Appendix F Full health economic report

Introduction

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on decision-making for the management of hyperphosphataemia.

This is the health economic analysis developed to support the guideline development group (GDG) in making recommendations. The analysis was conducted according to NICE methods outlined in the 'Guide to the methods of technology appraisals 2008' and 'The guidelines manual 2009'. It follows the NICE reference case (the framework NICE requests all cost-effectiveness analysis follow) in its methods.

Contents

Decision problem

Decision problems

Two questions were addressed, based on the literature that had been identified in the review of clinical effectiveness evidence:

- For people with stage 4 and 5 CKD (all ages) and on dialysis, which is the most cost-effective phosphate binder to use as first-line in the management of hyperphosphataemia and its associated outcomes, when compared with placebo or other treatments?
- For people with stage 4 and 5 CKD (all ages) and on dialysis, what is the cost effectiveness of the various sequences of phosphate binders in the management of hyperphosphataemia?

Both questions were explored using the same model structure and, as far as the underlying simulation of hyperphosphataemia in CKD stages 4 and 5 was concerned, the same model parameters. However, because the effectiveness evidence was predominantly in adults with CKD stage 5 on dialysis, the analysis presented directly applies to this population, and (to an extent) was extrapolated to people with CKD stages 4 and 5 pre-dialysis, and to children.

Population

The population in this analysis is adults, children and young people with CKD stages 4 and 5 (and on dialysis). However, because of insufficient data for children and people with CKD 4 and 5 pre-dialysis, it was not possible to conduct separate analyses for these groups.

Interventions and comparators

1. First-line phosphate binder use: various types of phosphate binders compared with calcium carbonate

2. Sequence (second line) of phosphate binder use: switching from a calcium-based to a non-calcium-based binder versus remaining on a calcium-based binder – for people who develop hypercalcaemia or do not tolerate calcium-based binders

Outcomes

To explore the economic consequences of phosphate binders (first-line and sequential use) for the management of hyperphosphataemia, we performed a cost–utility analysis, estimating expected costs and benefits (in terms of quality-adjusted life-years [QALYs]) for each comparator. Given that the interventions are not entirely mutually exclusive, the clinical outcome measures we used in these analyses to estimate differences in treatment effect are similar. The health benefits of using phosphate binders to improve serum phosphate control have been extrapolated from the relationship between serum phosphate level (and serum calcium level) and clinical outcomes (for example, the relationship between hyperphosphataemia and mortality).

Systematic review of published literature

Methods

The review generally adhered to the methodological guideline for short clinical guidelines set out in 'The guidelines manual 2009'. We performed a search for published health economic analyses addressing the questions of interest. We searched the following databases: MEDLINE, MEDLINE in-process, EMBASE, Cochrane Library Health Economic Evaluations Database and the NHS Economic Evaluation Database.

Inclusion and exclusion criteria

Studies were included or excluded from the review according to the criteria listed in Table 1.

Table 1: Inclusion/exclusion criteria for systematic review

	Inclusion	Exclusion
Population	• Chronic kidney disease (CKD) stage 4 or 5	• Not CKD stage 4 or 5 • Transplant recipient • Secondary hyperparathyroidism
Intervention	• All phosphate binders	• Not phosphate binders • Renal dialysis
Comparators	• No intervention • Other phosphate binders	• Not phosphate binders
Study design	• Cost-effectiveness analysis (CEA) • Cost-utility analysis (CUA)	• Not a CEA • Not a CUA

Search strategy

Electronic databases were searched for cost-effectiveness and cost–utility analyses by an information specialist. Appendix F1 shows the databases searched and the all the search terms used. Bibliographies of articles were also searched.

Identification of studies

Abstracts returned by the search strategy were examined by a single researcher and screened for inclusion or exclusion. Full texts were obtained and assessed for inclusion or exclusion. Articles that did not clearly meet the inclusion and exclusion criteria were included or excluded after discussion with a senior researcher.

Quality appraisal

The methodology checklist for economic evaluations that is set out in 'The guidelines manual 2009' was used to determine whether the included studies provide evidence that is useful to inform the decision-making of the GDG.

Results

The searches returned 358 separate references. The searches yielded a total of 358 unique citations. We reviewed the titles and abstracts of these studies

to identify relevant economic evaluations comparing both the costs and health consequences of the alternative modes of management under consideration. From the screening of abstracts, 338 were excluded, leaving 20 potentially relevant studies to be reviewed in full. After examining the full texts, 14 papers were excluded, and a total of 6 studies were included for this review.

Results of the included papers are summarised using the modified GRADE profile in Table 2. Costs were converted to Great British Pounds (GBP) using appropriate Power Purchasing Parity (PPP) conversion rates and uprated to 2010/2011GBP using the appropriate inflation factors.

Table 2: Modified GRADE profile for systematic review of economic evaluations of phosphate binders

Study	Intervention	Limitations	Applicability	Other comments	Incremental			Uncertainty
					Costs (2010/2011 £)	Effects	ICER	
Brennan A 2007	Lanthanum carbonate (as second-line therapy) vs calcium carbonate (CaCo3)	Minor limitations	Directly applicable	Assessed the cost effectiveness of lanthanum carbonate as a second-line therapy for patients in whom CaCo3 therapy has failed to control their phosphate levels. Data on efficacy of lanthanum were based on a 6-month RCT of 510 patients by Hutchinson et al. 2005. Mortality was the only clinical outcome modelled. Long-term survival data from the US renal database was used in preference to the UK renal registry database.	£443,000[a]	18 QALYs	£25,033 per QALY gained	£8935 to £123,831 per QALY gained (range in one-way sensitivity analyses)
Goto S 2011	Lanthanum (as second-line therapy) vs standard care (CaCo3, sevelamer, calcium lactate, vitamin D or cinacalcet)	Potentially serious limitations[b]	Partially applicable	Analysis was conducted alongside a 16 week RCT of 116 Japanese patients. Health effects and costs were modelled over the patients' lifetime.	£14,936[c]	0.632 QALYs	£23,632 per QALY gained	>97% probability ICER less than $50,000 per QALY gained
Huybrechts KF 2005	Sevelamer (first-line use) vs calcium based binders (acetate and carbonate)	Very serious limitations[d]	Not applicable[e]	Analysis was based on longer-term survival benefit of sevelamer attributed to decreased progression of coronary and aortic calcification – with resultant decrease in the risk of a cardiovascular event – reported in the RCT by Raggi et al. (2004). Model assumed no difference in phosphate binding capacity.	£318[f]	0.178 LYs	£1787 per LY gained	95% probability ICER less than $10,000 per LY gained

Study	Intervention	Limitations	Applicability	Other comments	Incremental			Uncertainty
					Costs (2010/2011 £)	Effects	ICER	
Manns B 2007	Sevelamer(first-line use) vs calcium carbonate	Minor limitations[g]	Partially applicable[h]	Effectiveness of sevelamer was based on RCT by Suki et al. 2005.	£31,599[l]	0.21 QALYs	£150,471 per QALY gained	15% probability ICER less than CAN$50,000 per QALY gained
Taylor MJ 2008	Sevelamer(first-line use) vs calcium based binders (acetate and carbonate)	Very serious limitations[j]	Directly applicable	Effectiveness was based on US trial by Block et al. (2007). Data on hospitalisation were obtained from the UK-based DOPPS study (Rayner et al. 2004). A 5-year time horizon was adopted.	£7173[k]	0.24 QALYs	£29,888 per QALY gained	£16,818 to £37,605 per QALY gained (range in one-way sensitivity analyses)
Vegter S 2011	Lanthanum carbonate (as second line therapy) vscalcium-based binders (acetate and carbonate)	Potentially serious limitations	Partially applicable	The effects of lowering PO4 on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy were not included. Also, effects of calcium were not modelled. Additionally, the majority of people treated with lanthanum were phosphate-binder naive, and so the trial was not truly reflective of lanthanum as second-line.	Pre-dialysis = (-£339,000); On dialysis = (£386,000)	Pre-dialysis = 44.1; On dialysis = 55.8	Pre-dialysis = dominating (NMB £1700 at WTP of £30,000/QALY). On dialysis = £6,900/QALY	Pre-dialysis (WTP 90% PI £1200 to £2,200/QALY at £30,000/QALY WTP) On Dialysis (90% PI £5500 to £8800/QALY) (cost of dialysis in additional life-years gained were excluded, but the authors included the cost savings from delaying commencement of dialysis in the pre-dialysis population. This had a large influence on the ICER)

[a] This study used the US average whole sale price of lantham carbonate converted to UK price using PPP (£1 to $0.64 [2004]), but it is unclear whether the price was inflated to 2005/06. Also, estimates were calculated based on a simulated cohort of 1000 patients.
[b] There is some uncertainty over the applicability of Japanese trial data to the UK. There may be differences in population risk and diet as well as healthcare use and unit costs.
[c] Converted from 2010 US Dollars using a PPP conversion rate of 0.659095 (www.oecd.org/std/ppp) then uprated to 2011 GBP by an inflation factor of 102.8%. (http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf). Also estimates were calculated based on a simulated cohort of 1000 patients.
[d] This study is not a cost–utility analysis as health gains (life years) were not weighted for HRQoL
[e] There is some uncertainty over the applicability of USA trial data to the UK. There may be differences in population risk and diet as well as healthcare use and unit costs. Also, the model assumed no difference in phosphate binding capacity.
[f] Converted from 2002 US Dollars to GBP using a PPP conversion rate of 0.627627 (www.oecd.org/std/ppp) then uprated to 2011 GBP by an inflation factor of 133.7%. (http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf). Estimates were calculated based on individual patient (discrete event) simulation.
[g] Cost of cardiovascular event and/or fractures not included separately (but probably lumped with the cost of hospitalisation). However, the estimates included were obtained from the best available source.

[h] There is some uncertainty over the applicability of USA and Canadian trial data to the UK. There may be differences in population risk and diet as well as healthcare use and unit costs. However, all important inputs were subjected to sensitivity analysis.
[i] Converted from 2004 CAN Dollars to USD using a PPP conversion rate of 1.230817 and then to GBP using a rate of 0.632511 (www.oecd.org/std/ppp) then uprated to 2011 GBP by an inflation factor of 123% (http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf). Estimates were calculated based on a simulated cohort of 1000 patients. NB costs of dialysis included in base-case analysis.
[j] Major methodological limitations were found, such as the adoption of an inadequate time horizon (5 years), the use of an inappropriate model structure (2 states; alive and dead), and inadequate assessment of uncertainty (PSA was not conducted). Also cost estimates were not from the best available source (obtained hospitalisation costs from CIPFA and not NHS reference costs)
[k] Uprated to 2011 GBP by an inflation factor of 110% (http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf). Estimates were calculated based on a simulated cohort of 1000 patients.
LY: life years
NMB: net monetary benefit
PI: probability interval
QALY: quality-adjusted life years
WTP: willingness-to-pay threshold

Discussion

For the purposes of this guideline, we were interested in several mutually exclusive treatments, but overall none of the studies assessed all the treatments of interest. Five of the studies were cost–utility analyses and 1 was a cost-effectiveness analysis (outcome was measured in terms of life years instead of QALYs). The study by Brennan et al. (2007) – which assessed the cost-effectiveness of lanthanum carbonate – was the only study that was both directly applicable to the UK and had only minor limitations. However, the authors only assessed the cost-effectiveness of lanthanum as second-line treatment in patients whose phosphate levels were poorly controlled by calcium carbonate, compared with remaining on calcium carbonate. The study by Taylor et al. (2008) was also directly applicable to the UK, but had very serious limitations (for example, the authors used a model time horizon of only 5 years). The study by Vegter et al. (2011) was partially applicable but had some potentially serious limitations, as most people treated with lanthanum carbonate were phosphate-binder-naive, and so was not truly reflective of Lanthanum as second line. Also, the analysis did not take into account the effects of phosphate on other important outcomes (such as cardio-vascular events, fractures, parathyroidectomy and renal transplants). Moreover, the effects of serum calcium were not modelled at all.

Overall, the studies all report widely different answers. However, it appears that studies funded by the manufacturers of proprietary phosphate binders all report that the technologies in question are associated with incremental cost-effectiveness ratios (ICERs) of between £20,000 to £30,000 per QALY gained. The only non-industry-funded paper (Manns et al. 2007) reported a conspicuously high ICER of £150,471 per QALY gained; however this is also the only model that includes dialysis costs in its base-case calculations, which is certain to decrease the cost effectiveness of binder treatment. The approach to modelling also appeared to be inadequate for capturing the relevant costs and outcomes in all the studies except the 1 by Huybrechts et al. (2005). However, the model used in the Huybrechts had a very serious limitation as it assumed from the outset that all the treatment options have

equivalent phosphate binding capacity, and health effects were reported in life years and not QALYs.

Because the identified studies were insufficient to answer the questions of interest, and their results were inconsistent, we proceeded to undertake a de novo economic evaluation.

De novo model: Methods

Model structure

The model uses a discrete event simulation approach, capturing costs and effects associated with events in a cohort of simulated individual patients. Discrete event simulation was considered to be the most appropriate structure for the analysis because of the complex relationships between the biochemical outcomes typically reported in the effectiveness evidence (serum phosphate and serum calcium concentrations) and long-term, patient-relevant outcomes such as cardiovascular risk, fractures and death. Because of the complex relationship between serum phosphate and serum calcium in CKD, and the effect of this relationship on clinical outcomes, the GDG agreed that it would be necessary to account for the impact of both biochemical parameters. For this reason, the effects of each treatment on serum phosphate and serum calcium were modelled to estimate long-term consequences for simulated patients. Figure 1 presents a schematic representation of the model structure, which was based on the natural history of CKD stage 5 and inputs from the GDG.

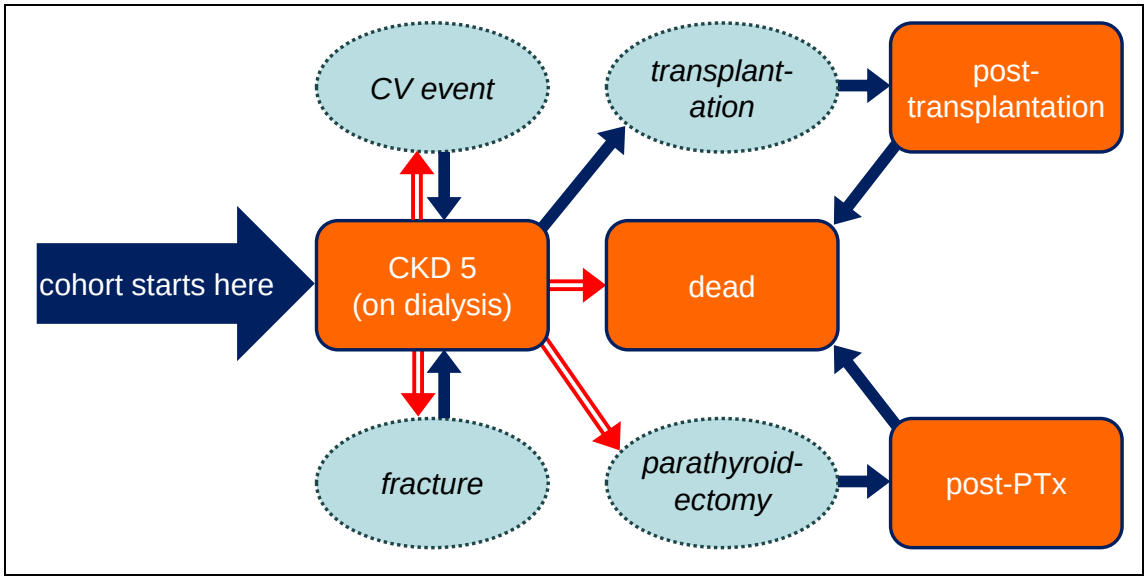


Figure 1: Model structure

In simulating the course of an individual patient, a virtual patient is created and assigned several characteristics, including age, sex, baseline serum

phosphate level and baseline serum calcium level, with these data drawn from distributions reflecting patients in the UK Renal Registry.

Based on these baseline characteristics, the model estimates the phosphate and calcium profiles of the simulated individual receiving 1 year's treatment with calcium carbonate, which is then used as a common baseline with reference to which the effects of all other treatments are estimated. The model then simulates relevant events using serum phosphate and serum calcium levels as surrogate predictors to calculate event probabilities. Costs and quality-of-life values are attached to the events and underlying states and aggregated for each individual. In this analysis, a cohort of 100,000 virtual patients was created in each treatment arm. Finally, the average cost and quality-of-life values for each cohort were calculated.

The relationships identified by the red outlined arrows in Figure 1 indicate transitions that were estimated using a surrogate relationship via the effect of treatment on biochemical measures (serum phosphate and serum calcium). These relationships – between biochemical parameters and long-term consequences – were parameterised using a formal systematic literature review (for details, please see Appendix F1). The post-parathyroidectomy, transplant and death states are effectively absorbing states.

Various combinations of treatment with phosphate binders were simulated over the lifetime of patients, and corresponding costs were attached to treatments and outcomes using an NHS and PSS perspective. We were only able to find substantial effectiveness evidence on calcium carbonate, calcium acetate, sevelamer hydrochloride and lanthanum carbonate, and so these were the only binders included in the model. Insufficient data were available to derive conclusions on the use of sevelamer carbonate, aluminium hydroxide and magnesium carbonate. The model was implemented in Visual Basic for Applications, using Excel as a ‘front-end’ in which parameters are specified and results collected and analysed. Costs and benefits were discounted at 3.5% per annum each.

Treatments simulated

First-line binders

To provide a cost–utility estimate for different phosphate binders used as first-line agents, a simplified scenario was assumed where patient cohorts were assigned to a single binder. Apart from dropout due to adverse events, no switching or addition of different binders was simulated, and serum phosphate and calcium levels were allowed to change based on the observed effect in the evidence base without additional intervention. Importantly, this means that the calcium level of simulated patients receiving calcium-based binders was allowed to rise indefinitely (which is likely to be at odds with current practice).

Sequential use of binders

As well as estimating the costs and effects of first-line treatment with various phosphate binders, the model was configured to simulate cohorts receiving predetermined sequences of binders, with patients switching between them as time progresses. Because the GDG believed that the main reason for switching in practice is hypercalcaemia associated with the use of calcium-based binders, the scenario of greatest interest was one in which people switched from a calcium-based to a non-calcium binder when simulated serum calcium levels exceeded 2.54 mmol/l (based on GDG advice). In this scenario, the sequences modelled are:

- Calcium carbonate → sevelamer hydrochloride
- Calcium carbonate → lanthanum carbonate
- Calcium acetate → sevelamer hydrochloride
- Calcium acetate → lanthanum carbonate
- Calcium carbonate alone (no switch)
- Calcium acetate alone (no switch)
- Sevelamer hydrochloride alone (no switch)
- Lanthanum carbonate alone (no switch)

The latter 4 strategies were included in the decision space to estimate the potential opportunity costs of switching treatment.

Sequences were modelled on basis of generic evidence (based on the network meta-analyses) because of the lack of primary evidence on the sequential use of binders.

Assumptions

All the assumptions and simplifications were checked with the GDG.

- Levels of blood calcium and blood phosphate determine the probability of:
  - fractures
  - cardiovascular events
  - the need for parathyroidectomy (or commencement of cinacalcet therapy for people who are unsuitable for parathyroidectomy; see NICE technology appraisal 117).
  - Death.
- The probabilities of joining the waiting list for renal transplantation and receiving a transplant are independent of blood calcium and blood phosphate
- The clinical effect achieved by phosphate binders in the evidence base at reported doses approximates clinical effect across a dose range
- There is no mixing of different phosphate binding agents for a single patient. When a prescriber wishes to change the phosphate binding agent they will switch entirely to the new agent.
- The utility associated with congestive heart failure as reported in the evidence base is an acceptable proxy for all cardiovascular events that occur in people with CKD stage 5 on dialysis.
- Patients who receive parathyroidectomy are no longer subject to differences in the relative effectiveness of phosphate binders. Although patients are likely to restart phosphate binders following parathyroidectomy (Stracke 1999), there is no evidence on the relative effectiveness of various binders in this population. Therefore, although the model reflects some costs (explicitly) and effects (implicitly) of the continued prescription of

phosphate binders, these values do not vary between different modelled cohorts. The GDG felt that this simplifying assumption was acceptable.

- Only patients with CKD stage 5 on dialysis will receive parathyroidectomy. We acknowledge that a small proportion of patients with CKD stage 4 or 5 who do not receive dialysis will receive parathyroidectomy; however, this simplifying assumption is acceptable as it is applied consistently to all phosphate binders in the model.
- The costs associated with the following procedures can be approximated by using weighted averages of corresponding heterogeneous values from NHS reference costs 2011:
  - fracture
  - parathyroidectomy
  - transplantation
  - biochemistry blood tests
  - dialysis.
- The prices of phosphate binders as listed in the British National Formulary (BNF) 63 (March 2012) can be used to approximate the average cost to the NHS.

Model parameters

Overriding principles

For all estimates, we attempted to find a source that had a large sample size, consisted of UK patients with a diagnosis of CKD stage 4 or 5, and was a recently published study. In instances where UK-based parameters were unavailable, we looked for sources from other countries with a similar disease profile; further details are provided below.

Clinical parameters and variables

Modelling biochemical profiles (serum phosphate and serum calcium) over time for an individual receiving calcium carbonate

The parameters used to estimate the serum phosphate and serum calcium profiles over time for a person receiving calcium carbonate were based on the German RCT reported by Braun et al. (2004). This data source was chosen as, from the assembled evidence on the effectiveness of calcium carbonate (see the full guideline, section 3.5), the Braun et al. trial was the largest with at least 1 year's follow-up in a European population. Serum phosphate and serum calcium levels of the participants were recorded weekly over a period of 52 weeks, and presented in a graph. Data were extracted and used in the model for baseline, 3 months' follow-up (12-week datapoints), 6 month's follow-up (mean of 24- and 28-week datapoints) and 1 year (52-week datapoints).

Table 3: Baseline profile for serum phosphate and serum calcium (calcium carbonate; Braun et al. 2004)

	Baseline	3 months	6 months	12 months
Serum phosphate	2.290 (SD: 0.509)	1.770 (SD: 0.407)	1.865 (SD: 0.509)	1.700 (SD: 0.475)
Serum calcium	2.320 (SD: 0.136)	2.480 (SD: 0.203)	2.445 (SD: 0.203)	2.470 (SD: 0.203)

To reflect interpatient variability in biochemistry, each simulated patient's profile is sampled from a multivariate normal distribution, parameterised using the reported mean and SD for the measure in the Braun et al. cohort at each of the 4 junctures (Table 3). To complete this calculation, it is necessary to specify the correlation between measurements at each juncture. Where available, these were estimated from studies in the effectiveness evidence base. Where a study reports SD at baseline (σ_b), SD at follow-up (σ_f) and the SD of changes between baseline and follow-up (σ_c), the correlation (C) between baseline and follow-up may be estimated by:

$$C = \frac{\sigma_b^2 + \sigma_f^2 - \sigma_c^2}{2 \times \sigma_b \times \sigma_f}. \quad (1)$$

C was calculated for each arm (regardless of treatment assignment) in each study reporting the necessary information for the juncture in question. These values were combined by a weighted average according to the number of people in the arm. Where no evidence was available, a correlation of 0.5 was assumed. The values used are shown in Table 4 and Table 5.

