurred whilst people are alive in the model are excluded). No analysis including all costs was available for comparison. Incremental costs and QALYs were similar in Mazairac 2016 and this analysis, although QALY gain varied by age subgroup. Average total costs and QALYs per person were not reported and so cannot be compared.

The two other published economic evaluations (Mazairac 2013 and Levesque 2015) were identified comparing HDF although these both compared HDF with low-flux HD and were based on a single RCT (the CONTRAST study). They both used resource use data collected within this. The two analyses differed with one taking a Dutch perspective and using the overall CONTRAST population and the other using a Canadian perspective and the Canadian subset of the CONTRAST population that the authors described as “all receiving high efficiency HDF” (defined as online HDF performed with an optimal convection fluid volume). Mazairac 2013 found that HDF was not cost effective compared to low flux HD (ICERs: £140,588 to £394,058 per QALY gained depending on age subgroup). HDF was still

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not cost effective when costs in additional years of life were excluded. Levesque 2015 (using only a subset of the population) found that HDF was not cost effective compared to low flux HD (ICERs: £30,316 per QALY gained). HDF was however cost effective when a shorter time horizon was used and was cost saving when costs in additional years of life were excluded (although the methods used in this analysis are somewhat unclear).

Mazairac 2013 reported higher average total costs per person for HD than in the new analysis undertaken for the guideline despite using a shorter time horizon. However, this was for a 45-65 year old subgroup (total were not reported for the under 45 years and over 65 years subgroups) whereas the new analysis uses the whole incident population which will include a large proportion of older patients who will have lower life expectancy and so lower costs. In addition the annual costs for HD in this Dutch analysis are over double the annual costs used in the new analysis using current UK costs. The difference in total costs per person with HDF compared to HD was lower than in the new analysis, although the difference in annual costs with HDF was higher. This can be explained by the much smaller difference in mortality in this analysis which will result in a less costs being accrued in additional survival time. The committee noted that the cost difference between high flux HD and HDF would be smaller because the cost of filters and water treatment is more similar. Total QALYs in the HD group were similar to the new analysis, despite being only a 5 year time horizon, but again this was for the 45-64 year old group only and so you would expect this to be higher than in the overall population which will have a substantial proportion over 65 years. QALY gain was smaller in Mazairac 2013 than the new analysis; this would be expected given that the mortality benefit seen in the CONTRAST trial is much smaller than the overall mortality benefit estimated from the meta-analysis of all studies reported in the guideline. The ICER was much higher in Mazairac 2013 than this analysis which would be expected given the higher cost difference and lower QALY difference with HDF. In contrast to this analysis, HDF was still not cost effective when costs in additional years of life were excluded in Mazairac. This is because cost differences with HDF based on data collected within the study and Dutch unit costs are much higher and QALY gains much lower as explained above.

Levesque 2015 reported higher average lifetime costs per person in the HD arm than in the new analysis. This seems to be due to higher life expectancy in the population (average QALYs in the HD arm are higher) and higher annual dialysis costs (~£3000 per year more). The HD mortality rate in the analysis is generally lower than in the new analysis – this is most likely because it uses the trial population which will be a selected population rather than the overall incident population used in the new analysis. Incremental lifetime costs with HDF over HD are lower in Levesque 2015 than in this new analysis. This is because overall HDF has lower costs than HD in this analysis; although intervention costs are higher, these are offset by a reduction in medication costs. The committee discussed the relatively high cost difference in medication between the two arms in this study and could not see how this would happen in modern UK practice. Incremental QALYs are also higher in this analysis; a larger mortality reduction was seen in the subgroup used in the Levesque analysis than from the overall mortality benefit estimated from the meta-analysis of all studies reported in the guideline and a quality of life benefit was also included which was not in the new analysis.
Conclusion = evidence statement

This original cost–utility analysis found that HDF was not cost effective compared to high flux HD (ICER: £61,903 per QALY gained) using the NICE reference case and standard decision making criteria; however this was due to the high cost of dialysis in additional years of life. HDF was cost effective compared to HD when only intervention-related cost differences were considered (that is general dialysis-related costs were excluded) (ICER: £4,348. This analysis was assessed as directly applicable with minor limitations.

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References

1. Baboolal K, McEwan P, Sondhi S, Spiewanowski P, Wechowski J, Wilson K. The cost of renal dialysis in a UK setting - A multicentre study. Nephrology Dialysis Transplantation. 2008; 23(6):1982-1989

2. Byrne C, Caskey F, Castledine C, Dawnay A, Ford D, Fraser S et al. UK Renal Registry: 19th Annual Report of the Renal Association. Nephron. 2017; 137(Suppl 1):1-398

3. Coventry LINk. Renal patient transport: recommendations to improve patient transport for renal patients in Coventry. Coventry. Coventry LINk, 2011. Available from: http://www.healthwatchcoventry.co.uk/files/Coventry%20LINK%20renal%20patient%20transport%20report%20FINAL.pdf

4. Curtis L, Burns A. Unit costs of health and social care 2016. Canterbury. Personal Social Services Research Unit University of Kent, 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/

5. Davis S. Assessing technologies that are not cost-effective at a zero price: Report by the Decision Support Unit. Sheffield. 2014. Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/Not_CE_at_zero_price_FINAL_14.07.14.pdf

6. Department of Health. NHS reference costs 2016/2017. Available from: https://improvement.nhs.uk/resources/reference-costs/ Last accessed: 17/01/2018.

7. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. Journal of the American Society of Nephrology. 2012; 23(6):1087-96

8. Grun RP, Constantinovici N, Normand C, Lamping DL, North Thames Dialysis Study Group. Costs of dialysis for elderly people in the UK. Nephrology, Dialysis, Transplantation. 2003; 18(10):2122-7

9. Hoenich N, Mactier R, Morgan I, Boyle G, Croft D, Rylance P et al. Guideline on water treatment systems, dialysis water and dialysis fluid quality for haemodialysis and related therapies. The Association of Renal Technologists, 2016.

10. Hospital Estates and Facilities Statistics. Water services. 2016/17. Available from: http://hefs.hscic.gov.uk/ReportFilterConfirm.asp?FilterOpen=&Year=2016%2F2017+01&Level=T&Section=S+09&SHA=&Org_Type=&Foundation=&Site_Type=&PFI=&getReport=Get+Report Last accessed: 15/02/2018.

11. Joint Formulary Committee. British National Formulary (BNF) Online. 2017. Available from: https://bnf.nice.org.uk/ Last accessed: 02/08/2017.

12. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrology, Dialysis, Transplantation. 2012; 27 (Suppl 3):iii73-80

13. Lebourg L, Amato S, Toledano D, Petitclerc T, Creput C. [Online hemodiafiltration: is it really more expensive?]. Nephrologie & Therapeutique. 2013; 9(4):209-14

ISBN: 978-1-4731-3107-1

14. Levesque R, Marcelli D, Cardinal H, Caron ML, Grooteman MP, Bots ML et al. Cost-effectiveness analysis of high-efficiency hemodiafiltration versus low-flux hemodialysis based on the Canadian Arm of the CONTRAST Study. Applied Health Economics & Health Policy. 2015; 13(6):647-59

15. Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value in Health. 2008; 11(4):733-41

16. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. Journal of the American Society of Nephrology. 2010; 21(10):1798-807

17. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G et al. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. Kidney International. 1996; 50(4):1293-302

18. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. Journal of the American Society of Nephrology. 2013; 24(3):487-97

19. Mesaros-Devcic I, Tomljanovic I, Mikolasevic I, Dvornik S, Vujicic B, Pavletic-Persic M et al. Survival of patients treated with online hemodiafiltration compared to conventional hemodialysis. Collegium Antropologicum. 2013; 37(3):827-32

20. NatCen Social Reasearch UCL. Health survey for England 2015 trend tables: Adult tables. NHS Digital, 2016. Available from: http://digital.nhs.uk/catalogue/PUB22616

21. National Clinical Guideline Centre. Intravenous fluid therapy in adults in hospital. NICE clinical guideline 174. London. National Clinical Guideline Centre, 2013. Available from: http://guidance.nice.org.uk/CG174

22. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf

23. National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. London. National Institute for Health and Clinical Excellence, 2008. Available from: https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf

24. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal 2013. London. National Institute for Health and Clinical Excellence, 2013. Available from: http://publications.nice.org.uk/pmg9

25. National Institute for Health and Clinical Excellence. Hyperphosphataemia in chronic kidney disease: management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease. NICE clinical guideline 157. London. National Institute for Health and Clinical Excellence, 2013. Available from: http://guidance.nice.org.uk/CG157

26. National Kidney Care Audit. Patient transport survey national summary report: Reporting on the survey carried out in October 2010. Available from: https://digital.nhs.uk/catalogue/PUB02700

ISBN: 978-1-4731-3107-1

27. NHS Supply Chain Catalogue February 2017. NHS Supply Chain, 2017. Available from: http://www.supplychain.nhs.uk/

28. Oates T, Cross J, Davenport A. Cost comparison of online haemodiafiltration with high-flux haemodialysis. Journal of Nephrology. 2012; 25(2):192-7

29. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrology Dialysis Transplantation. 2013; 28(1):192-202

30. Park KW, Kyun Bae S, Lee B, Hun Baek J, Woo Park J, Jin Moon S et al. The effect of on-line hemodiafiltration on heart rate variability in end-stage renal disease. Kidney Research and Clinical Practice. 2013; 32(3):127-133

31. Schiffl H. Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. European Journal of Medical Research. 2007; 12(1):26-33

32. Tosh J, Trowman R. Briefing paper for methods review working party on treatment sequences and downstream costs. London. National Institute for Health and Care Excellence, 2011. Available from: https://scharr.dept.shef.ac.uk/nicedsu/methods-development/nice-methods-guide-updates/

33. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. Journal of the American Society of Nephrology. 2000; 11(12):2344-50

34. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrology Dialysis Transplantation. 2000; 15(Suppl 1):43-8

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

ISBN: 978-1-4731-3107-1