Table 4: Correlation matrix – serum phosphate

	Baseline	3 months	6 months	12 months
Baseline	1			
3 months	0.572[a]	1		
6 months	0.266[a]	0.5[b]	1	
12 months	0.309[a]	0.5[b]	0.5[b]	1

[a] weighted average of calculated correlations from studies reporting baseline, follow-up and mean change.

[b] assumed in absence of evidence.

Table 5: Correlation matrix – serum calcium

	Baseline	3 months	6 months	12 months
Baseline	1			
3 months	0.539[a]	1		
6 months	0.517[a]	0.5[b]	1	
12 months	0.577[a]	0.5[b]	0.5[b]	1

[a] weighted average of calculated correlations from studies reporting baseline, follow-up and mean change.

[b] assumed in absence of evidence.

Modelling the effect of different binders on serum phosphate and serum calcium profiles over time

Effect measures are drawn from a synthesis of direct and indirect evidence comparing each drug with calcium carbonate (see full guideline, section 3.5.2). A total of 6 network meta-analyses are used – phosphate and calcium each analysed at 3 months, 6 months and 1 year. The mean difference in the relevant measure for each treatment compared with calcium carbonate is combined with each virtual patient's simulated baseline profile to provide an estimate of their profile with the treatment in question over the first year.

Extrapolating treatment effect beyond first year

Because it was only possible to synthesise evidence on the treatments of interest over the first year of treatment, we had to rely on assumptions to

project the future biochemical profile of simulated patients. Different approaches were adopted for the 2 measures:

- For **serum phosphate**, no further changes in level were simulated beyond year 1 in the base case. This means that each simulated individual's serum phosphate level remains constant at the level reached after 12 months of treatment. This was judged appropriate as it was the simplest approach in the absence of meaningful evidence, and was also a reflection of the relatively laminar trends in serum phosphate seen in the latter phase of follow-up in studies of a year's duration.
- For **serum calcium**, it would not be appropriate to assume no further changes, as the continued use of calcium-based phosphate binders in particular will clearly have implications for a patient's calcium levels. For this reason, the linear trend observed across the empirical 12 months' treatment was extrapolated into the future. The average increase or reduction over the period (sampled baseline profile plus treatment effect) was extended indefinitely. With more data, it may have been possible to project a more realistic trend than a simple linear one; however, inspection of the available evidence did not provide an unambiguous indication of the likely trajectory (see also the CGTSU analysis of Dias et al. [Appendix G]).

Estimating treatment effect when switching treatment

Similarly, in the analysis of sequences of phosphate binders, we had no direct evidence with which to estimate the biochemical profile of people switching from one phosphate binder to another. This necessitated reliance on the same evidence used to parameterise first-line treatment effect, coupled with some additional assumptions. Again, our approach differed between measures:

- For **serum calcium**, first-line treatment evidence was applied in a 3-stage process:
  - Firstly, the baseline (calcium carbonate) profile of the simulated patient over the first year of treatment was combined with effectiveness evidence relating to the new treatment.

  - Secondly, the change in serum calcium over the theoretical year's treatment was calculated and averaged.
  - Lastly, this average rate of change in calcium was applied to the patient's calcium levels going forward (starting from the level reached at the end of treatment with the previous binder). For the same reasons considered above, this trajectory was continued indefinitely beyond the year's treatment with the new binder.

- For **serum phosphate**, the first-line treatment evidence could not be applied in a similar way, because the trials in the effectiveness evidence-base comprise participants with established hyperphosphataemia, invariably demonstrated via a pre-randomisation washout phase, with the result that the initial phase of treatment features an exaggerated drop in serum phosphate. It would be misleading to apply such a dramatic effect in a second-line context, and would result in artificially low phosphate levels. Therefore, a modified version of the approach used for calcium was adopted in the base case:

  - A theoretical profile was estimated in the same way by combining the baseline (calcium carbonate) profile with effectiveness evidence.
  - The change in serum phosphate from 6 months to 12 months was calculated and averaged.
  - This average change in phosphate was applied to the patient's phosphate level across the whole first year of treatment with the binder they had switched to. As in the first-line context, an effect on phosphate was not projected beyond a year's treatment.

Hypocalcaemia and hypophosphataemia

As a simplifying measure, hypocalcaemia and hypophosphataemia are assumed to be trivially controlled in this model, with calcium levels constrained to be 2 mmol/l or greater and phosphate limited to at least 1 mmol/l. This assumption reflects the fact that a variety of strategies can be used to manage hypocalcaemia and hypophosphataemia, including

manipulation of binder regimen, diet, dialysate and, where necessary, prescription of minimally expensive supplements. Therefore, whenever either measure is projected to fall below the relevant minimum level, it is assumed to reach a floor at that lower bound. No additional costs, benefits or disutilities are assumed.

Simulating relevant events using phosphate and calcium as surrogate predictors to calculate event probabilities

The events that were deemed relevant for this analysis are:

- all-cause mortality
- cardiovascular events
- kidney failure (a requirement for renal replacement therapy – for people with CKD stage 4 and 5 pre-dialysis)
- the need for a parathyroidectomy (or cinacalcet therapy, for those unable to undergo surgery) – for people on dialysis
- fractures.

The estimates used to calculate the event probabilities were obtained from a systematic review of prognostic evidence, which is reported in full in appendix F1. In brief: we identified 36 studies in adults and children with CKD (stage 4 or 5) relating serum phosphate and serum calcium in a single multivariate model to the relevant events. The studies were all observational in design, with very limited evidence in children. The measures of effect were adjusted for a variety of variables and reported in various formats, either as continuous data (for example an increase in risk per 1 mmol/l increase in serum phosphate), or as categorical – binary or ordered – data with a variety of cut-offs (for example, a relative risk for phosphate levels ≥2 mmol/l when compared with the risk for levels <2 mmol/l). A meta-analysis of the various measures of effect was not performed because it would be inappropriate to pool estimates that come from a heterogeneous collection of multivariable models. Instead, the evidence was systematically appraised and the most appropriate individual study(s) were selected. Overriding selection criteria were as follows:

- The selected study should report outcomes that correspond as closely as possible to the events simulated in the model.
- The selected study should report a population that closely matches the UK population (ideally, it should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.

For full details of systematic review of prognostic studies, see appendix F1.

All-cause mortality

In order to model the mortality of people with CKD stages 4 and 5, we obtained from the UK Renal Registry hazard ratios of death (stratified according to age) for people with end-stage renal disease (ESRD) compared with the general population, and applied these ratios to general population mortality estimates from UK life tables. As people get older, the hazard ratios of death decrease; this is because the hazard of death increases with age in the general population. For example, a 22-year old with ESRD faces an instantaneous risk of death 27 times greater than a 22 year-old without ESRD, whereas a 90 year-old with ESRD is only 2.5 times more likely to die than a person of the same age without ESRD.

We did not find any evidence on the interaction between the type of renal replacement therapy (that is, either dialysis or renal transplantation) and age, which we would have ideally used to analyse how the relative likelihood of death changes with age. To approximate this, we assumed a linear relationship over time, and split the hazard ratio of death between the hazard in people who have undergone transplantation and those who are on dialysis (HR=0.2; Jain et al. 2009), assuming this hazard ratio remains constant over time. This implies that, in the model, people who are on dialysis are 5 times more likely to die at any given time than those who have received a renal transplant. This was applied to the various populations up until the age of 80, beyond which we assumed that there is no difference in mortality between people on dialysis and people who have received renal transplantation. This assumption was necessary to prevent people on renal transplants being less

likely to die than the general population (thus conferring an unrealistic survival advantage to people on renal transplants). This is because age has a confounding effect on the hazard ratio of death between renal transplantation and dialysis which, because of data constraints, we are unable to account for empirically. Accordingly, beyond the age of 80, all simulated patients are subject to the hazard ratio for people with ESRD, regardless of the type of renal replacement therapy they have received.

Excess mortality

The estimates used in the model for predicting the additional hazard of death faced by people with CKD stages 4 and 5 on dialysis (using serum phosphate and serum calcium levels) were drawn from a retrospective cohort study of 7076 patients from the UK renal registry reported by Tangri et al. (2011). The study reports hazard ratios for mortality – from multivariate Cox regression analysis – which suggest that high phosphate and calcium levels are independently associated with an increased risk of death.

Table 6: Relationship between serum phosphate, serum calcium and mortality (Tangri et al. 2011)

Serum phosphate		**Serum calcium**	
mg/dl	**HR (95% CI)**	**mg/dl**	**HR (95% CI)**
<3.5	0.74 (0.53–1.03)	<8.4	1.35 (0.24–7.56)
3.5–5.5	1 (Ref)	8.4–9.5	1 (Ref)
5.5–6.5	1.17 (0.94–1.46)	9.5–10.4	1.13 (0.83–1.53)
6.5–7.5	1.42 (1.06–1.90)	>10.4	1.35 (0.93–1.65)
>7.5	1.64 (1.02–2.63)		

In order to extrapolate results beyond the reported range, our base-case model relied on a function fitted to these data, as illustrated in Figure 2. We fitted a quadratic function to the log hazard ratios, and this provided an acceptable fit to the data (r^2>0.87, in each case). An alternative mode of calculation, in which the reported hazard ratios were applied to simulated patients in each category (that is, as a step function) was tested in sensitivity analysis.

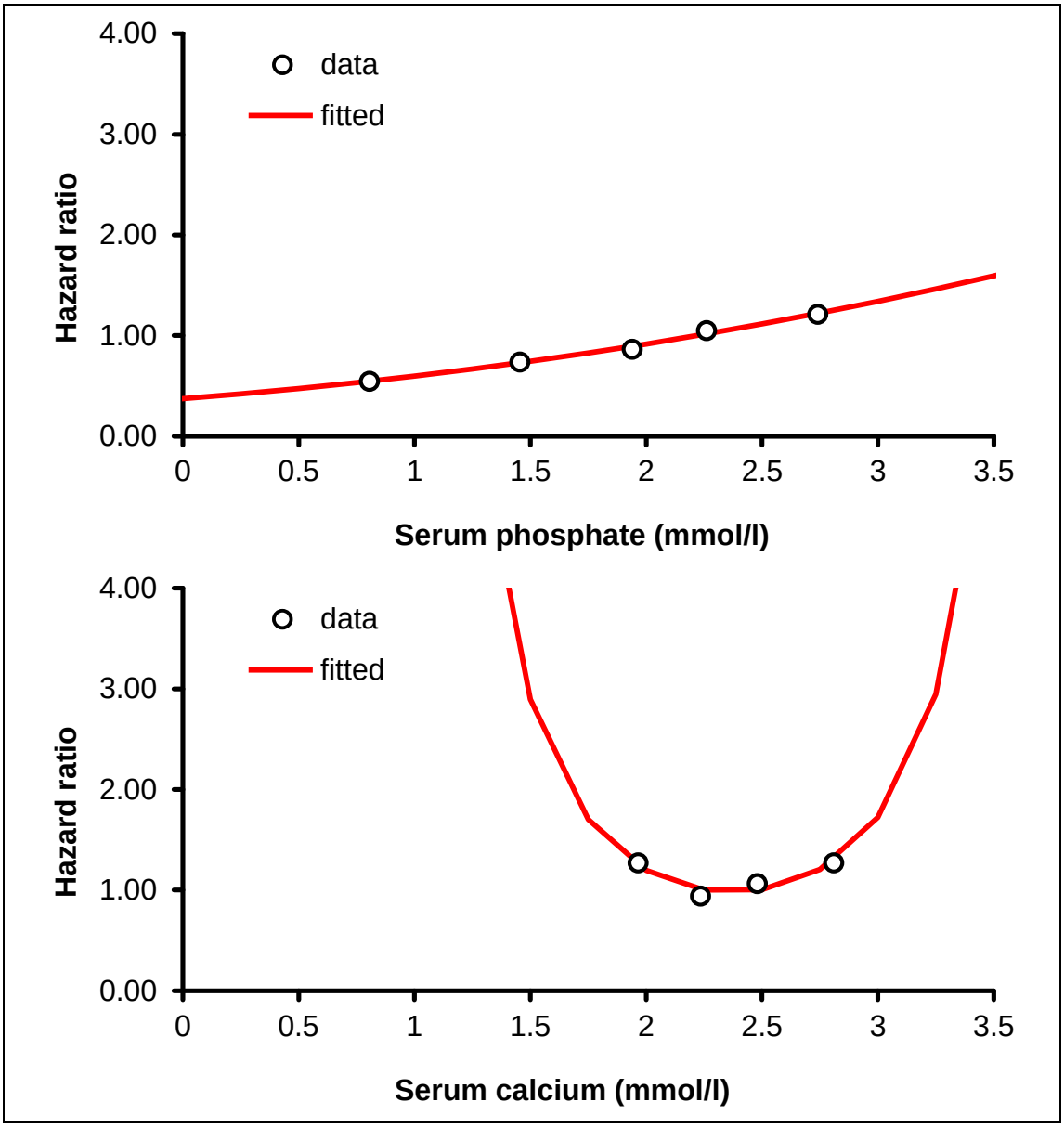


Figure 2: Relationship between serum phosphate, serum calcium and mortality – raw data and fitted functions

Cardiovascular events

The estimates used in the model for predicting cardiovascular events from phosphate and calcium levels were based on a retrospective cohort study of 14,829 USA patients by Slinin et al. (2005). Although many other studies report the association between biochemical parameters and cardiovascular mortality, this was the only study we identified that assessed the relationship between both phosphate and calcium and all fatal and non-fatal cardiovascular events. A cardiovascular event was defined as hospitalisation with ischaemic heart disease, congestive heart failure, stroke, transient

ischaemic attack, or peripheral vascular disease. The results suggest that high levels of phosphate and calcium are independently associated with increased risk of a cardiovascular event.

Table 7: Relationship between serum phosphate, serum calcium and cardiovascular events (Slinin et al. 2005)

Serum phosphate		**Serum calcium**	
mg/dl	**HR (95% CI)**	**mg/dl**	**HR (95% CI)**
≤4.4	1 (Ref)	≤8.7	1 (Ref)
4.5–5.3	1.06 (1.00–1.13)	8.8–9.2	1.03 (0.97–1.09)
5.4–6.3	1.13 (1.06–1.19)	9.3–9.6	1.04 (0.97–1.10)
6.4–7.7	1.14 (1.07–1.22)	9.7–10.2	1.03 (0.97–1.10)
>7.5	1.25 (1.17–1.33)	>10.2	1.08 (1.01–1.15)

As for mortality, the base-case model relied on a function fitted to these data, as illustrated in Figure 3, and we tested the alternative, categorical approach in sensitivity analysis.

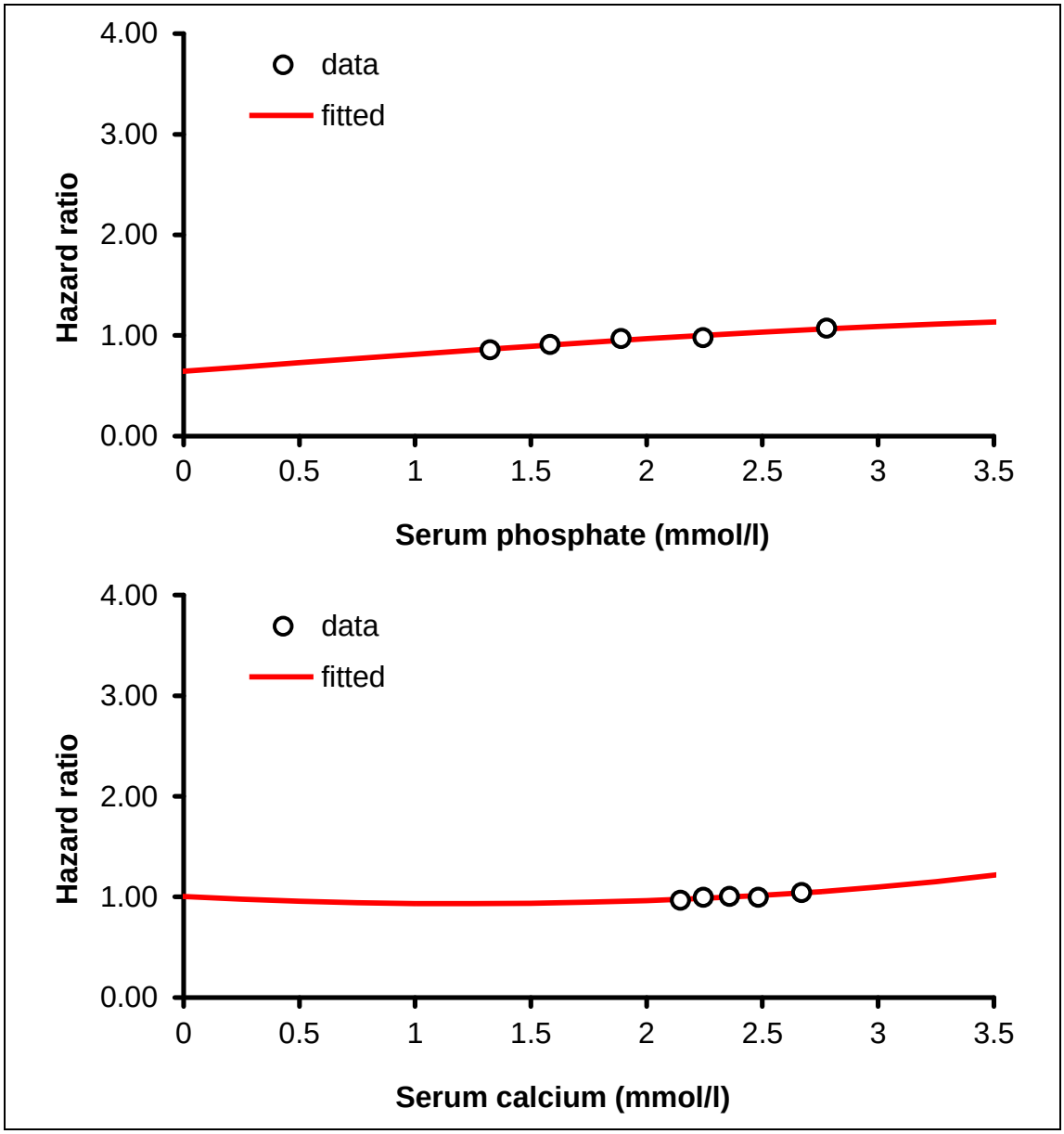


Figure 3: Relationship between serum phosphate, serum calcium and cardiovascular events – raw data and fitted functions

Fracture events

The estimates for predicting bone fractures from phosphate levels were obtained from a retrospective cohort study of 40,538 USA patients by Block et al. (2004). The results suggest that serum phosphate is a significant predictor of fracture events (HR=1.12 per mg/dl [95% CI 1.03–1.22]). However, calcium was not shown to have an effect.

Parathyroidectomy

The estimates used in the model to predict parathyroidectomy from phosphate and calcium levels were based on a prospective cohort study of 17,236 patients randomly sampled from the UK, France, Germany, Italy, Spain, USA and Japan by Young et al. (2005). The results showed that high levels of phosphate and calcium were independently associated with an increased risk of parathyroidectomy (phosphate HR=1.17 per mg/dl [95% CI 1.09–1.25]; calcium HR=1.58 per mg/dl [95% CI 1.35–1.85]).

We accounted for both surgical and medical parathyroidectomy (cinacalcet for people in whom surgery is contraindicated).

Estimated costs and effects for people needing a parathyroidectomy were derived from the cinacalcet model published by the Peninsula Technology Assessment Group (Garside et al. 2007). We updated the cost parameters in this model to match those used in our model (see 'Costs', below), and configured it to simulate 2 arms: 1 comprising people undergoing surgical parathyroidectomy, and 1 for people taking cinacalcet. We then ran the model for every age from 18 years to 120 years (that is, changing only the starting age of the cohort for each iteration), capturing the resultant costs and QALYs for each arm. From these data, we were able to create a meta-model for each treatment path with the starting age of the cohort as a covariate of expected costs and QALYs. We found that quartic functions gave excellent fits to the data (all r^2 values >0.9999).

Table 8: Meta-model of PenTAG model for people needing parathyroidectomy

Surgery
Discounted costs (£) exc. dialysis = $25{,}947 - 664.16Age + 7.158Age^2 - 0.0354Age^3 + 0.00006Age^4$
Discounted costs (£) inc. dialysis = $386{,}001 - 9653.82Age + 96.597Age^2 - 0.429Age^3 + 0.00066Age^4$
Discounted QALYs (£) = $14.598 + -0.356Age + 0.0035Age^2 - 0.00001Age^3 + 0.00000002Age^4$
Cinacalcet
Discounted costs (£) exc. dialysis = $143{,}484 - 3779.94Age + 41.475Age^2 - 0.211Age^3 + 0.0004Age^4$
Discounted costs (£) inc. dialysis = $499{,}791 - 13159.4Age + 143.486Age^2 - 0.724Age^3 + 0.0014Age^4$
Discounted QALYs (£) = $12.419 - 0.319Age + 0.0034Age^2 - 0.00002Age^3 + 0.00000003Age^4$

Therefore, when a simulated patient in our model needs a parathyroidectomy, they are assigned the discounted costs and QALYs pertaining to their age in

the meta-model. The default treatment option is surgery; however, a proportion of patients are assumed to be unsuitable for surgery and receive cinacalcet instead (in line with the recommendations of NICE technology appraisal 117). As in the original PenTAG model, the proportion of people who are assumed to be unsuitable for surgery is 15% until the age of 55, with a subsequent increase of 0.5% for each year above that age.

Renal transplantation

Transplantation is an absorbing state within the model. It is acknowledged that many people who have received a transplant experience recurrent kidney failure and will require further treatment with phosphate binders; however, we did not identify evidence that looked at the use of different binders in this population specifically. Therefore, it was inferred that conclusions from a pre-transplant population could be generalised to this setting, so it was not necessary to investigate a separate decision-point. For this reason, all simulated patients are handled identically, regardless of treatment assignment, when they reach the transplantation event.

The path to transplantation is modelled as a two-stage event – entering the waiting list and, once on the list, receiving a transplant. Neither event is dependent on the simulated patient's serum phosphate or serum calcium level; this dictates that, in the model, the choice of binder has no direct influence on the likelihood of receiving a transplant.

Rates of renal transplantation were based on estimates from the UK Renal Registry database. The registry provides ORs (from logistic regression) for getting on the waiting list, stratified according to age and gender. These ORs were applied to baseline rate of people joining the waiting list (51.2% over 2 years, also reported in the Renal Registry). Exactly the same process was used for the likelihood of having a transplant – using ORs from the Renal Registry for receiving a transplant given that an individual is on the waiting list. Separate odds ratios were provided in the registry for receiving transplants from brain-stem-dead donors and from cardiac-dead/living donors.

Adverse events

On GDG advice, 4 adverse events were considered important, and data on each were extracted from the assembled evidence: diarrhoea, constipation, nausea/vomiting and upper abdominal pain. Unfortunately, because of patchy reporting of AEs, it was not possible to derive connected evidence networks including all 4 binders, which would have enabled estimation of relative probability of these events in network meta-analyses, which would have been our preferred approach for deriving model parameters. Since this approach was not possible, we simply pooled the observed event rate for each of the binders in all relevant trial arms reporting the event in question. This approach is suboptimal, because it breaks the randomisation of the trials; however, in the absence of a coherent evidence network, we considered it the best feasible solution. The derived event rates are shown in Table 9.

Table 9: Adverse event rates used in model

Adverse event	Calcium carbonate	Calcium acetate	Sevelamer hydrochloride	Lanthanum carbonate
Diarrhoea	0.178/year	0.205/year	0.170/year	0.159/year
Constipation	0.132/year	0.094/year	0.142/year	0.198/year
Nausea and vomiting	0.423/year	0.515/year	0.352/year	0.557/year
Abdominal pain upper	0.355/year	0.040/year	0.082/year	0.101/year

Discontinuation due to adverse events

We only used data reflecting discontinuations due to adverse events; although several studies reported withdrawal for any reason, it was important not to double-count the likelihood of switching treatment because of hypercalcaemia (which is modelled separately, as described above).

As with adverse event rates, it was impossible to derive connected evidence networks including all 4 binders, so we relied on pooled event rates again (noting, once more, that this approach is suboptimal, because it breaks the randomisation of the trials).

The derived event rates are shown in Table 10.

Table 10: Discontinuation due to adverse events: rates used in model

Binder	Discontinuation rate (95% CI)
Calcium carbonate	0.065/year (0.024/year, 0.105/year)
Calcium acetate	0.064/year (0.018/year, 0.111/year)
Sevelamer hydrochloride	0.031/year (0.016/year, 0.046/year)
Lanthanum carbonate	0.037/year (0.027/year, 0.046/year)

Health-related quality of life

Kidney disease

The unit of measure for quality of life used in the health economic analysis was the QALY, in line with 'The guidelines manual 2009'. The QALY provides a comparable measure of health-state utility and is bounded between 1 (perfect health) and zero (dead). The quality of life (utility) of different health states within the model was drawn from available evidence.

To obtain a utility value for CKD stage 5 on dialysis, we relied on the meta-analysis conducted by Liem et al. (2008). This study provides separate pooled health state valuations for people undergoing haemodialysis and peritoneal dialysis. We reanalysed these data to give a single summary estimate. Values included were restricted to those obtained using the EQ-5D index measure. Eight studies were included, giving a utility value of 0.565 (95% CI 0.514, 0.616) for people in the CKD stage 5 on dialysis health state.

Table 11: Utility values for CKD stage 5 on dialysis

	Reference	Publication year	n	EQ-5D index mean valuation	SD
Haemodialysis	Lee et al.	2005	99	0.44	0.32
	Manns et al.	2003	151	0.62	0.26*
	Roderick et al.	2005	269	0.60	0.28
	Roderick et al.	2005	314	0.60	0.31
	Sennfalt et al.	2002	27	0.44	0.08
	Wasserfallen et al.	2004	455	0.62	0.30
Peritoneal dialysis	Lee et al.	2005	74	0.53	0.34
	Manns et al.	2003	41	0.56	0.27*
	Sennfalt et al.	2002	27	0.65	0.15
	Wasserfallen et al.	2004	50	0.58	0.32
				0.565 (SE 0.026)	

*Standard deviation not reported. To enable inclusion in the meta-analysis, an estimate of the SD was obtained from the mean SD of other valuations in the dialysis type.

In a time trade-off study, Gorodetskaya et al. (2005) showed that the relative improvement in utility between CKD stage 4 and CKD stage 5 on dialysis was 10.4%. This value was applied to the CKD stage 5 on dialysis estimate obtained from Liem et al. to estimate a utility value for CKD stage 4 of 0.624.

An estimate of utility for patients who were post-kidney transplantation was also obtained from Liem et al. (2008) and was estimated to be 0.809. A utility decrement associated with a decreased health state immediately following surgery and potential complications as reported by Hamidi (2009) was also included.

Table 12: Quality of life – kidney disease

Health state	Utility (95% CI)
CKD stage 4	0.624
CKD stage 5 on dialysis	0.565 (0.514, 0.616)
Post-transplantation	0.809 (0.711, 0.906)

Quality of Life – Complications and Adverse Events

The principal complications associated with hyperphosphataemia as used in the health economic analysis were cardiovascular events and fracture. The utility estimate for cardiovascular events was informed by Block et al. (2004), who found that congestive heart failure was the most common reason for cardiovascular-related admissions among people with ESRD. In a study

investigating the impact of pharmacist interventions, Holland (2007) obtained health utility values for UK patients with congestive heart failure receiving standard medical management. The trial population utility was calculated to be 78% of that expected of the general UK population adjusted for age and sex. Once incurred, this disutility was applied indefinitely.

A review by Peasgood (2009) on utility values for people who suffered fractures was used to estimate the percentage reduction in utility that would be expected to occur in the year following a fracture compared with the general population of the same age and sex. A single average disutility value of 0.928 was used for all fractures, accounting for the wide range of disutility associated with different types of fracture. This disutility was applied for a year, as this was the length of time examined in the source data.

Utility decrements associated with adverse events of phosphate binder treatment – constipation, diarrhoea, nausea and vomiting, and upper abdominal pain – are shown in Table 13 below.

Table 13: Utility decrements for associated events

Event	Utility decrement	Duration	Source
Cardiovascular event	78%	Indefinite	Holland et al. 2007
Fracture	93%	1 year	Peasgood et al. 2009
Transplant	87%	1 month	Hamidi et al. 2009
Adverse events:			
Diarrhoea	92% (based on absolute decrement of -0.06)	5 days	Szabo et al. 2008
Constipation	85%	5 days	Belsey 2010
Nausea/vomiting	91% (based on absolute decrement of -0.07)	5 days	Szabo et al. 2008
Upper abdominal. pain	73%	5 days	Latimer 2009

All utility decrements were applied multiplicatively, as per the interim recommendation of the NICE technology appraisal programme's decision support unit (Ara and Wailoo, 2011).

Costs

Methods for obtaining cost estimates in the health economic analysis were in accordance with 'The guidelines manual 2009'. Cost estimates for dialysis, kidney transplant, parathyroidectomy, cardiovascular events and fractures

were obtained from the NHS reference cost guide 2011, using weighted averages of costs across procedure codes. Adjustments were made to account for extended length of stay.

Drug costs

The costs of phosphate-binders used in the management of hyperphosphataemia were obtained from the BNF 63 (March 2012). The GDG considered that local arrangements on pricing might vary; however, the BNF has been used to provide a nationally consistent estimate. Where different formulations and tablet strengths resulted in different costs per gram of phosphate binder, a central value was used. The impact of variation in absolute and relative costs was explored in sensitivity analysis.

Non-phosphate binder drug costs, such as those used after transplantation, were also obtained from BNF 63 (March 2012).

Doses, adverse events and discontinuations

The average dose at which each binder was delivered to achieve the clinical effect observed in the evidence base was used in the analysis. This allows the cost needed to achieve a particular dose to directly link to the clinical effect observed at that dose. The average daily doses are as follows: calcium carbonate 3.66 grams/day, calcium acetate 4.82 grams/day, sevelamer hydrochloride 6.37 grams/day, and lanthanum carbonate 1.93 grams/day. See Table 14 for details.

Table 14: Mean binder dose reported in effectiveness evidence

Study	Mean dose (mg per day)
Calcium carbonate	
Braun J et al. (2004)	3900 (SD: 1700)
De Santo et al. (2006)	NR
Freemont AJ et al. (2005)	NR
Hutchison AJ et al. (2005)	3893 (SD: 2371)
Janssen MJ et al. (1995)	NR
Janssen MJ et al. (1996)	3460 (SD: 490)
Kakuta T et al. (2011)	NR
Spasovski GB et al. (2006)	NR
Tzanakis IP et al. (2008)	2608 (SD: NR)
Pooled average[a]	**3655 (95%CI: 3496, 3815)**
Calcium acetate	
Barreto DV et al. (2008)	NR
Chertow GM et al. (2003)	4600 (SD: 2100)
Evenepoel P et al. (2009)	4500 (SD: 2200)
Janssen MJ et al. (1995)	NR
Janssen MJ et al. (1996)	4900 (SD: 490)
Navarro-Gonzalez JF et al. (2011)	1500 (SD: NR)
Qunibi W et al. (2008)	5500 (SD: NR)
Spiegel DM et al. (2007)	NR
Pooled average[a]	**4823 (95% CI: 4663, 4982)**
Lanthanum carbonate	
Ferreira A et al. (2008)	NR
Fishbane S et al. (2010)	NR
Kakuta T et al. (2011)	1935 (SD: 825)
Navarro-Gonzalez JF et al. (2011)	NR
Qunibi W et al. (2008)	NR
Pooled average[a]	**1935 (95% CI: 1865, 2005)**
Sevelamer hydrochloride	
Barreto DV et al. (2008)	NR
Block GA et al. (2005)	8000 (SD: NR)
Braun J et al. (2004)	5900 (SD: 2400)
Chertow GM et al. (2002)	6500 (SD: 2900)
Chertow GM et al. (2003)	6700 (SD: 3400)
De Francisco et al. (2010)	6480 (SD: 2296)
De Santo et al. (2006)	NR
Evenepoel P et al. (2009)	5800 (SD: 2600)
Ferreira A et al. (2008)	5000 (SD: 2700)
Fishbane S et al. (2010)	7300 (SD: 3000)
Kakuta T et al. (2011)	NR
Navarro-Gonzalez JF et al. (2011)	4800 (SD: NR)
Qunibi W et al. (2008)	7300 (SD: NR)
Pooled average[a]	**6367 (95% CI: 6156, 6577)**

[a] fixed-effects meta-analysis of studies reporting mean dose and SD

Using the costing data above, an average daily cost for each phosphate binder was estimated (Table 15).

Table 15: Cost of phosphate binders used in model

Binder	Average daily dose (g)	Cost per g (£)	Cost per day (£)
Calcium carbonate	3.66	0.07	0.27
Calcium acetate	4.82	0.11	0.52
Sevelamer hydrochloride	6.37	0.82	5.22
Lanthanum carbonate	1.93	2.25	4.36

Table 16: Costs

Event costs	Value	Notes
Cardiovascular event	£1,308.88	NHS reference costs 2011. Hospital procedures are coded to allow activity-based analysis of costs and resources. Using these codes, we can calculate the approximate cost to the NHS of a cardiovascular event to be used in the model. A weighted average of the following event codes was used:* EB07H (Arrhythmia or Conduction Disorders with complications (CC)), PA23A (Cardiac Conditions with CC), EB01Z (Non interventional acquired cardiac conditions), EB05Z (Cardiac Arrest), EB06Z (Cardiac Valve Disorders), EB10Z (Actual or Suspected Myocardial Infarction), EB03H (Heart Failure or Shock with CC), AA22A (Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy with CC), DZ20Z (Pulmonary Oedema), QZ17A (Non-Surgical Peripheral Vascular Disease with Major CC), QZ17B (Non-Surgical Peripheral Vascular Disease with Intermediate CC). A weighted average of the cost of excess bed days associated with the above procedures was included.
Fracture	£2,089.23	NHS reference costs 2011. A weighted average of the following event codes were used:* HD39A (Pathological Fractures with Major CC), HD39B (Pathological Fractures with CC.
Parathyroidectomy	£2,604.14	NHS reference costs 2011. A weighted average of the following event codes were used:* KA03A (Parathyroid Procedures with CC), KA03B (Parathyroid Procedures without CC).
Transplantation	£22,558.09	NHS reference costs 2011. A weighted average of the following event codes were used:* LA01A (Kidney Transplant 19 years and over from Cadaver non-Heart beating donor), LA02A (Kidney Transplant 19 years and over from Cadaver Heart beating donor), LA03A (Kidney Transplant 19 years and over from Live donor). Additional drug costs (recommended doses in BNF 63, assuming a 70 kg adult): • All patients receive postoperative basiliximab (per NICE Technology Appraisal 85); 2 vials per person. • 75% of people receive tacrolimus immunotherapy; 17.5 mg/kg/d for first 15 days. • 25% of people receive ciclosporin immunotherapy; 12.5 mg/kg/d for first 15 days. See below for maintenance immunotherapy costs.
Adverse events:		
Diarrhoea	£36.00	Each assumed to incur 1 GP appointment (costed as per Personal Social Services Research Unit 2011).
Constipation	£36.00	
Nausea/vomiting	£36.00	
Upper abdominal pain	£36.00	
Intervention costs	**Value**	**Notes**
Cost per quarter		
Calcium carbonate	£24.91	Calculated as below.

Intervention costs	Value	Notes
Calcium acetate	£47.54	
Sevelamer hydrochloride	£476.25	
Lanthanum carbonate	£398.22	
Unit cost (per g)		
Calcium carbonate	£0.07	Costs per pack from BNF March 2012. Cost per gram is calculated by dividing grams per unit dose by number of unit doses per pack. Calcichew is used for calculations of calcium carbonate cost/gram. PhosLo is used for calculations of calcium acetate cost/gram. Lanthanum tablets are supplied in different strength formulations, which result in a different cost per gram (lanthanum 500 mg tablet: £2.54/gram, 750 mg tablet: £2.25/gram, 1000 mg tablet £1.79/gram). Because it lies in the middle of this range, the cost/gram of the lanthanum 750 mg tablet is used in the model.
Calcium acetate	£0.11	
Sevelamer hydrochloride	£0.82	
Lanthanum carbonate	£2.25	
Assumed dose (g/d)		
Calcium carbonate	3.66	Pooled evidence from effectiveness evidence base (that is, the average dose at which each binder was delivered in studies included in the effectiveness synthesis).
Calcium acetate	4.82	
Sevelamer hydrochloride	6.37	
Lanthanum carbonate	1.93	

State costs per quarter	Value	Notes
CKD stage 5 on dialysis	£25.00	excluding dialysis costs
After transplantation (maintenance per quarter)	£819.69	Calculated using recommended doses in BNF 63, assuming a 70 kg adult: • 75% of people receive tacrolimus immunotherapy; 6mg/kg/d as maintenance. • 25% of people receive ciclosporin immunotherapy; 4mg/kg/d as maintenance.

Unit costs	Value	Notes
PTH test	£10.00	NHS reference costs 2011. Cost of ‘other’ biochemistry test.
Calcium test	£1.00	NHS reference costs 2011 Cost of ’standard‘ biochemistry test.
Phosphorus test	£1.00	NHS reference costs 2011 Cost of ’standard‘ biochemistry test.
Dialysis cost per session:		
Home haemodialysis	£122.85	NHS reference costs 2011
Hospital haemodialysis	£159.77	
Satellite haemodialysis	£158.25	
Continuous ambulatory PD	£51.36	

Unit costs	Value	Notes
Automated PD	£57.16	
Immunosuppressants:		
Basiliximab (per 20 mg vial)	£842.38	BNF 63 March 2012
Tacrolimus (per mg)	£1.61	
Ciclosporin (per mg)	£0.03	

Dialysis

The costs associated with dialysis are substantial and are not significantly affected by the choice of phosphate binder. In order to isolate the relative impact of different phosphate binders, dialysis costs were excluded from the model in its base case. This decision has precedent in NICE decision-making (for example, see technology appraisal 117). The impact of inclusion and exclusion of dialysis costs was assessed in sensitivity analyses.

Results: First-line use

Model outputs

Figure 4 shows the modelled distribution of phosphate levels at baseline and at 1 year, respectively, of 100,000 simulated patients for each phosphate binder.

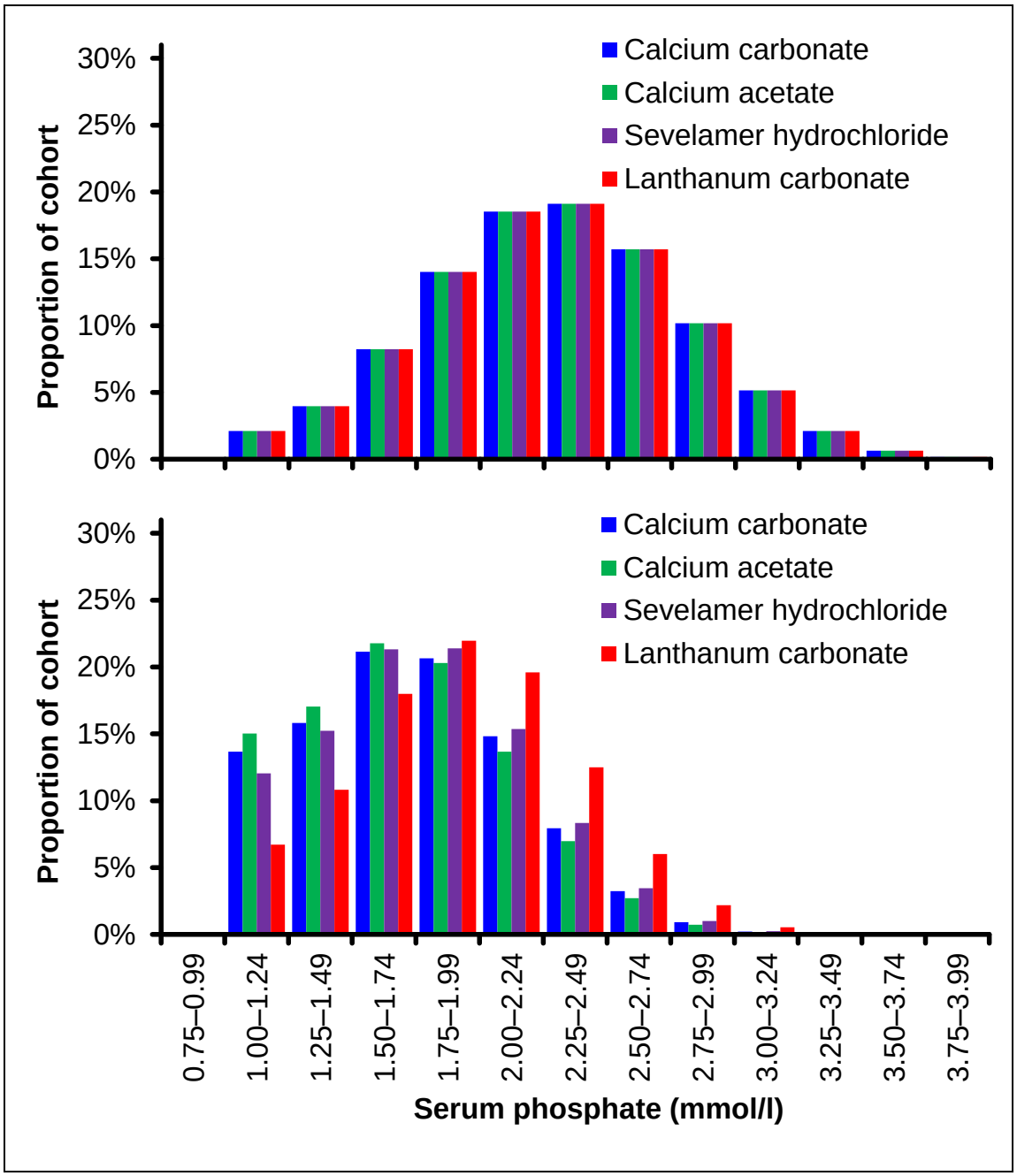


Figure 4: simulated serum phosphate distribution at baseline (top) and at 1 year (below)

The model reflects the evidence that all phosphate binders are efficacious in lowering serum phosphate levels. The distribution of phosphate levels is most favourable for people receiving calcium acetate, with slightly higher levels in people receiving calcium carbonate and sevelamer hydrochloride. The simulated lanthanum carbonate arm is visibly somewhat higher than the other 3 binders. This is a direct reflection of the effectiveness evidence used to parameterise the model (see, in particular, the network meta-analysis of serum phosphate at 360 days in section 3.5.2 of the full guideline, which suggests that calcium acetate has a 0.612 probability of being the most effective binder [median rank 1, 95% CI 1 to 4], whereas lanthanum carbonate has a 0.004 probability of being the most effective binder [median rank 5, 95% CI 3 to 5]).

Conversely, the model predicts that serum calcium levels of cohorts receiving non-calcium binders are lower than those of groups receiving calcium-based binders (Figure 5). Sevelamer hydrochloride is associated with the most favourable distribution of calcium levels, quite closely followed by lanthanum carbonate. Calcium acetate is inferior to the calcium-free options, but appears consistently superior to calcium carbonate.

Again, these findings are a direct reflection of the effectiveness evidence used to parameterise the model (see, in particular, the network meta-analysis of serum calcium at 360 days in section 3.5.2 of the full guideline, which suggests that sevelamer hydrochloride has a 0.775 probability of being the most effective binder [median rank 1, 95% CI 1 to 2], lanthanum carbonate has a 0.220 probability of being the most effective binder [median rank 2, 95% CI 1 to 3], and the probability that either of the calcium-based binders is best is negligible, although calcium acetate is very likely to be superior to calcium carbonate).

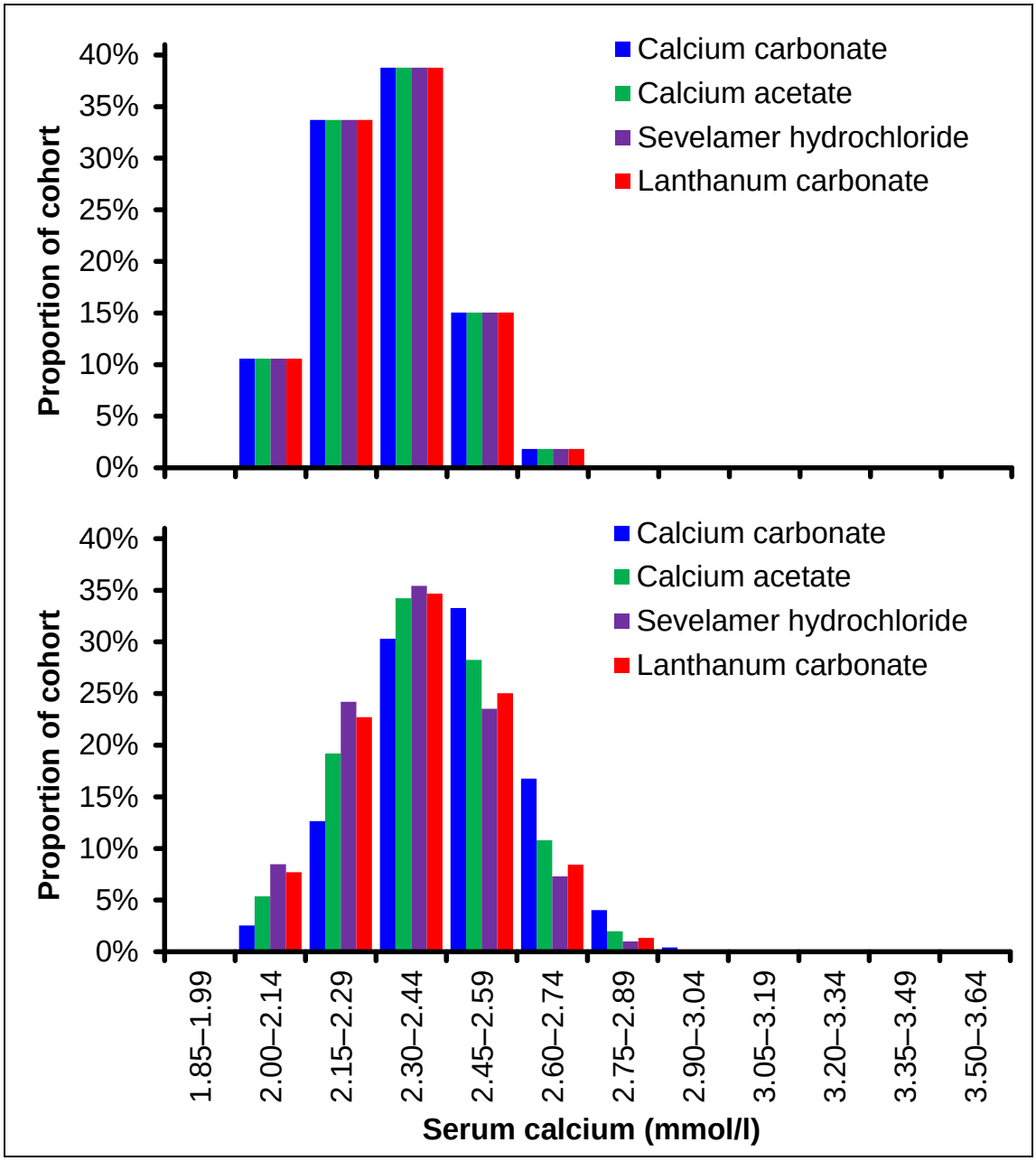


Figure 5: Simulated serum calcium distribution at baseline (top) and at 1 year (bottom)

Based on the simulated distributions, the model estimated the proportions of people in each cohort whose phosphate levels were 1.78 mmol/L or higher (that is, outside the target range) at 1 year, and found these proportions to be very similar to those reported in published trials (Table 17). Calcium acetate appears to be better at controlling serum phosphate when compared with the other alternatives.

Table 17: Modelled serum phosphate and serum calcium levels

Binder	Serum phosphate (mmol/l)				Serum calcium (mmol/l)		
	Baseline	1 year	≥1.78 at 1 year	Empirical*	Baseline	1 year	≥2.54 at 1 year
Calcium carbonate	2.29	1.69	42.9%	38.5%	2.32	2.43	33.5%
Calcium acetate	2.29	1.66	40.2%	35.7%	2.32	2.38	23.5%
Sevelamer hydrochloride	2.29	1.72	45.8%	not reported	2.32	2.34	16.1%
Lanthanum carbonate	2.29	1.87	59.2%	53.4%	2.32	2.36	19.3%

* pooled proportion of participants reported to be within phosphate target in papers reporting at 1 year's follow-up

As expected, the simulated proportions of people with calcium levels of 2.54 mmol/l or higher favours the non-calcium binders (sevelamer hydrochloride in particular, as shown in Table 17). The effectiveness trials do not typically report the proportion of participants within calcium target at specified follow-up intervals in the same way as seen for serum phosphate. For this reason, it was not possible to compare modelled with observed data in the same way as above. Some trials report people experiencing hypercalcaemia as an adverse event, with a variety of definitions adopted. The proportion of modelled patients with serum calcium levels above target provides a fair reflection of the **relative** incidence of such empirical events (most events in calcium carbonate, somewhat fewer with calcium acetate, substantially less with non-calcium binders), though **absolute** numbers are much higher in the model. In view of the different events being compared, this is an unsurprising finding.

Clinical outcomes

Modelled survival, average per-person incidence of fractures and cardiovascular events and probability of progression to renal transplantation and parathyroidectomy for the 4 phosphate binders are shown in Table 18.

Table 18: Predicted outcomes by phosphate-binding agent over lifetime

Binder	Overall survival		Lifetime fractures	Lifetime CV* events	% Receiving transplantation	% Requiring parathyroidectomy
	Mean	Median				
Calcium carbonate	7.071	3.770	0.017	0.390	18.0%	5.2%
Calcium acetate	7.341	3.988	0.018	0.402	18.9%	5.2%
Sevelamer hydrochloride	7.596	4.138	0.018	0.412	19.8%	5.5%
Lanthanum carbonate	7.304	3.942	0.019	0.397	18.8%	5.7%

* Cardiovascular events

Clinical outcomes are relatively similar for all 4 phosphate binders.

Longest mean survival is observed in people receiving non-calcium binders, sevelamer hydrochloride in particular. The incidence of other events (fractures, cardiovascular events, parathyroidectomy) is predominantly associated with expected survival – that is, the longer individual patients live, the greater the probability of experiencing such events.

Modelled survival curves (Figure 6) show that there are small differences between the binders. Calcium carbonate is associated with shortest overall survival, and sevelamer hydrochloride the longest, with calcium acetate and lanthanum carbonate sharing a very similar profile between the two. When extended follow-up is shown (Figure 7), it can be seen that all treatments appear to result in prolonged survival for a proportion of patients. This reflects the part of the cohort that receives transplantation, which is associated with substantially greater survival than remaining on dialysis.

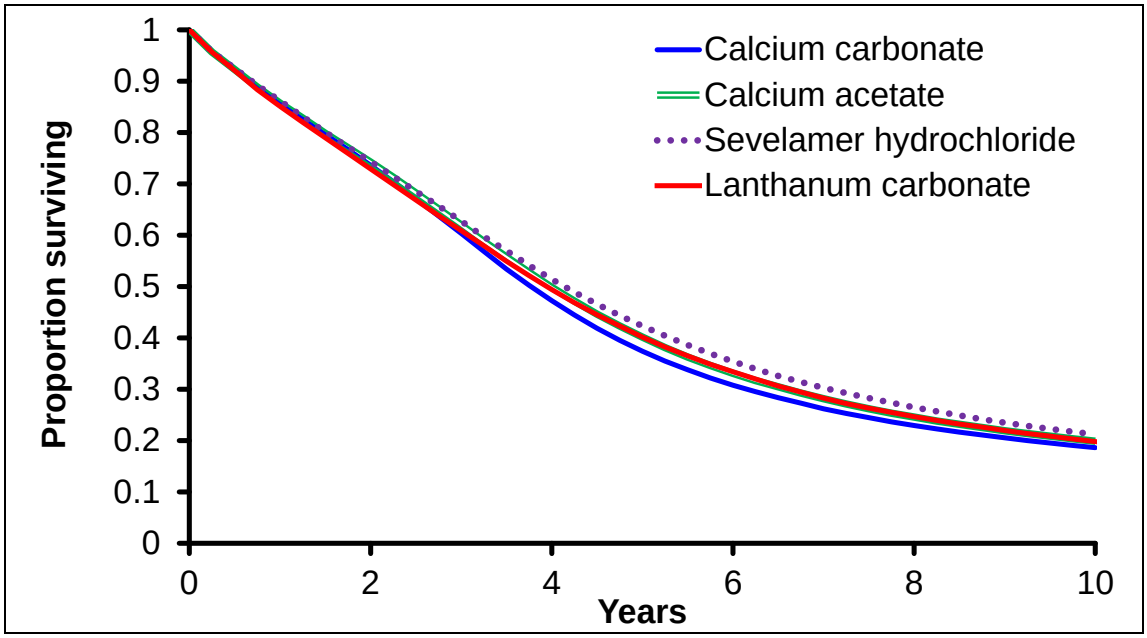


Figure 6: Modelled survival curves (first 10 years)

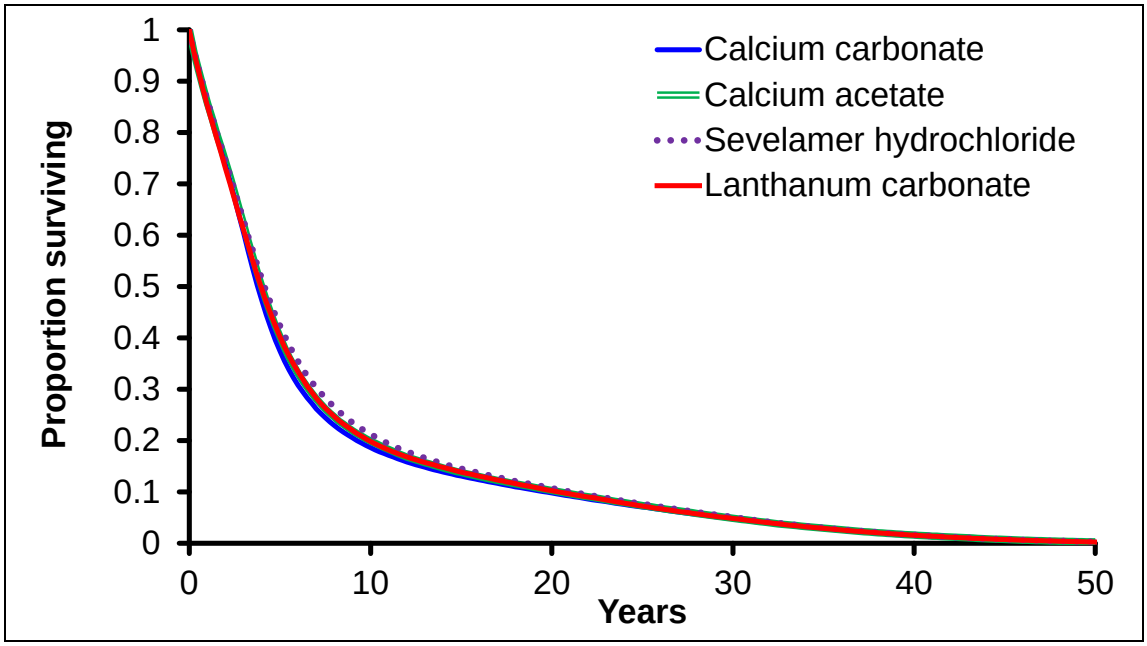


Figure 7: Modelled survival curves (50-year follow-up)

Modelled survival can be compared with that observed in head-to-head trials to explore model validity. Very few trials report mortality data; the best source is the long-term follow-up reported by Suki et al. (2007) of a trial comparing sevelamer hydrochloride with calcium-based binders. There is excellent agreement between modelled survival and the empirical data, both in absolute and relative terms (Figure 8). An advantage for people treated with sevelamer hydrochloride begins to become apparent at around 2 years' follow-up and widens somewhat thereafter. The comparator arm of the RCT comprised participants taking a mixture of calcium-based phosphate binders; however, their survival experience is most comparable with the calcium carbonate arm of the model – those taking calcium acetate are simulated to experience somewhat superior survival. The hazard ratio for overall survival between the sevelamer hydrochloride arm and the calcium carbonate arm of the model is 0.937; this compares very well with the reported hazard ratio of 0.93 in the trial.

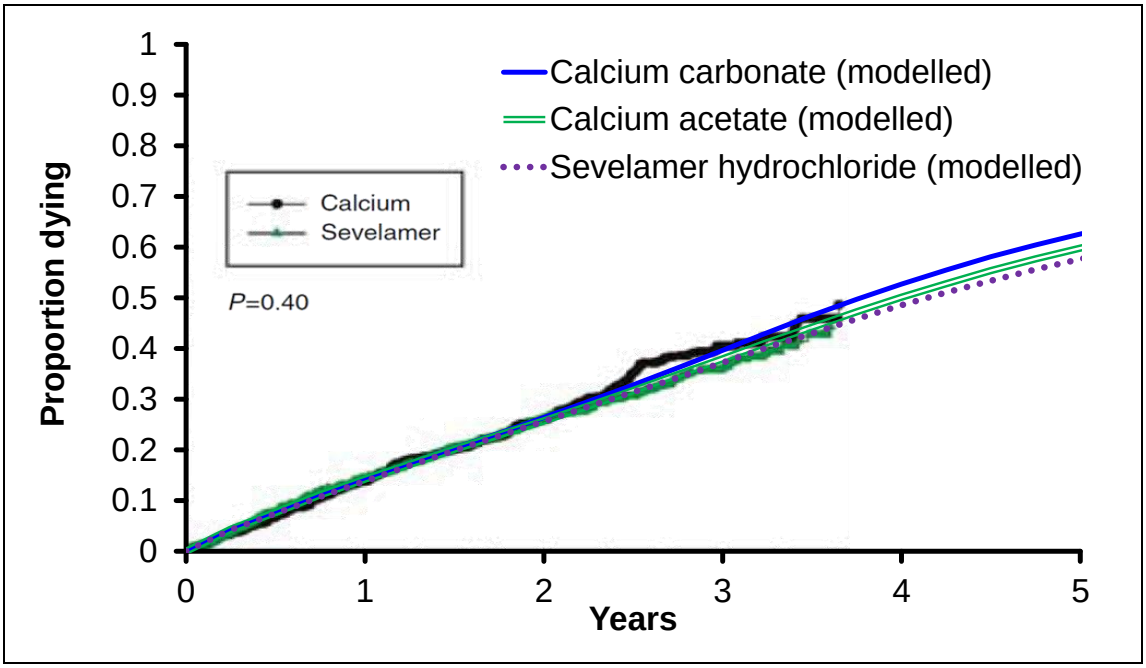


Figure 8: Modelled survival curves – observed survival data from Suki et al. (2007) overlaid

We also attempted to compare modelled survival with that reported in long-term follow-up of a trial comparing lanthanum carbonate with other binders (Wilson et al. 2009, reporting extended follow-up from the RCT reported by Finn et al., 2006). However, the differences, here, were too great. In particular, trial participants were very much younger (mean age 54) than those modelled (mean age 64.8), with the result that absolute overall survival was longer in both trial arms. In this instance, the findings in Wilson et al. suggest that a (small, statistically non-significant) benefit in favour of lanthanum carbonate was apparent from the earliest stages of follow-up. Our model does not replicate this finding; it instead shows a small benefit for lanthanum carbonate compared with calcium carbonate emerging only after around 3 years' follow-up. In this respect, it may be important that we were unable to include data on the serum phosphate profile of people in this trial in the synthesis underpinning our modelled treatment effect (see the full guideline, section 3.5.2).

Table 19 shows the predicted lifetime incidence of adverse events associated with different phosphate-binding treatments.

Table 19: Average lifetime episodes of adverse events

Binder	Diarrhoea	Constipation	Nausea/vomiting	Upper abdominal pain
Calcium carbonate	0.731	0.337	1.809	0.154
Calcium acetate	0.664	0.481	1.605	1.191
Sevelamer hydrochloride	0.612	0.748	2.068	0.380
Lanthanum carbonate	0.623	0.524	1.321	0.302

Cost–utility results: base case

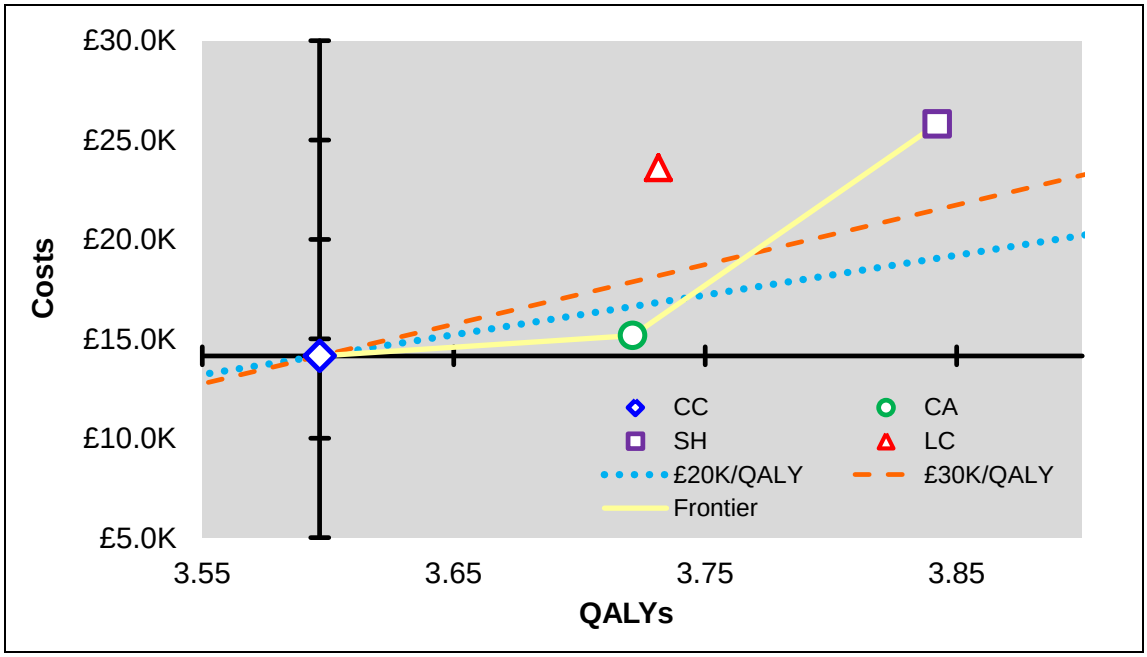
In its base case (Table 20), the economic model suggests that calcium acetate provides good value for money compared with calcium carbonate, providing an average health gain of one-eighth of a QALY at an additional cost of just over £1000, equating to an ICER of around £8000 per QALY gained.

Table 20: Results for first-line use

	Discounted		Incremental		
Binder	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
Calcium carbonate	£14,151	3.597			
Calcium acetate	£15,171	3.721	£1020	0.124	£8197
Lanthanum carbonate	£23,615	3.731	extendedly dominated		
Sevelamer hydrochloride	£25,823	3.842	£10,652	0.121	£87,916

Sevelamer hydrochloride was found to be the most effective treatment; however, the additional health gains predicted, when compared with calcium acetate, come at a cost of almost £90,000 per QALY. The simulated cohort receiving lanthanum carbonate accrued marginally greater health gains than the cohort receiving calcium acetate, but at a much higher cost. It is said to be extendedly dominated, in this analysis, which indicates that – regardless of the assumed maximum acceptable ICER threshold – better value can be achieved by using calcium acetate and/or sevelamer hydrochloride.

Figure 9 illustrates these results on the cost–utility plane.



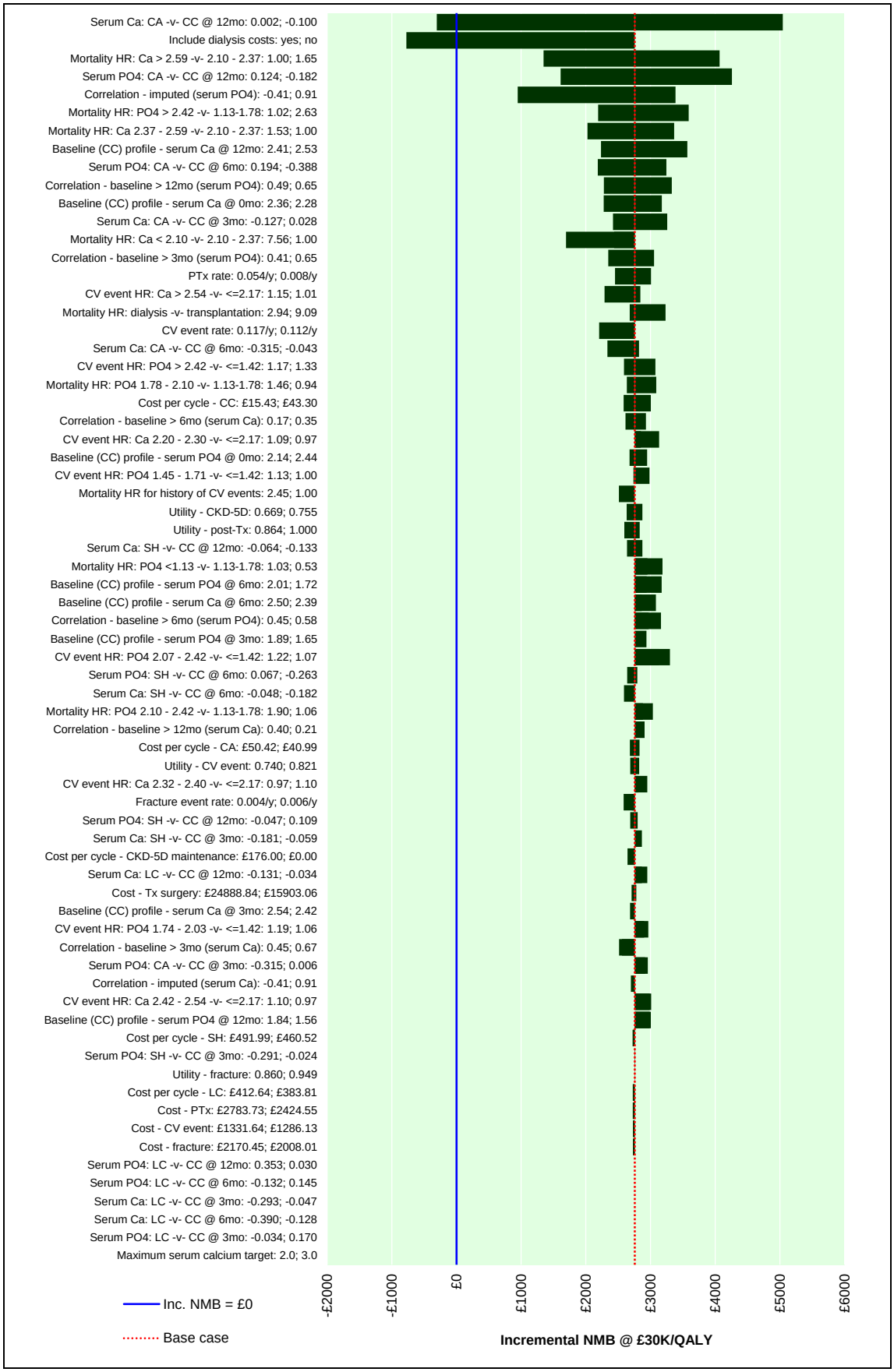
148 **Figure 9: Cost–utility plane for first-line use**

149 ## *Sensitivity analysis*

150 ### One-way sensitivity analysis

151 One-way sensitivity analyses were conducted to explore the impact on the
152 results of changing the value of 1 parameter while keeping the value of all
153 other parameters unchanged. It also highlights areas where further
154 exploration of uncertainty may be useful.

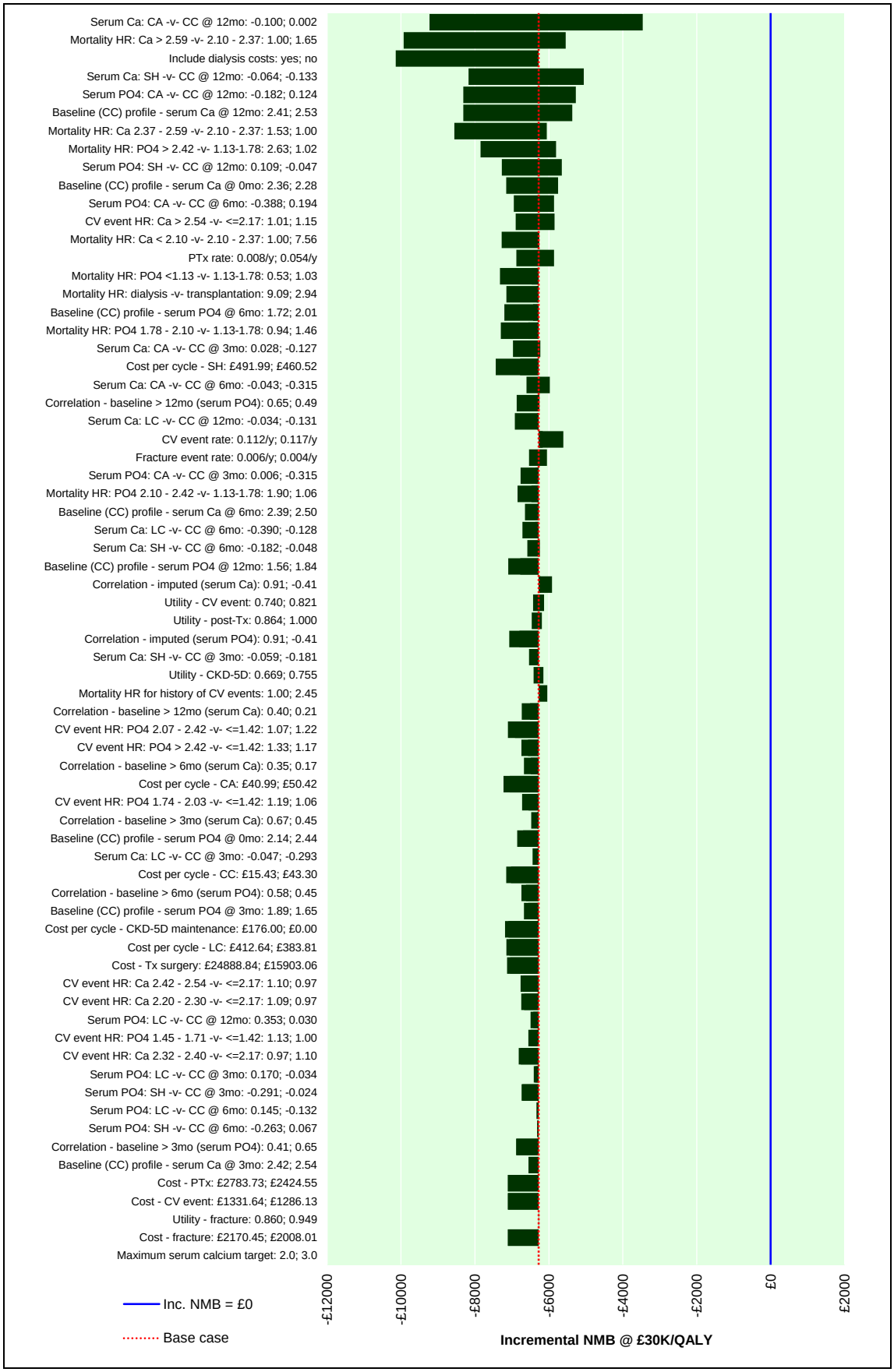
155 As illustrated in Figure 10, calcium acetate remained good value for money
156 compared with calcium carbonate, except when the difference in serum
157 calcium at 12 months was varied so that calcium acetate was associated with
158 higher levels than calcium carbonate (mean difference +0.002 mmol/l,
159 compared with a base-case point estimate of −0.049 mmol/l).



160 **Figure 10 One-way sensitivity analysis: calcium acetate compared with**
161 **calcium carbonate (first line)**

Including dialysis costs in calculations also had an important impact on findings; however, it should be understood that this comes about because time on dialysis is minimised by the inferior survival profile of calcium carbonate (in other words, calcium carbonate looks more cost effective **because** people are dying earlier). Independently varying all other parameters within plausible ranges had no effect on the implied decision.

The finding that sevelamer hydrochloride and lanthanum carbonate are associated with high opportunity costs is entirely robust to individual parameter variations. No variation had a qualitative impact on model results, with all ICERs remaining well above £30,000 per QALY gained. Figure 11 shows results for the comparison between sevelamer hydrochloride and calcium acetate. The comparison between lanthanum carbonate and calcium acetate (not shown) is similarly invariate to parameter alterations, but with even lower estimated incremental net monetary benefit.



176 **Figure 11 One-way sensitivity analysis: sevelamer hydrochloride**
177 **compared with calcium acetate (first line)**

Results: Sequential use

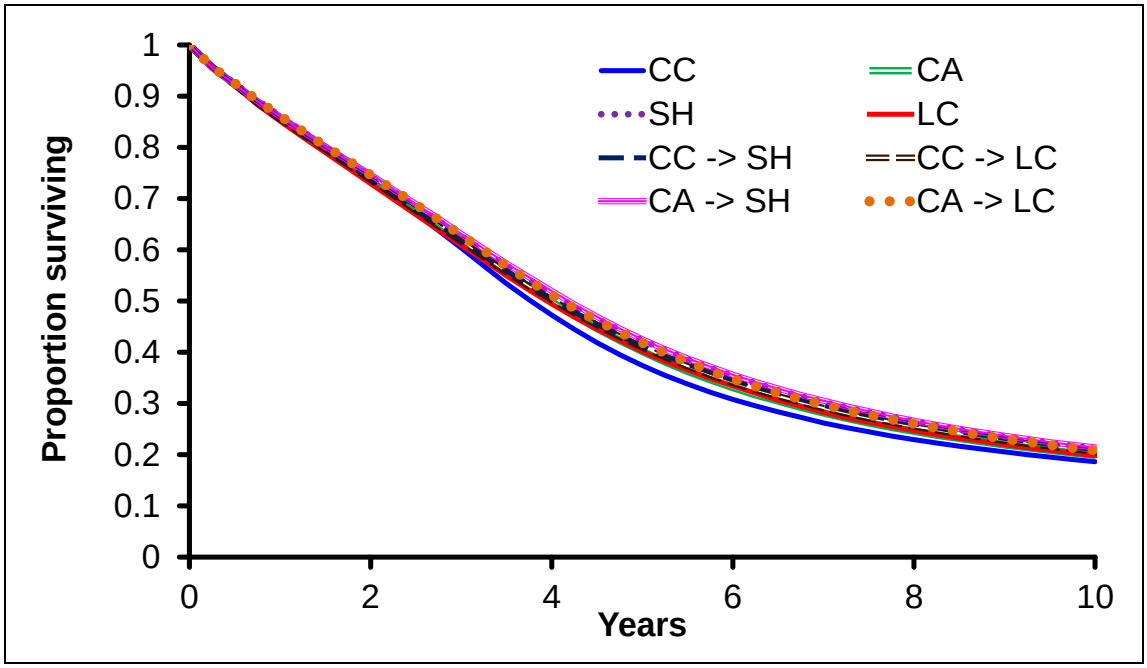
Model outputs

Clinical outcomes

Modelled survival, average per-person incidence of fractures and cardiovascular events and probability of progression to renal transplantation and parathyroidectomy for the 8 modelled strategies are shown in Table 21.

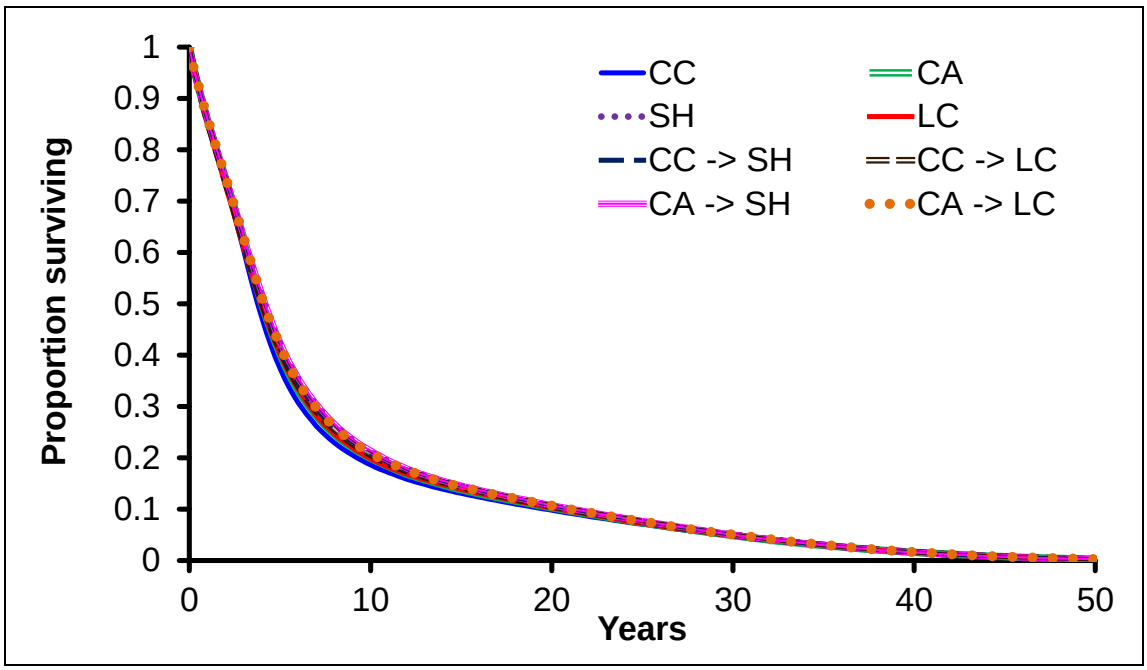
As in the first-line setting, clinical outcomes are relatively similar for all modelled approaches. Longest mean survival is observed in people receiving calcium acetate and/or sevelamer hydrochloride. The incidence of other events (fractures, cardiovascular events, parathyroidectomy) is predominantly associated with expected survival – that is, the longer individual patients live, the greater the probability of experiencing such events.

Modelled survival curves (Figure 12) show small differences. Indefinite calcium carbonate therapy is clearly associated with somewhat reduced overall survival; however, the differences between the other treatments appear small.



195 **Figure 12: Modelled overall survival – first 10 years**

196



197 **Figure 13: Modelled overall survival – 50 years' follow-up**

Table 21: Survival and other events of interest

Sequence	Overall survival		Lifetime fractures	Lifetime CV* events	% Receiving transplantation	% Requiring parathyroidectomy
	Mean	Median				
Calcium carbonate (no switch)	7.071	3.770	0.017	0.390	18.0%	5.2%
Calcium acetate (no switch)	7.341	3.988	0.018	0.402	18.9%	5.2%
Sevelamer hydrochloride (no switch)	7.596	4.138	0.018	0.412	19.8%	5.5%
Lanthanum carbonate (no switch)	7.304	3.942	0.019	0.397	18.8%	5.7%
Calcium carbonate → Sevelamer hydrochloride	7.510	4.040	0.018	0.409	19.6%	5.4%
Calcium carbonate → Lanthanum carbonate	7.460	4.019	0.018	0.406	19.3%	5.5%
Calcium acetate → Sevelamer hydrochloride	7.620	4.186	0.019	0.415	19.9%	5.4%
Calcium acetate → Lanthanum carbonate	7.549	4.114	0.017	0.410	19.6%	5.4%

* Cardiovascular

Cost–utility results: base case

Base-case cost–utility results for the sequential treatment scenarios are tabulated in Table 22. Figure 14 illustrates these results on the cost–utility plane.

Table 22: Cost–utility results for sequential use

Binder sequence	Discounted		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
Calcium carbonate (no switch)	£14,151	3.597			
Calcium acetate (no switch)	£15,171	3.721	£1020	0.124	£8197
Calcium acetate → Lanthanum carbonate	£18,965	3.810	extendedly dominated		
Calcium carbonate → Lanthanum carbonate	£19,124	3.765	dominated		
Calcium acetate → Sevelamer hydrochloride	£19,856	3.844	£4684	0.123	£38,078
Calcium carbonate → Sevelamer hydrochloride	£20,132	3.798	dominated		
Lanthanum carbonate (no switch)	£23,615	3.731	dominated		
Sevelamer hydrochloride (no switch)	£25,823	3.842	dominated		

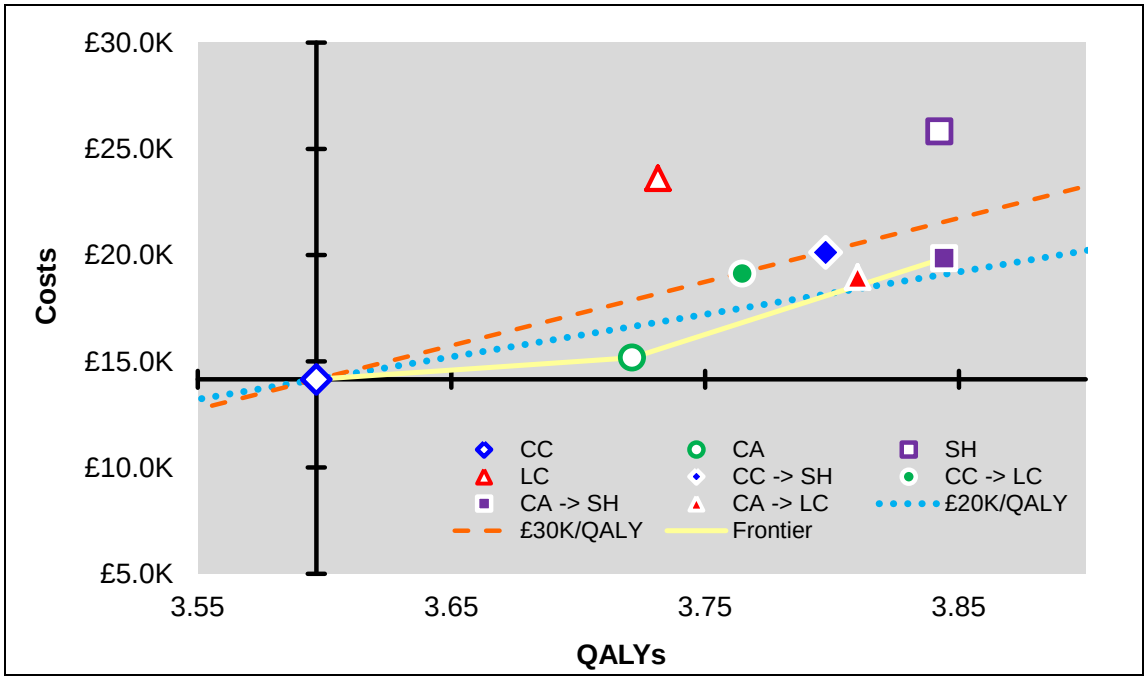


Figure 14: Cost-utility plane for sequential use

As in the first-line-only setting, reliance on calcium acetate as an initial binder appears to provide good value for money, tending to provide conspicuously greater QALY gains than calcium carbonate as an initial binder, at a net cost that is either modestly increased or reduced.

If remaining on calcium acetate indefinitely is considered a clinically appropriate option, it may be hard to justify switching to a non-calcium binder, even in people with raised serum calcium. This is because, although switching strategies are associated with QALY gains, the extra acquisition costs of the non-calcium binders make the opportunity cost of adopting them represent an ineffective use of NHS resources (the ICER for the best-value alternative – switching from calcium acetate to sevelamer hydrochloride – approaches £40,000 per QALY gained). The extremely high ICER estimated for first-line sevelamer hydrochloride, compared with a strategy starting with calcium acetate and switching to sevelamer hydrochloride, suggests that very nearly all the benefit of sevelamer hydrochloride is preserved by reserving it for people with hypercalcaemia, where the benefit comes at a much reduced cost.

For patients who are unable to tolerate calcium acetate, the cost effectiveness of switching to non-calcium binders should be judged against the only plausible alternative, which is indefinite treatment with calcium carbonate. Because calcium carbonate is a less effective choice than calcium acetate, this comparison is more favourable to the calcium-free alternatives, with ICERs in the range of £20,000–£30,000 per QALY.

If calcium-based binders are considered to be fundamentally contraindicated in any individual case, the only remaining options are sevelamer hydrochloride and lanthanum carbonate. The relative cost effectiveness of strategies switching from calcium-based binders to either of these is difficult to distinguish. Although the model estimates an ICER of £26,090 for the comparison between the two, this is based on small differences in costs and QALYs, and it is notable that the 2 options have similar ICERs compared with a common baseline of indefinite calcium acetate treatment (£38,078 per QALY gained for switching to sevelamer hydrochloride and £42,683 per QALY gained for switching to lanthanum carbonate). Accordingly, if either treatment is considered acceptable value for money, it is very likely that the other would have to be judged similarly.

Sensitivity analysis

One-way deterministic sensitivity analysis

In one-way sensitivity analysis, very few alterations to individual model parameters affected the apparent superiority of indefinite calcium acetate therapy when compared with strategies that transferred people to a non-calcium binder when their serum calcium reached a given threshold. Assuming a cost–utility threshold of £20,000 per QALY, no parameter alterations made a difference to results in the comparison of first-line calcium acetate followed by a switch to sevelamer hydrochloride with indefinite calcium acetate (incremental net monetary benefit less than zero in all cases).

When the threshold was raised to £30,000 per QALY, 3 parameters appeared important (see Figure 15 and Figure 16):

- When the effectiveness of calcium acetate (serum calcium level at 12 months) was reduced, this resulted in improved cost-effectiveness for switching strategies. When calcium acetate was assumed to be no better than calcium carbonate at controlling serum calcium, the ICER for calcium acetate → sevelamer hydrochloride compared with indefinite calcium acetate was £26,157 per QALY. Unsurprisingly, this finding is consistent with the comparison between indefinite calcium carbonate and switching from calcium carbonate to a calcium-free alternative.
- Similarly, when the effectiveness of calcium-free binders was increased, this resulted in improved cost effectiveness for strategies switching to them. In particular, the mean difference in serum calcium level at 12 months for non-calcium binders compared with calcium carbonate was important. If it is assumed that the true values of these parameters are at the lower bounds of the 95% credibility intervals estimated in the network meta-analysis (−0.133 mmol/l for sevelamer hydrochloride; −0.131 mmol/l for lanthanum carbonate), the ICER for either switching strategy compared with indefinite calcium acetate falls a little below £30,000 per QALY (calcium acetate → sevelamer hydrochloride = £28,122 per QALY; calcium acetate → lanthanum carbonate = £23,933 per QALY).

- Additionally, the impact of hypocalcaemia on mortality proved to be a potentially significant model parameter. The hazard ratio for people with serum calcium lower than 2.10 mmol/l, compared with people with levels of 2.10–2.37 mmol/l, is associated with very significant parameter uncertainty in the source study (Tangri et al. 2011), with a confidence interval spanning from 0.24 to 7.56. When the model was adjusted to adopt the upper end of this range – people with hypocalcaemia experiencing over 7 times the risk of death than those with normal levels – the model estimated that the use of strategies switching to calcium-free binders would be associated with ICERs of less than £30,000 per QALY gained. However, the plausibility of this dramatic hazard may be open to question.

In addition, analyses in which the calcium level at which simulated patients were switched to non-calcium binders was raised from its base-case value of 2.54 mmol/l were associated with some improvement in estimated value for money for switching strategies. However, even when a switching threshold of 3 mmol/l was used, the ICER for calcium acetate → sevelamer hydrochloride compared with indefinite calcium acetate remained slightly above £30,000 per QALY.

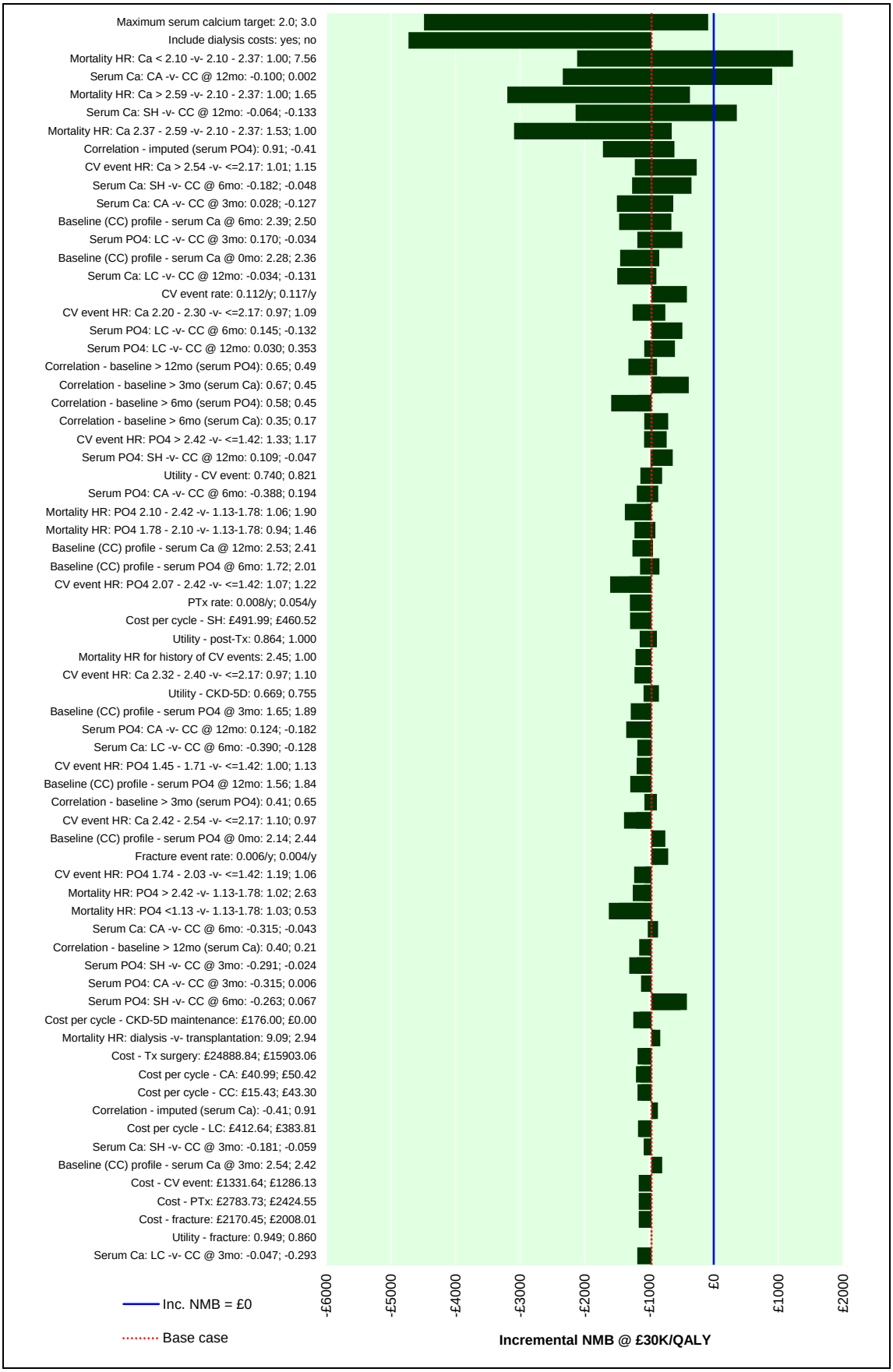


Figure 15 One-way sensitivity analysis: calcium acetate → sevelamer hydrochloride compared with calcium acetate (no switch)

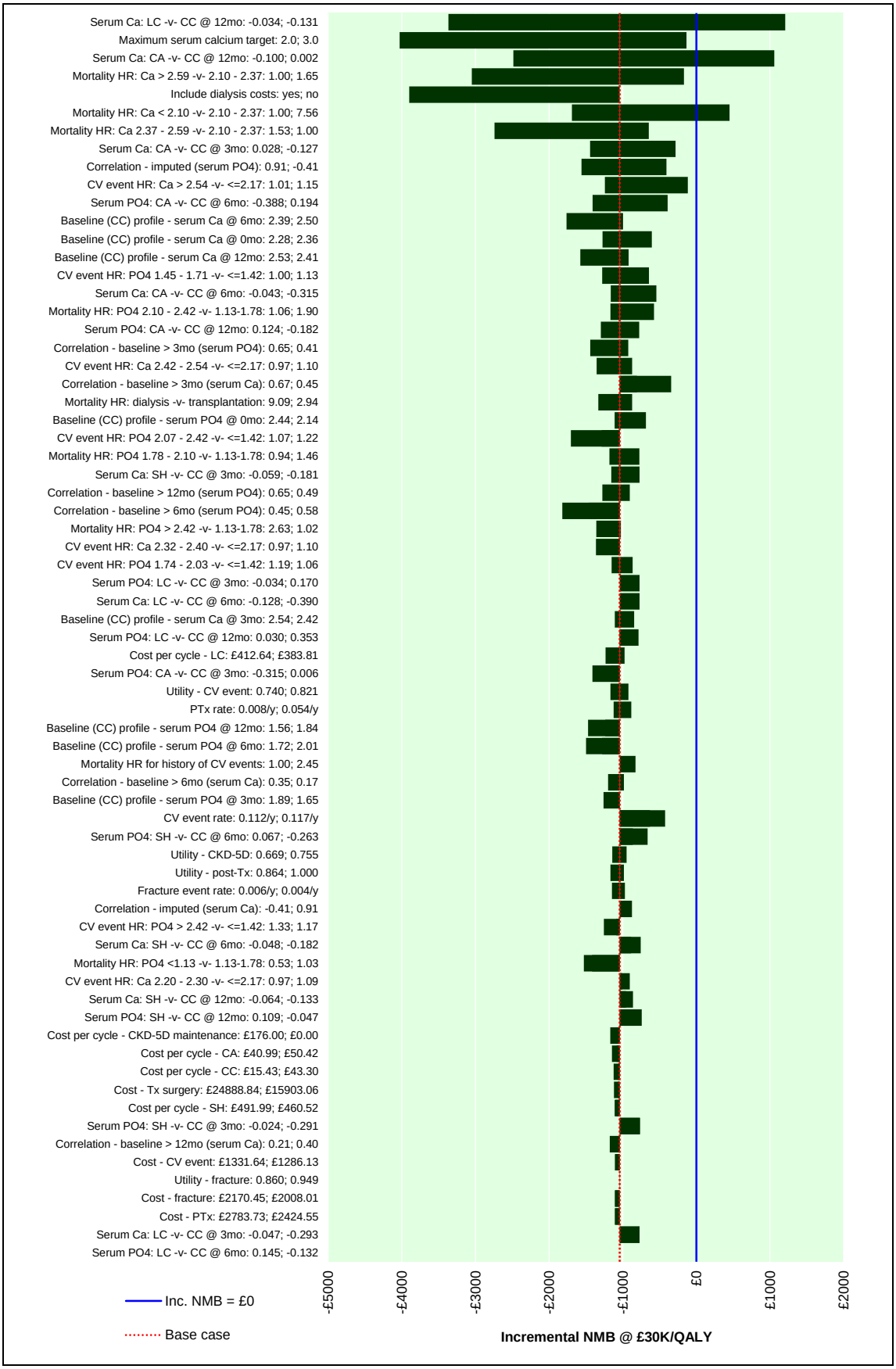


Figure 16 One-way sensitivity analysis: calcium acetate → lanthanum carbonate compared with calcium acetate (no switch)

For the comparison of strategies switching to sevelamer hydrochloride and those switching to lanthanum carbonate, plausible alterations to a large number of parameters result in the apparent superiority of one or other option over the other (Figure 17). This reinforces the view that it is difficult to distinguish between these options from a health-economic perspective. Additional research on the relative effectiveness of the treatments would be necessary, if it is judged worthwhile to establish which is superior.

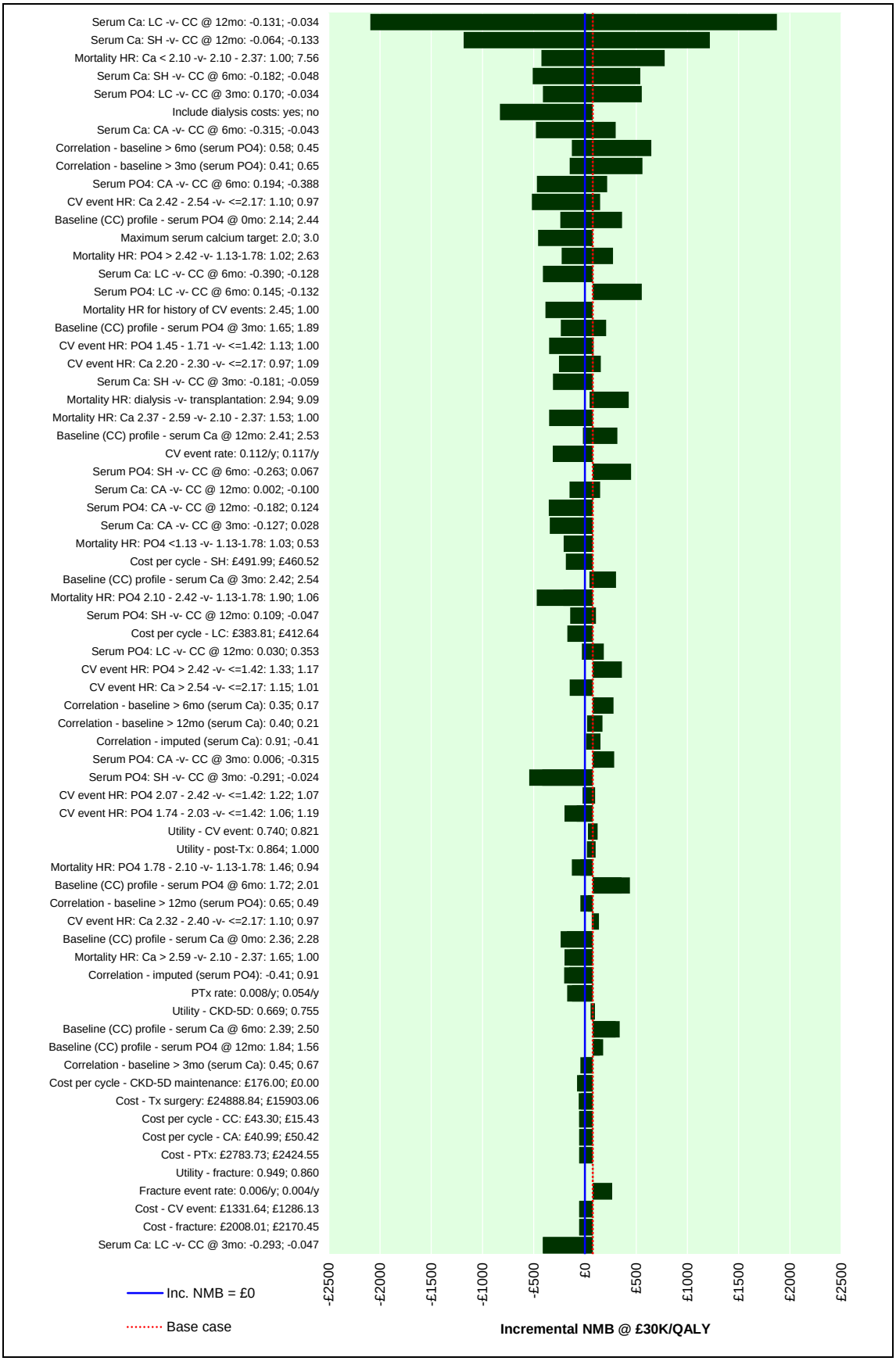


Figure 17 One-way sensitivity analysis: calcium acetate → sevelamer hydrochloride compared with calcium acetate → lanthanum carbonate

Subgroup analysis – patients 65 years or older

Because some evidence has suggested a particular advantage for non-calcium binders in people aged 65 years or older (see full guideline, section 3.5.2), a subgroup analysis was undertaken in which a cohort of people of that age was simulated. Other than limiting the age of the cohort, no model parameters were altered (so the relationship between treatment and serum phosphate and serum calcium remained the same as in the whole population, as did the relationship between these markers and the outcomes of interest). Results are shown in Table 23. Expected QALY gains are much lower, as would be expected; however, in incremental terms, there is very little difference between this analysis and that performed in the whole population, This suggests that either the apparent additional benefit for patients 65 years or older is an artefactual finding or that there are interactions between age, binder assignment, biochemical control and/or event risk that the model fails fully to reflect.

Table 23: Cost–utility results for sequential use – patients 65 years or older

	Discounted		Incremental		
Binder sequence	**Costs (£)**	**Effects (QALYs)**	**Costs (£)**	**Effects (QALYs)**	**ICER (£/QALY)**
Calcium carbonate (no switch)	£3,343	1.643			
Calcium acetate (no switch)	£3,749	1.706	£406	0.063	£6,441
Calcium acetate → Lanthanum carbonate	£5,335	1.742	£1,586	0.036	£43,778
Calcium carbonate → Lanthanum carbonate	£5,344	1.709	dominated		
Calcium acetate → Sevelamer hydrochloride	£5,680	1.749	£345	0.006	£54,193
Calcium carbonate → Sevelamer hydrochloride	£5,776	1.723	dominated		
Lanthanum carbonate (no switch)	£8,063	1.678	dominated		
Sevelamer hydrochloride (no switch)	£9,282	1.750	£3,602	0.001	£3,239,076

Discussion

Principal findings

The base-case economic model suggests that calcium acetate, when compared with calcium carbonate, sevelamer hydrochloride and lanthanum

carbonate, is likely to be the preferred first-line phosphate binder for the management of hyperphosphataemia in people with CKD stage 5 who are on dialysis.

When second-line treatment options are taken into account, the most effective strategy is to commence with calcium acetate but switch to sevelamer hydrochloride or lanthanum carbonate if hypercalcaemia develops. However, remaining on calcium acetate remains a viable option from a health-economic perspective, and the switching approaches are associated with substantially increased costs. Therefore, if all simulated strategies are seen as realistic options, it is unlikely that the health gains provided by the more expensive binders are sufficient to counterbalance the extra expense they entail (unless it can be assumed that society's maximum acceptable ICER threshold is approximately £40,000 per QALY). There may be an exception to this conclusion for people who are unable to tolerate calcium acetate; in this circumstance, switching to sevelamer hydrochloride or lanthanum carbonate in people with hypercalcaemia could be seen as an effective use of resources when compared with the alternative of indefinite treatment with calcium carbonate.

In patients for whom calcium-based binders are considered to be fundamentally contraindicated, the only remaining options are sevelamer hydrochloride and lanthanum carbonate. In these circumstances, either option is likely to be judged acceptable from a health-economic perspective.

Comparison with other cost–utility models

As noted in our systematic review of published economic evaluations of phosphate binders (page 5), no previous analyses have attempted to compare any more than 2 possible approaches. As a result, it is not possible to make direct comparisons between the present model and other published analyses. However, we can compare the pairwise models with the relevant portions of our model.

In our systematic review, only 1 analysis was judged to be both directly applicable to the setting of present interest and subject to only minor internal limitations – Brennan's 2007 pairwise comparison of lanthanum carbonate with calcium carbonate in a second-line setting (see Table 2). This model produced results that are comparable with ours: they estimate an ICER of £25,033 per QALY gained for switching to lanthanum carbonate compared with remaining on calcium carbonate, whereas our model suggests an ICER of £29,619 for the same comparison. Overall QALYs are somewhat higher and overall costs are much higher in both arms of our model than in the Brennan study; however, their model does not include transplantation as a possible event, which explains much of these discrepancies.

Two other models address second-line lanthanum carbonate. The first (Goto et al. 2011) compares switching to lanthanum carbonate with 'conventional treatment' (predominantly calcium carbonate or sevelamer hydrochloride), and produces results that are broadly in line with those of Brennan et al. and the present analysis, though more favourable to lanthanum carbonate (giving an ICER of £23,632 per QALY gained). The second (Vegter et al. 2011) is more favourable still, with an ICER in the second-line setting of £6900 per QALY gained. The effectiveness data used in this model are not fully reported, so it is difficult to understand differences in outputs fully. It appears that our model estimates rather greater QALY gains for strategies including lanthanum carbonate; however these come at an even greater incremental cost, with the net result that our ICERs are a good deal higher.

The 3 other models that were identified (Huybrechts et al. 2005, Manns et al. 2007, Taylor et al. 2008) explore first-line use of sevelamer hydrochloride compared with calcium-based binders (predominantly calcium carbonate). They estimate very widely different results (ICERs ranging from £1787 per life-year gained to £150,471 per QALY gained). However, all 3 agree that incremental QALY gains of around 0.2 might be expected from sevelamer hydrochloride, and this is comparable with our estimate (we estimate that first-line sevelamer hydrochloride produces 0.246 more discounted QALYs than calcium carbonate). Differences between model results, therefore, are largely

ascribable to estimated costs. The Manns et al. analysis includes dialysis costs in its base case, which as discussed above is bound to reduce the cost effectiveness of life-prolonging interventions. Huybrechts et al. and Taylor et al. find that the additional cost of the sevelamer hydrochloride itself is largely offset by a reduction in costs of cardiovascular hospitalisations. Our model does not replicate this finding.

No published models use a strategy that relies preferentially on calcium acetate as a comparator. Since our analysis indicates that such an approach is likely to be attractive from a health-economic point of view, we believe it is significant that no one has previously compared a new intervention or strategy to this optimal approach.

Limitations of the analysis

The model has good validity over its first year, accurately reflecting biochemical measures seen in the trials underpinning it. It also makes a relatively good prediction of observed survival with the treatments of interest over the first 3 years of treatment. However, beyond the first year of the model, biochemical profiles are estimated on the basis of extrapolation and simplification and, while this approach had its face validity endorsed by the GDG, it is impossible to tell how well the model fits the (unknown) reality.

It is arguable that, as they extend into the future, the biochemical profiles of occasional simulated patients become implausible (especially as regards modelled serum calcium, which may rise very high in a few instances). However, this is only a problem if it results in implausible effects: if the level of risk that is predicted is realistic, then it does not matter that the value of the predictor may be unlikely. For this reason, it should be remembered that the sole purpose of biochemical parameters in the model is to estimate the risks faced by patients.

The use of serum phosphate and serum calcium alone as determinants of treatment effect is an acknowledged simplification of a highly complex biological interaction. Moreover, it is well known that serum calcium is a

suboptimal index of calcium balance in humans, perhaps especially in those with advanced kidney disease (Houillier et al. 2006). If people who are exposed to excess calcium intake in their phosphate binding regimen are subject to greater risks than can be inferred from their serum calcium levels, the model will underestimate the benefit of switching such people to calcium-free binders.

When simulating second-line treatment for people experiencing hypercalcaemia, the model is necessarily reliant on evidence of the effectiveness of treatments in a broader population. If people with hypercalcaemia respond differently to treatment than people without, it follows that the model over or underestimates the treatment effect that can be achieved in reality; it is possible that different cost–utility conclusions would be reached if more specific evidence were available.

It is a significant weakness of this analysis that it has not proved computationally feasible to undertake full probabilistic sensitivity analysis, to explore the implications of parameter uncertainty for decision-making. A wide range of one-way sensitivity analyses was undertaken; this enables a fair degree of inference on the impact of such 'second-order' uncertainty and, in the light of these analyses, it is possible to state with some confidence that the options identified as optimal in the base-case analysis would be associated with the highest probability of cost effectiveness in a fully probabilistic analysis. However, it is not possible to quantify these probabilities in the absence of such an analysis.

It is possible that the model somewhat underestimates the effectiveness of lanthanum carbonate in both first- and second-line settings, since it was not possible to include data on phosphate control from what is by far the largest and longest trial of the drug in the evidence-base (Finn et al. 2006; see the full guideline, section 3.5.2). It is speculated that, were these data available to incorporate into the analysis, apparent differences between treatments – perhaps especially between sevelamer hydrochloride and lanthanum carbonate in the first-line setting – would be somewhat reduced. However, the

use of lanthanum carbonate would still be associated with a very high ICER compared with calcium acetate. An additional gain of at least 0.3 QALYs would be necessary to counterbalance the costs estimated here, assuming conventional cost–utility thresholds, and there is no evidence that an underestimate of such magnitude is plausible.

It is regrettable that there was insufficient evidence to provide a worthwhile model for people in CKD stages 4 and 5 who have not yet commenced dialysis, and for children at any stage of disease. There was also insufficient evidence to perform any meaningful modelling to support a recommendation on aluminium hydroxide, magnesium carbonate or sevelamer carbonate.

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Any errors that remain are the responsibility of the developers.

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Appendix F1: Systematic review of prognostic studies

Methods

We performed a systematic review of prognostic studies assessing the relationship between serum phosphate and serum calcium and the following: death, cardiovascular events, fractures, kidney failure and parathyroidectomy in people with CKD. The review generally adhered to the methods stipulated in The guidelines manual 2009'. Where non-standard methods were used or there were deviations from the manual, details are provided under the specific review question.

Inclusion and exclusion criteria

Studies were included or excluded from the review with regard to the criteria listed in Table 24 below.

Table 24: Inclusion and exclusion criteria

	Inclusion	Exclusion
Prognostic factor	• serum phosphate and serum calcium	• surrogate of a surrogate • not phosphate and calcium
Outcome	• mortality, cardio-vascular events, kidney failure, parathyroidectomy or fractures	• not mortality, parathyroidectomy, cardiovascular events, kidney failure or fractures
Population	• CKD stage 4 or 5 (pre-dialysis) • CKD stage 5 on dialysis	• not CKD stage 4 or 5 • renal transplant recipient
Study design	• cohort (retrospective & prospective)	• review article, case report, case control, commentary, editorial
Measure of effect	• hazard ratios, relative risks or odds ratios	• not hazard ratios, relative risks or odds ratios
Analysis	• Multivariate	• Univariate

Search strategy

Electronic databases were searched for cost-effectiveness and cost-utility analyses by an information specialist. The databases searched and the full search strategy is provided below. Bibliographies of articles were also searched.

Identification of studies

Abstracts returned by the search strategy were examined by a single researcher and screened for inclusion or exclusion using 'Rev-Pal'. Full texts were obtained and assessed for inclusion or exclusion. Articles that did not clearly meet the inclusion and exclusion criteria were included or excluded after discussion with a senior researcher.

Quality appraisal

The methodology checklist for prognostic studies which is set out in 'The guidelines manual 2009' was used to determine whether the included studies provide evidence that is useful to inform the decision-making of the GDG.

Data extraction

We extracted information on the type of study design, participants, prognostic factor (exposure), measure of effect, type of analysis, and covariates, together with the outcomes of mortality, cardiovascular events, kidney failure, and parathyroidectomy. We extracted the sample size, and the adjusted hazard ratio or relative risk per unit baseline serum levels of phosphate and calcium (1 mg/dL) where both biochemical markers were reported and analysed in the same multivariate model. In instances where the hazard ratios were reported for ranges (categories with upper and lower bounds) of serum phosphate and serum calcium exposure, we assigned the midpoint of each range, as the exposure (level of serum phosphorous) that corresponds to the reported relative risk as described in the study by Palmer et al. (2011). We then used these category-specific estimates of risk to derive relative risk estimates per unit increase in exposure – using methods described by Hartemink et al. – if

these data were reported. This method assumes that the relationship between the relative risk of an outcome and the exposure are approximately linear.

A meta-analysis was not conducted because it would be inappropriate to pool estimates from various multivariate models which have adjusted for different variables. So we appraised the evidence systematically and selected the most appropriate study(s): ones with a population that most closely matches that of the UK, that report data in the most useful way, or that are the most powerful (based on sample size and number of events).

Results

The searches returned 1699 separate references. From the screening of abstracts, 1554 were excluded, leaving 145 potentially relevant studies to be reviewed in full. After examining the full texts, 109 papers were excluded, and a total of 36 studies were included for this review. Results and characteristics of the included studies are summarized in Table 25 to Table 33 below.

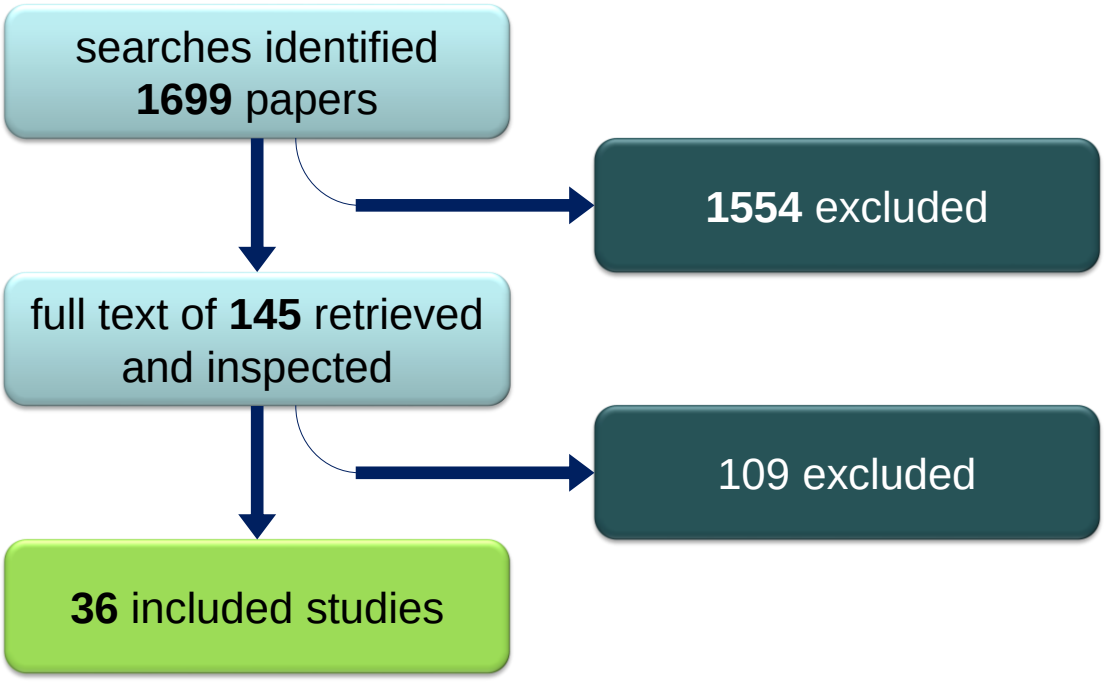

Table 25: Relative risk of death (all cause) predicted by PO4– and Ca2+ in CKD stage 5 on dialysis

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Block GA (1998)	6407	1.06 (1.06–1.06)	1.1–4.5 4.4–5.5 5.6–6.5 6.6–7.8 7.9–16.9	1.0 (0.87–1.13) 1. (Ref) 1.02 (0.88–1.18) 1.18 (1.02–1.38) 1.39 (1.20–1.61)		3.7–8.6 8.7–9.1 9.2–9.5 9.6–10.1 10.2–17.5	0.96 (0.75–1.18) 1.05 (0.87–1.23) 1 (Ref) 0.95 (0.75–1.10) 0.91 (0.71–1.10)
Block GA (2004)	40538		<3 3–4 4–5 5–6 6–7 7–8 8–9 >9	1.10 (0.98–1.24) 1.00 (0.93–1.08) 1.00 (ref) 1.07 (1.01–1.14) 1.26 (1.18–1.33) 1.43 (1.32–1.54) 1.68 (1.52–1.86) 2.02 (1.79–2.27)		<8 8.0–8.5 8.5–9.0 9.0–9.5 9.5–10.0 10.0–10.5 10.5–11.0 >11	0.72 (0.66–0.78) 0.80 (0.75–0.86) 0.89 (0.84–0.94) 1.00 (ref) 1.06 (0.99–1.13) 1.15 (1.06–1.24) 1.27 (1.13–1.42) 1.41 (1.17–1.70)
Block GA (2004)	19186		<3 3–5 5–6 6–7 7–8 >8	1.06 (0.85–1.33) 1 (Ref) 1.07 (0.98–1.16) 1.15 (1.04–1.27) 1.23 (1.07–1.41) 1.44 (1.25–1.66)		<9.0 9.0–10.2 >10.2	0.94 (0.80–1.10) 1 (Ref) 1.14 (1.04–1.24)
Bradbury BD (2007)	4802	0.99 (0.95–1.04)	<3.5 3.5–5.5 >5.5	1.34 (1.05–1.70) 1 (Ref) 1.15 (0.96–1.36)	1.16 (1.07–1.26)	<8.4 8.4–9.5 >9.5	0.85 (0.66–1.09) 1 (Ref) 1.18 (1.05–1.57)
Danese MD (2008)	22937		3.5–5.5 >5.5	1 (Ref)[a] 1.20 (1.10–1.30)[b]		8.4–9.5 >9.5	1 (Ref)[c] 1.21 (1.13–34)[d]
Floege J (2011)	7970		<3.5 3.5–5.5 5.5	1.18 (1.01–1.37) 1.0 (Ref) 1.32 (1.13–1.55)		<8.4 8.4–9.5 9.5–11.0 >11.0	0.98 (0.83–1.16) 1.00 (Ref) 1.05 (0.90–1.22) 1.70 (1.19–2.42)
Foley RN (1996)	433		<6.0 >6.0	1 (Ref) 0.96		<8 >8	1.74 1 (Ref)
Iseki K (1996)	1982	0.97				1.068	
Jadoul M (2007)	538		≤4.5 >4.5	1.00 (Ref) 1.11		≤9.5 >9.5	1.00 (Ref) 1.16

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Kalantar-Zadeh K (2006)	58058		<3 3.0–3.99 4.0–4.99 5.0–5.99 6.0–6.99 7.0–7.99 8.0–8.99 >9	1.3 (1.2–1.6) 0.90 (0.70–1.10) 0.95 (0.8–1.20) 1 (Ref) 1.25 (1.15–1.35) 1.35 (1.25–1.45) 1.5 (1.1.3–1.7) 1.9 (1.55–2.25)		<8 8.0–8.49 8.5–8.99 9.0–9.49 9.5–9.99 10.0–10.49 10.5–10.99 >11.0	0.99 (0.85–1.13) 0.90 (0.84–0.96) 0.92 (0.88–0.96) 1 (Ref) 1.04 (0.99–1.09) 1.10 (1.05–1.15) 1.30 (1.20–1.40) 1.38 (1.22–1.54)
Kimata N (2007)	5041	1.00 (0.94–1.07)	<3.5 3.5–4.5 4.5–5.5 5.5–6.5 >6.5	1.61 1.21 1.0 (Ref) 1.05 1.33	1.22 (1.09–1.36)	<8.4 8.4–9.0 9.0–9.5 9.5–10.4 >10.4	0.90 1.00 (Ref) 0.98 1.12 1.53
Lacson E Jr (2009)	78420	1.18 (1.13–1.23)	≤3.5 3.51–4.0 4.01–4.5 4.51–5.0 5.01–5.5 5.51–6.0 6.01–6.5 6.51–7.0 7.01–7.5 7.51–8.0 8.01–8.5 8.51–9.5 >9.5	0.80 0.75 0.74 0.80 1 (Ref) 1.10 1.30 1.40 1.50 1.50 2.00 2.00 2.70	1.14 (1.11–1.18)	≤8.0 8.01–8.5 8.51–9.0 9.01–9.5 9.51–10.0 10.01–10.5 10.51–11 >11	0.80 0.85 1.0 1.0 (Ref) 1.10 1.25 1.30 1.40
Lowrie EG (1992)	13535		<2 2–3 3–5 5–7 7–9 9–11 >11	2.40 1.60 0.80 1 (Ref) 1.50 2.40 3.70		<6 6–7 7–8 8–9 9–10 10–12 >12	0.45 0.60 0.80 0.75 1 (Ref) 1.3 3.25
Maeno Y (2009)	635	1.43 (0.88–2.33)			1.07 (0.32–3.58)		
Matos JP (2011)	3082	1.06 (1.00–1.12)			1.03 (0.97–1.10)		

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Melamed ML (2006)	1007		<4.3 1.04 (0.70–1.53) 4.3–5.1 1.0 (Ref) 5.1–6.0 1.01 (0.69–1.47) >6.0 1.54 (1.01–2.53)		<8.97 0.92 (0.60–1.39) 8.97–9.33 1.0 (Ref) 9.33–9.73 1.13 (0.78–1.64) >9.73 1.05 (0.69–1.62)
Nakai S (2008)	27404	1.08 (1.06–1.10)	<3 1.142 (0.990–1.316) 3.0–3.9 1.102 (0.999–1.215) 4.0–4.9 1.000 (Ref) 5.0–5.9 1.105 (1.017–1.202) 6.0–6.9 1.172 (1.065–1.289) 7.0–7.9 1.425 (1.265–1.605) 8.0–8.9 1.893 (1.620–2.213) >9 1.985 (1.621–2.432)	1.05 (1.02–1.08)	<7 1.008 (0.835–1.217) 7.0–7.9 1.067 (0.879–1.296) 8.0–8.9 0.992 (0.916–1.074) 9.0–9.9 1.000 (Ref) 10.0–10.9 1.098 (1.020–1.182) >10 1.243 (1.113–1.388)
Naves-Diaz M (2011)	16173		<3 1.70 (0.90–2.50) 3.0–4.0 1.25 (0.95–1.25) 4.0–5.0 1.15 (0.95–1.35) 5.0–5.5 1 (Ref) 5.5–6.5 1.30 (1.09–1.51) 6.5–7.5 1.04 (1.05–1.75) >7.5 2.30 (1.30–3.30)		<8.0 3.9 (2.06–5.20) 8.5–9.0 1.6 (1.40–1.80) 9.0–9.5 1.30 (1.10–1.50) 9.5–10.5 1 (Ref) 10.5–11 1.35 (1.10–1.60) >11 1.75 (1.25–2.25)
Noordzij M (2005)	1629		HD <3.5 0.7 (0.5–1.1) 3.5–5.5 1.0 (Ref) >5.5 1.4 (1.1–1.7)		HD <8.4 1.3 (0.7–2.4) 8.4–9.5 1.0 (Ref) >9.5 1.0 (0.8–1.4)
			PD <3.5 0.8 (0.4–1.7) 3.5–5.5 1.0 (Ref) >5.5 1.6 (1.1–2.4)		PD <8.4 1.4 (0.5–4.2) 8.4–9.5 1.0 (Ref) >9.5 0.9 (0.6–1.4)
Rodriguez-Benot A (2005)	385	1.26 (1.08–1.46)	<3 0.41 (0.05–3.17) 3–5 1 (Ref) 5.01–6.5 1.94 (1.17–3.19) >6.5 2.02 (1.10–3.73)	0.96 (0.93–0.99)	
Slinin Y (2005)	14829		≤4.4 1 (Ref) 4.5–5.3 1.02 (0.96–1.09) 5.4–6.3 1.02 (0.96–1.08) 6.4–7.5 1.10 (1.04–1.17) >7.5 1.19 (1.12–1.27)		≤8.7 1 (Ref) 8.8–9.2 1.07 (1.01–1.14) 9.3–9.6 1.05 (0.99–1.12) 9.7–10.2 1.11 (1.04–1.18) >10.2 1.14 (1.07–1.21)

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Stevens LA (2004)	515	1.56 (1.15–2.12)	<5.5 5.5–6.0 6.0–7.0 >7.0	1 (Ref) 1.32 (0.79–2.22) 1.53 (1.02–2.30) 1.82 (1.16–2.84)	1.35 (0.61–2.98)	<10 10.0–10.2 10.2–10.6 >10.6	1 (Ref) 1.15 (0.62–2.13) 0.98 (0.52–1.82) 1.33 (0.79–2.25)
Tangri N (2011)	7076		<3.5 3.5–5.5 5.5–6.5 6.5–7.5 >7.5	0.74 (0.53–1.03) 1 (Ref) 1.17 (0.94–1.46) 1.42 (1.06–1.90) 1.64 (1.02–2.63)		<8.4 8.4–9.5 9.5–10.4 >10.4	1.35 (0.24–7.56) 1 (Ref) 1.13 (0.83–1.53) 1.35 (0.93–1.65)
Tentori F (2008)	25588		<3.6 3.6–5.0 5.1–6.0 6.1–7.0 >7.0	1.06 (0.94–1.10) 1 (Ref) 1.02 (0.94–1.01) 1.18 (1.08–1.28) 1.43 (1.32–1.56)		<8.6 8.6–10.0 >10.0	1.02 (0.94–1.10) 1 (Ref) 1.16 (1.08–1.25
Wald R (2008)	1846		≤3 3.1–4.0 4.1–5.0 5.1–6.0 >6	0.98 (0.71–1.36) 1.07 (0.84–1.35) 1 (Ref) 1.04 (0.84–1.28) 1.24 (1.03–1.51)		≤8 8.1–9.0 9.1–10.0 10.1–11.0 >11	1.09 (0.83–1.44) 1.04 (0.88–1.23) 1 (Ref) 0.96 (0.79–1.16) 1.15 (0.84–1.56)
Young EW (2005)	17236	1.04 (1.02–1.06)	<2.5 2.5–3.0 3.0–3.5 3.5–4.0 4.0–4.5 4.5–5.0 5.0–5.5 5.5–6.0 6.0–6.5 6.5–7.0 >7.0	1.6 1.2 1.23 1.08 1.01 1 (Ref) 1.12 1.06 1.15 1.28 1.35	1.10 (1.06–1.15)	<7.8 7.8–8.4 8.4–9.0 9.0–9.5 9.5–9.9 9.9–10.4 10.4–10.9 10.9–11.4 >11.4	0.66 1.04 0.98 1 (Ref) 1.03 1.11 1.14 1.18 1.22

[a] KDOQI recommended target for serum phosphate.
[b] Hazard ratio for serum phosphate outside KDOQI target.
[c] KDOQI recommended target for serum calcium.
[d] Hazard ratio for serum calcium outside KDOQI target.

Table 26: Relative risk of death (all cause) predicted by PO4– and Ca2+ in CKD stages 4 and 5 pre-dialysis

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Bellasi A (2011)	1716		<3.3 0.47 (0.43–1.28) 3.3–3.7 1 (Ref) 3.8–4.2 0.64 (0.36–1.14) >4.2 2.49 (1.44–4.32)	1.01 (0.78–1.31)	
Kestenbaum B (2006)	6730	1.23 (1.12–1.36)	<2.5 0.95 (0.69–1.32) 2.5–2.999 1 (Ref) 3.0–3.499 1.15 (0.95–1.39) 3.5–3.999 1.32 (1.09–1.61) 4.0–4.499 1.34 (1.05–1.71) 4.5–4.999 1.83 (1.33–2.51) >5.0 1.90 (1.30–2.79)	1.02 (0.90–1.16)	
Kovesdy CP (2008)	515	1.65 (1.30–2.09) per standard deviation		1.10 (0.89–1.35) per standard deviation	
Levin A (2008)	4231	1.02 (1.01–1.04)		NS; variable eliminated from final model	
Voormolen N (2007)	448	1.62 (1.02–2.58)		1.32 (0.69–2.52)	

Table 27: Relative risk of Parathyroidectomy predicted by PO4– and Ca2+ in CKD–5D

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Jorna FH (2004)	202	1.107[a] (1.035–1.184)	≤5.73[b] 1 (Ref) >5.73[b] 2.63 (1.22–5.26)		≤9.86[c] 1 (Ref) >9.86[c] 3.23 (1.19–8.23)
Slinin Y (2007)	10588		≤4.4 1 (Ref) 4.5–5.3 1.34 (0.89–2.01) 5.4–6.3 2.07 (1.43–2.98) 6.4–7.5 2.17 (1.52–3.11) >7.5 2.92 (2.06–4.15)		≤8.7 1 (Ref) 8.8–9.2 1.73 (1.20–2.49) 9.3–9.6 2.60 (1.84–3.66) 9.7–10.3 3.38 (2.41–4.73) >10.3 5.09 (3.64–7.10)
Young EW (2005)	17236	1.17 (1.09–1.25)		1.58 (1.35–1.85)	

[a] Hazard ratio per 0.1 mmol/L increase.
[b] converted from mmol/L to mg/dl using conversion factor of (*3.0974).
[c] converted from mmol/L to mg/dl using conversion factor of (*4.008).

Table 28: Relative risk of end-stage renal failure predicted by PO4– and Ca2+ in CKD stages 4 and 5 pre-dialysis

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Levin A (2008)	4231	1.019[a] (1.010–1.029)		NS; excluded from final model	
Schwarz S (2006)	985	1.29 (1.12–1.48)	<3.3 1 (Ref) 3.3–3.8 0.83 (0.54–1.27) 3.81–4.3 1.24 (0.82–1.88) >4.3 1.60 (1.06–2.41)	0.80 (0.63–1.02)	<9.1 1 (Ref) 9.1–9.4 0.88 (0.61–1.25) 9.41–9.7 0.89 (0.62–1.68) >9.7 0.80 (0.63–1.02)
Staples AO (2010)	4166		Normal[b] 1 (Ref) High[b] 1.41 (1.25–1.59)		<8.5 1.29 (1.06–1.58) ≥8.5 1 (Ref)
Tangri N (2011)	8391	1.34 (CI not provided)		0.82 (CI not provided)	
Bellasi A (2011)	1716		<3.3 0.61 (0.30–1.24) 3.3–3.7 1 (Ref) 3.8–4.2 1.36 (0.84–2.18) >4.2 2.88 (1.77–4.67)	0.75 (0.61–0.92)	

[a] per 0.1mg/dl increase.
[b] the definition of hyperphosphataemia was adjusted for age as follows: ≥6.5mg/dl for 2 to 5 years; ≥5.8 for 6 to 12 years; ≥4.5 for 13 to 20 years.

Table 29: Relative risk of fractures predicted by PO4– and Ca2+ (both CKD populations)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Block GA (2004)	40538	1.12 (1.03–1.22)			

Table 30: Relative risk of a cardiac event predicted by PO4– and Ca2+ (CKD stage 5 on dialysis)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Block GA (2004)	40538		4–5 1 (Ref)		

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
			5–6 1.10 6–7 1.15 7–8 1.29 8–9 1.28 >9 1.38		
Foley RN (1996)	433				New IHD[a] 4.33[b] Recurrent IHD[a] 7.05[b] New CF[c] 2.43[b] Recurrent CF[c] 2.66[b]
Wald R (2008)	1846		Reported composite endpoint of all-cause death and first cardiac hospitalisation		
Slinin Y (2005)	14829		≤4.4 1 (Ref) 4.5–5.3 1.06 (1.00–1.13) 5.4–6.3 1.13 (1.06–1.19) 6.4–7.7 1.14 (1.07–1.22) >7.5 1.25 (1.17–1.33)		≤8.7 1 (Ref) 8.8–9.2 1.03 (0.97–1.09) 9.3–9.6 1.04 (0.97–1.10) 9.7–10.2 1.03 (0.97–1.10) >10.2 1.08 (1.01–1.15)

[a] Ischemic Heart Disease.
[b] Relative risk of death associated with calcium ≤8.8mg/dl compared with calcium >8.8.
[c] cardiac failure.

Table 31: Relative risk of a cardiac event predicted by PO4– and Ca2+ (CKD stages 4 and 5 pre-dialysis)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Kestenbaum B (2006)	6730	1.35 (1.09–1.67)			

Table 32: Prognostic studies CKD stage 5 on dialysis

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Block GA (1998)	USA	6407	Retrospective cohort	2	Cox proportional hazards model	Data was obtained from 2 USRDS (US Renal Data System) special studies; the CMAS (Case mix Adequacy Studies) and the DMMS (Dialysis Morbidity and Mortality Study) wave 1. Both studies represent a random national sample of prevalent HD patients in the US	Y	N	Y	Y	Y	Y
Block GA (2004)	USA	40538	Retrospective cohort	2	Cox proportional hazards model	Sample taken from the Fresenius Medical Care North America Patient Statistical Profile system	Y	?	Y	Y	Y	Y
Block GA (2004)	USA	19186	Retrospective cohort	2	Time dependent cox proportional hazards	Data from DaVita (a large dialysis provider) were merged with data from the USRDS	Y	?	Y	Y	Y	Y
Bradbury BD (2007)	USA	4802	Retrospective cohort using incident cases	not stated (study lasted for 8 years)	Cox proportional hazards	Data from DOPPS phase 1 and 2	?	Y	N	Y	Y	Y
Danese MD (2008)	USA	22937	Retrospective cohort using incident cases	2	Time dependent cox proportional hazards	Fresenius Medicare database Lexington MA	Y	?	Y	Y	Y	Y
Floege J (2011)	12 European countries including UK	7970	Retrospective cohort	2	Baseline and time dependent cox proportional hazards	Data obtained from participating European Fresenius medical care (EU-FME) dialysis facilities from 11 countries including the UK	Y	?	?	Y	Y	Y
Foley RN (1996)	Canada	433	Prospective cohort	3.5	Cox proportional hazards model	Patients enrolled from 2 hospitals in Canada	Y	?	?	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Iseki K (1996)	Japan	1982	Retrospective cohort	not stated (data collected over a period of 20 years)	Cox proportional hazards model	Data obtained from OKIDS registry in japan	Y	?	?	Y	N	Y
Jadoul M (2007)	Belgium	538	Retrospective analysis of DOPPS phase 2 data	2	Cox proportional hazards model	Data obtained from DOPPS 2 study	Y	?	?	?	N	Y
Jorna FH (2004)	Netherlands	202	Retrospective cohort	3.5	Cox proportional hazards model	Data obtained from a dialysis centre in the Netherlands	Y	?	?	Y	Y	Y
Kalantar-Zadeh K (2006)	USA	58058	Retrospective cohort	2	Time dependent and fixed covariate cox regression models	Obtained historical data on all HD patients from all DaVita dialysis facilities in the US	Y	?	Y	Y	Y	Y
Kimata N (2007)	Japan	5041	Prospective cohort	5	Cox proportional hazards model	Data derived from 2 studies; the phase 1 and phase 2 DOPPS	Y	?	?	Y	Y	Y
Lacson E Jr (2009)	USA	78420	Retrospective cohort	1	Cox proportional hazards model	Data obtained from the knowledge centre (Fresenius medical care)	Y	?	Y	Y	Y	Y
Lowrie EG (1992)	USA	13535	Retrospective analysis of previously published data	1	Logistic regression models	Sample consisted of patients on HD from National medical care affiliated dialysis facilities in 1989	Y	?	?	Y	N	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Maeno Y (2009)	Japan	635	Prospective cohort	4.5	Kaplan–Meir and cox proportional hazard models	Participants sampled from a hospital kidney centre in Japan	Y	Y	Y	Y	Y	Y
Matos JP (2011)	Brazil	3082	Retrospective cohort	5	Kaplan–Meir and cox proportional hazard models	All incident patients on HD at all centres franchised by Fresenius medical care in Brazil	Y	?	?	Y	Y	Y
Melamed ML (2006)	USA	1007	Prospective cohort	2.5	Cox proportional hazards model	HD and PD patients from the CHOICE (choices for healthy outcomes in caring for ESRD)	Y	?	?	Y	Y	Y
Nakai S (2008)	Japan	27404	Retrospective cohort	3	Cox proportional hazards model	Data obtained from the Japanese society for dialysis therapy registry	Y	?	?	Y	Y	Y
Naves-Diaz M (2011)	Argentina, Brazil, Colombia, Argentina, Chile, Mexico and Venezuela	16173	Retrospective cohort	1.3	Cox proportional hazards model	Data from 6 Latin American countries in 183 different dialysis facilities associated with or operated by Fresenius medical care in the CORES study	Y	?	?	Y	Y	Y
Noordzij M (2005)	Netherlands	1629	Prospective multicentre cohort	7	Multivariate cox regression models	All incident patients in 38 dialysis units in the NECOSAD (Netherlands cooperative study on the adequacy of dialysis) study, Netherlands	Y	?	Y	Y	Y	Y
Rodriguez-Benot A (2005)	Spain	385	Prospective cohort	11	Cox proportional hazards model	Patients were recruited from HD centres participating in a dialysis program (specific details not provided) over 11 years. Mean FU and number of centres not provided	Y	?	Y	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Slinin Y (2005)	USA	14829	Retrospective cohort	3.9	Cox regression	Data was obtained from the USRDS waves 1, 2, 3 and 4 studies (Dialysis morbidity and mortality study) a historical cohort study of dialysis patients from over 1300 randomly sampled dialysis units in the US	Y	?	?	Y	Y	Y
Slinin Y (2007)	USA	10588	Retrospective cohort	3.6	Cox regression	Data was obtained from the USRDS waves 1, 2, 3 and 4 above was linked to Medicare claims data to identify associations of parathyroidectomy. Patients without a unique USRDS ID number or DOB, or who died before the study start date or were not covered by Medicare insurance were further excluded from the initial sample of 16,733	Y	Y	N	Y	Y	Y
Stevens LA (2004)	Canada	515	Retrospective cohort	2.6	Cox proportional hazards model	Data obtained from the British Columbia renal agency provincial database – PROMIS (patient registration, outcome and management information system) – which is routinely collected for administration purposes	Y	Y	Y	Y	Y	Y
Tangri N (2011)	UK	7076	Retrospective cohort	2	cox proportional hazards model	UK renal registry	Y	?	Y	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Tentori F (2008)	UK, France, Germany, Japan, USA, Spain, Italy, Australia, Canada, New Zealand, Belgium, Sweden	25588	Prospective cohort	1.4	Cox proportional hazards model	Used data from DOPPS 1, 2 and 3 from a total of 12 countries	Y	?	Y	Y	Y	Y
Wald R (2008)	USA	1846	Retrospective cohort	4.48	Cox proportional hazard model exploring baseline–time dependent and cumulative time dependent associations of biochemical markers	Used data from the HEMO study (RCT)	Y	?	?	Y	Y	Y
Young EW (2005)	UK, France, Germany, Italy, Spain, USA and Japan	17236	Prospective cohort	variable	Cox proportional hazards model	Study conducted as part of DOPPS 1 which comprised of participants from randomly selected representative samples of haemodialysis facilities across 7 countries: UK, USA, Japan, France, Germany, Italy and Spain	Y	?	Y	Y	Y	Y

Table 33: Prognostic studies CKD stages 4 and 5 pre-dialysis

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Bellasi A (2011)	Italy	1716	Retrospective cohort	3	Cox proportional hazards model	Data was obtained from the patient records of a large renal database (PIRP) sponsored by the Emilia-Romagna Health Institute, Italy	Y	?	?	Y	?	Y
Kestenbaum B (2006)	USA	6730	Retrospective cohort	2.1	Cox proportional hazards model	Data was obtained from 8 veteran affairs medical centres	Y	?	N	Y	Y	Y
Kovesdy CP (2008)	USA	515	Retrospective cohort	2.3	Cox proportional hazards model	Data was obtained from Salem veteran affairs medical centre CA	N	?	?	Y	Y	Y
Levin A (2008)	Canada	4231	Retrospective cohort	4	Cox proportional hazards model	Data was obtained from the patients' registration and outcomes management information system (PROMIS) database, which captures all nephrology referrals	Y	Y	?	Y	Y	Y
Schwarz S (2006)	USA	985	Retrospective cohort	2.1	Cox proportional hazards model	Data was obtained from Salem veteran affairs medical centre CA	Y	?	Y	Y	N	Y
Staples AO (2010)	USA	4166	Retrospective cohort	not stated	Kaplan–Meier analysis and Cox proportional hazards model. In addition, the definition of hyperphosphataemia was adjusted for age as follows: ≥6.5mg/dl for 2 to 5 years; ≥5.8 for 6 to 12 years; ≥4.5 for 13 to 20 years	Data was obtained from the NAPRTCS database; details not provided	Y	?	?	Y	?	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Tangri N (2011)	Canada	8391	Prospective cohort	2	Series of 7 Cox proportional hazards models analysed using metrics of discrimination (c-statistic) and goodness of fit (Akaike information criteria – AIC)	The 'development' cohort derived from the nephrology clinic electronic health record at Sunnybrook hospital (a part of the university of Toronto health network). The 'validation' cohort was derived from the British Columbia renal registry (patient registration and outcome management information services)	Y	?	Y	Y	N	Y
Voormolen N (2007)	Netherlands	448	Retrospective cohort	1	Linear regression and Cox proportional hazards regression	Data was obtained from CKD stage 4 and 5 patients attending outpatient clinics of 8 hospitals.	Y	Y	?	Y	N	Y

Y = Yes (low risk of bias); N = (High risk of bias); ? = Unclear (uncertain risk)

Prognosis Search terms and data bases

Database: Ovid MEDLINE(R) <1946 to January Week 4 2012>
Searched 2nd February 2012
Search Strategy:
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1 exp Renal Insufficiency, Chronic/ (72342)
2 ckd.tw. (6037)
3 ((chronic or progress*) adj1 kidney disease*).tw. (11246)
4 ((chronic or progress*) adj1 renal disease*).tw. (3643)
5 ((chronic or progress*) adj1 kidney failure).tw. (934)
6 ((chronic or progress*) adj1 renal failure).tw. (20273)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (796)
8 (end-stage renal or endstage renal or end stage renal).tw. (20741)
9 ((renal or kidney*) adj3 insufficien*).tw. (17610)
10 or/1-9 (103926)
11 exp Renal Dialysis/ (83839)
12 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (21765)
13 (haemodialys* or hemodialys*).tw. (49589)
14 or/11-13 (96208)
15 10 or 14 (157541)
16 Hyperphosphatemia/ (445)
17 hyperphosphat*.tw. (2817)
18 Phosphates/ (50176)
19 (phosphate* or phosphorus).tw. (196706)
20 or/16-19 (221029)
21 exp risk/ (691239)
22 exp Regression Analysis/ (234698)
23 hazard ratio*.tw. (26796)
24 (proportional adj3 hazard*).tw. (22009)
25 (relative adj3 risk).tw. (40262)
26 (cox adj3 model*).tw. (17427)
27 (regression or survival).tw. (721422)
28 exp Survival Analysis/ (143979)
29 Prognosis/ (311994)
30 prognos*.tw. (290710)
31 or/21-30 (1710738)
32 exp Mortality/ (241619)
33 mortality.tw. (359627)
34 exp Cardiovascular Diseases/mo [Mortality] (83622)
35 Death, Sudden, Cardiac/ (9318)
36 Coronary Artery Disease/ (29528)
37 ((Cardiovascular or cv* or cardiac or heart or valvular or coronary) adj3 (disease* or event* or death*)).tw. (271418)
38 (myocardial infarction* or MI or heart attack*).tw. (124520)
39 exp Vascular Calcification/ (63)
40 (vascular adj3 calcificat*).tw. (1885)
41 Fractures, Bone/ (42935)
42 fracture*.tw. (140512)

43 ((time or need or progress* or requir*) adj3 (rrt or renal replacement or dialys* or transplant* or kidney failure* or renal failure*)).tw. (21115)
44 exp Disease progression/ (94983)
45 or/32-44 (1097358)
46 15 and 20 and 31 and 45 (900)
47 Animals/ not Humans/ (3556824)
48 46 not 47 (885)
49 limit 48 to english language (789)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 01, 2012>
Searched 2nd February 2012
Search Strategy:
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1 exp Renal Insufficiency, Chronic/ (0)
2 ckd.tw. (683)
3 ((chronic or progress*) adj1 kidney disease*).tw. (1151)
4 ((chronic or progress*) adj1 renal disease*).tw. (122)
5 ((chronic or progress*) adj1 kidney failure).tw. (16)
6 ((chronic or progress*) adj1 renal failure).tw. (461)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (58)
8 (end-stage renal or endstage renal or end stage renal).tw. (955)
9 ((renal or kidney*) adj3 insufficien*).tw. (433)
10 or/1-9 (2884)
11 exp Renal Dialysis/ (0)
12 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (607)
13 (haemodialys* or hemodialys*).tw. (1685)
14 or/11-13 (2077)
15 10 or 14 (4310)
16 Hyperphosphatemia/ (0)
17 hyperphosphat*.tw. (110)
18 Phosphates/ (0)
19 (phosphate* or phosphorus).tw. (11517)
20 or/16-19 (11558)
21 exp risk/ (0)
22 exp Regression Analysis/ (0)
23 hazard ratio*.tw. (1748)
24 (proportional adj3 hazard*).tw. (1096)
25 (relative adj3 risk).tw. (1149)
26 (cox adj3 model*).tw. (982)
27 (regression or survival).tw. (35730)
28 exp Survival Analysis/ (0)
29 Prognosis/ (0)
30 prognos*.tw. (12489)
31 or/21-30 (45615)
32 exp Mortality/ (0)
33 mortality.tw. (18145)
34 exp Cardiovascular Diseases/mo [Mortality] (0)

35 Death, Sudden, Cardiac/ (0)
36 Coronary Artery Disease/ (0)
37 ((Cardiovascular or cv* or cardiac or heart or valvular or coronary) adj3 (disease* or event* or death*)).tw. (12388)
38 (myocardial infarction* or MI or heart attack*).tw. (4595)
39 exp Vascular Calcification/ (0)
40 (vascular adj3 calcificat*).tw. (157)
41 Fractures, Bone/ (0)
42 fracture*.tw. (8563)
43 ((time or need or progress* or requir*) adj3 (rrt or renal replacement or dialys* or transplant* or kidney failure* or renal failure*)).tw. (830)
44 exp Disease progression/ (0)
45 or/32-44 (40143)
46 15 and 20 and 31 and 45 (29)
47 Animals/ not Humans/ (0)
48 46 not 47 (29)
49 limit 48 to english language (26)

Database: Embase <1980 to 2012 Week 04>
Searched 3rd February 2012
Search Strategy:
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1 chronic kidney disease/ (17757)
2 ckd.tw. (9425)
3 ((chronic or progress*) adj1 kidney disease*).tw. (16162)
4 ((chronic or progress*) adj1 renal disease*).tw. (4373)
5 ((chronic or progress*) adj1 kidney failure).tw. (1071)
6 ((chronic or progress*) adj1 renal failure).tw. (24174)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (1077)
8 (end-stage renal or endstage renal or end stage renal).tw. (25901)
9 ((renal or kidney*) adj3 insufficien*).tw. (21240)
10 or/1-9 (90715)
11 exp dialysis/ (38268)
12 exp renal replacement therapy/ (111243)
13 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (25518)
14 (haemodialys* or hemodialys*).tw. (59992)
15 or/11-14 (147875)
16 hyperphosphatemia/ (3488)
17 hyperphosphat*.tw. (3470)
18 phosphate/ (58409)
19 (phosphate* or phosphorus).tw. (218257)
20 Phosphate intake/ (871)
21 Phosphate blood level/ (6353)
22 Phosphorus/ (48317)
23 or/16-22 (266141)
24 10 or 15 (206143)
25 risk/ or risk assessment/ or risk benefit analysis/ or risk factor/ or risk management/ or risk reduction/ (902646)

26 exp regression analysis/ (166256)
27 hazard ratio*.tw. (35151)
28 (proportional adj3 hazard*).tw. (28669)
29 (relative adj3 risk).tw. (46422)
30 (cox adj3 model*).tw. (23878)
31 (regression or survival).tw. (893088)
32 exp survival/ (422394)
33 prognosis/ (363940)
34 prognos*.tw. (375534)
35 or/25-34 (2157040)
36 exp mortality/ (498606)
37 mortality.tw. (452560)
38 exp cardiovascular disease/ (2438507)
39 Heart death/ (11991)
40 coronary artery disease/ (128398)
41 ((Cardiovascular or cv* or cardiac or heart or valvular or coronary) adj3 (disease* or event* or death*)).tw. (352709)
42 (myocardial infarction* or MI or heart attack*).tw. (160440)
43 blood vessel calcification/ (2191)
44 (vascular adj3 calcificat*).tw. (2464)
45 fracture/ (49227)
46 fracture*.tw. (164870)
47 ((time or need or progress* or requir*) adj3 (rrt or renal replacement or dialys* or transplant* or kidney failure* or renal failure*)).tw. (27881)
48 exp disease course/ (1574605)
49 or/36-48 (4221057)
50 23 and 24 and 35 and 49 (2025)
51 Nonhuman/ not Human/ (3079395)
52 50 not 51 (1998)
53 limit 52 to english language (1792)
54 limit 53 to embase (1614)
55 limit 54 to (conference abstract or conference paper or "conference review") (353)
56 54 not 55 (1261)

Medline, Medline in process and Embase.

Parathyroidectomy

Database: Ovid MEDLINE(R) <1946 to February Week 5 2012>
Searched 12th March 2012
Search Strategy:
---
1 exp Renal Insufficiency, Chronic/ (72891)
2 ckd.tw. (6251)
3 ((chronic or progress*) adj1 kidney disease*).tw. (11611)

4 ((chronic or progress*) adj1 renal disease*).tw. (3665)
5 ((chronic or progress*) adj1 kidney failure).tw. (940)
6 ((chronic or progress*) adj1 renal failure).tw. (20355)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (813)
8 (end-stage renal or endstage renal or end stage renal).tw. (20974)
9 ((renal or kidney*) adj3 insufficien*).tw. (17714)
10 or/1-9 (104869)
11 exp Renal Dialysis/ (84297)
12 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (21896)
13 (haemodialys* or hemodialys*).tw. (49905)
14 or/11-13 (96751)
15 10 or 14 (158763)
16 Hyperphosphatemia/ (465)
17 hyperphosphat*.tw. (2847)
18 Phosphates/ (50470)
19 (phosphate* or phosphorus).tw. (198417)
20 or/16-19 (222861)
21 exp risk/ (699678)
22 exp Regression Analysis/ (238272)
23 hazard ratio*.tw. (27714)
24 (proportional adj3 hazard*).tw. (22452)
25 (relative adj3 risk).tw. (40665)
26 (cox adj3 model*).tw. (17823)
27 (regression or survival).tw. (731771)
28 exp Survival Analysis/ (146323)
29 Prognosis/ (314577)
30 prognos*.tw. (293677)
31 or/21-30 (1731265)
32 Parathyroidectomy/ (3405)
33 parathyroidectom*.tw. (4552)
34 or/32-33 (5780)
35 parathyroid glands/ (9298)
36 parathyroid*.tw. (34911)
37 35 or 36 (37065)
38 Endocrine Surgical Procedures/ (163)
39 General Surgery/ (31212)
40 Surgical Procedures, Operative/ (47136)
41 Surgical Procedures, Minimally Invasive/ (14191)
42 (remov* or surg* or excis* or dissect* or endoscop* or laparoscop*).tw. (1612584)
43 or/38-42 (1648688)
44 37 and 43 (7365)
45 34 or 44 (10259)
46 15 and 20 and 31 and 45 (107)
47 Animals/ not Humans/ (3588944)
48 46 not 47 (102)
49 limit 48 to english language (90)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 09, 2012>
Searched 12th March 2012
Search Strategy:
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1 exp Renal Insufficiency, Chronic/ (0)
2 ckd.tw. (726)
3 ((chronic or progress*) adj1 kidney disease*).tw. (1207)
4 ((chronic or progress*) adj1 renal disease*).tw. (125)
5 ((chronic or progress*) adj1 kidney failure).tw. (16)
6 ((chronic or progress*) adj1 renal failure).tw. (448)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (65)
8 (end-stage renal or endstage renal or end stage renal).tw. (983)
9 ((renal or kidney*) adj3 insufficien*).tw. (408)
10 or/1-9 (2955)
11 exp Renal Dialysis/ (0)
12 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (640)
13 (haemodialys* or hemodialys*).tw. (1665)
14 or/11-13 (2095)
15 10 or 14 (4366)
16 Hyperphosphatemia/ (0)
17 hyperphosphat*.tw. (116)
18 Phosphates/ (0)
19 (phosphate* or phosphorus).tw. (11725)
20 or/16-19 (11767)
21 exp risk/ (0)
22 exp Regression Analysis/ (0)
23 hazard ratio*.tw. (1835)
24 (proportional adj3 hazard*).tw. (1127)
25 (relative adj3 risk).tw. (1184)
26 (cox adj3 model*).tw. (1006)
27 (regression or survival).tw. (36853)
28 exp Survival Analysis/ (0)
29 Prognosis/ (0)
30 prognos*.tw. (12873)
31 or/21-30 (47024)
32 Parathyroidectomy/ (0)
33 parathyroidectom*.tw. (149)
34 or/32-33 (149)
35 parathyroid glands/ (0)
36 parathyroid*.tw. (1012)
37 35 or 36 (1012)
38 Endocrine Surgical Procedures/ (0)
39 General Surgery/ (0)
40 Surgical Procedures, Operative/ (0)
41 Surgical Procedures, Minimally Invasive/ (0)
42 (remov* or surg* or excis* or dissect* or endoscop* or laparoscop*).tw. (81126)

43 or/38-42 (81126)
44 37 and 43 (215)
45 34 or 44 (286)
46 15 and 20 and 31 and 45 (3)
47 Animals/ not Humans/ (0)
48 46 not 47 (3)
49 limit 48 to english language (2)

Database: Embase <1980 to 2012 Week 10>
Searched 12th March 2012
Search Strategy:
---
1 chronic kidney disease/ (18214)
2 ckd.tw. (9687)
3 ((chronic or progress*) adj1 kidney disease*).tw. (16585)
4 ((chronic or progress*) adj1 renal disease*).tw. (4411)
5 ((chronic or progress*) adj1 kidney failure).tw. (1074)
6 ((chronic or progress*) adj1 renal failure).tw. (24277)
7 (end-stage kidney or endstage kidney or end stage kidney).tw. (1104)
8 (end-stage renal or endstage renal or end stage renal).tw. (26169)
9 ((renal or kidney*) adj3 insufficien*).tw. (21369)
10 or/1-9 (91745)
11 exp dialysis/ (38678)
12 exp renal replacement therapy/ (112096)
13 ((renal or peritoneal or kidney*) adj3 dialys*).tw. (25785)
14 (haemodialys* or hemodialys*).tw. (60404)
15 or/11-14 (149064)
16 hyperphosphatemia/ (3519)
17 hyperphosphat*.tw. (3505)
18 phosphate/ (58850)
19 (phosphate* or phosphorus).tw. (219725)
20 Phosphate intake/ (880)
21 Phosphate blood level/ (6463)
22 Phosphorus/ (48645)
23 or/16-22 (267829)
24 10 or 15 (208035)
25 risk/ or risk assessment/ or risk benefit analysis/ or risk factor/ or risk management/ or risk reduction/ (915126)
26 exp regression analysis/ (168725)
27 hazard ratio*.tw. (36028)
28 (proportional adj3 hazard*).tw. (29250)
29 (relative adj3 risk).tw. (46822)
30 (cox adj3 model*).tw. (24413)
31 (regression or survival).tw. (905379)
32 exp survival/ (428889)
33 prognosis/ (367094)
34 prognos*.tw. (380154)

35 or/25-34 (2183570)
36 parathyroidectomy/ (5670)
37 parathyroidectom*.tw. (5107)
38 36 or 37 (7173)
39 exp parathyroid gland/ (7638)
40 parathyroid*.tw. (38169)
41 39 or 40 (39941)
42 endocrine surgery/ (831)
43 general surgery/ (5128)
44 surgery/ (151302)
45 minimally invasive surgery/ (19145)
46 minimally invasive procedure/ (3181)
47 (remov* or surg* or excis* or dissect* or endoscop* or laparoscop*).tw. (1966767)
48 or/42-47 (2020147)
49 41 and 48 (8540)
50 38 or 49 (12297)
51 23 and 24 and 35 and 50 (182)
52 Nonhuman/ not Human/ (3097690)
53 51 not 52 (180)
54 limit 53 to english language (156)
55 limit 54 to embase (139)
56 limit 55 to (conference abstract or conference paper or "conference review") (27)
57 55 not 56 (112)

Appendix F2: Table of all model parameters

Parameter	Value	Source / notes
Cohort characteristics at baseline		
Mean age	64.8	UK Renal Registry 2010
Sex (% male)	0.617	
Serum phosphate (mmol/l)	1.600	
Serum calcium (mmol/l)	2.315	
Existing cardiovascular morbidity:		
18–34	1.1%	
35–44	6.8%	
45–54	13.3%	
55–64	25.7%	
65–74	29.5%	
75+	32.5%	
Baseline model		
Biochemical progression with calcium carbonate:		
Serum phosphate (mmol/l)		Braun et al. 2004
0 months	2.290	
3 months	1.770	
6 months	1.840	
12 months	1.700	
Serum calcium (mmol/l):		
0 months	2.320	
3 months	2.480	
6 months	2.430	
12 months	2.470	
Correlation between baseline and follow-up:		
Serum phosphate (mmol/l)		

Parameter	Value	Source / notes
3 months	0.572	Calculation based on Evenepoel P et al. (2009)
6 months	0.266	Calculation based on De Francisco et al. (2010) and Fishbane S et al. (2010)
12 months	0.309	Calculation based on Chertow GM et al. (2003), Braun J et al. (2004) and Kakuta T et al. (2011)
Serum calcium (mmol/l)		
3 months	0.539	Calculation based on Evenepoel P et al. (2009)
6 months	0.517	Calculation based on De Francisco et al. (2010) and Fishbane S et al. (2010)
12 months	0.577	Calculation based on Braun J et al. (2004) and Kakuta T et al. (2011)
Treatment effects (compared with calcium carbonate)		
Calcium acetate:		Pooled from effectiveness evidence using network meta-analysis
Serum phosphate (mmol/l):		
3 months	-0.154	
6 months	-0.097	
12 months	-0.029	
Serum calcium (mmol/l):		
3 months	-0.050	
6 months	-0.179	
12 months	-0.049	
Sevelamer hydrochloride:		
Serum phosphate (mmol/l):		
3 months	-0.158	
6 months	-0.098	
12 months	0.031	
Serum calcium (mmol/l):		
3 months	-0.120	
6 months	-0.115	
12 months	-0.099	

Parameter	Value	Source / notes
Lanthanum carbonate:		
Serum phosphate (mmol/l):		
3 months	0.068	
6 months	0.006	
12 months	0.191	
Serum calcium (mmol/l):		
3 months	-0.170	
6 months	-0.259	
12 months	-0.083	
Hazard ratios for all-cause mortality		
Phosphate (mmol/l):		Tangri et al.
<1.13	0.740	
1.13–1.78	1.000	
1.78–2.10	1.170	
2.10–2.42	1.420	
>2.42	1.640	
Calcium (mmol/l):		
<2.10	1.350	
2.10–2.37	1.000	
2.37–2.59	1.130	
>2.59	1.350	
Mortality HR for history of cardiovascular events in people with CKD stage 5 on dialysis	1	HR=2.1 in Trespalacios et al. Heart failure as a cause for hospitalization in chronic dialysis patients. Am J Kidney Dis. 2003 Jun;41(6):1267-77. However, applying this independently double counts the effect of treatment on overall mortality; therefore, no additional effect was assumed in base case
Hazard ratios for cardiovascular event		
Phosphate (mmol/l):		Slinin et al.
≤1.42	1.000	

Parameter	Value	Source / notes
1.45–1.71	1.060	
1.74–2.03	1.130	
2.07–2.42	1.140	
>2.42	1.250	
Calcium (mmol/l):		
≤2.17	1.000	
2.20–2.30	1.030	
2.32–2.40	1.040	
2.42–2.54	1.030	
>2.54	1.080	
Rate of cardiovascular events per cycle	0.029	Block et al. 2004
Predicting fracture events		
HR per mg/dl serum phosphate	1.120	Block et al. 2004
Rate of fractures per quarter in regression cohort	0.001	
Predicting the need for parathyroidectomy		
HR for phosphate at 1 year (per 0.1 mmol/l)	1.626	Young et al.
Baseline rate of progression to parathyroidectomy per quarter	0.004	
Probability of transplantation		
Getting on the waiting list:		
Probability of joining waiting list within 2 years of dialysis	0.512	UK Renal Registry 2010
% men	0.607	
OR: women compared with men	1.000	
Per-quarter probability of receiving transplant from waiting list	0.053	NHSBT 2010–11
Brainstem-dead donors:		
Proportion of transplants	0.414	UK Renal Registry 2010
% men	0.603	
OR: women compared with men	0.820	
Cardiac-dead or living donors:		

Parameter	Value	Source / notes
Proportion of transplants	0.586	UK Renal Registry 2010
OR: women compared with men	0.900	
Adverse events		
Diarrhoea (rate per quarter):		Pooled rates from effectiveness evidence base
Calcium carbonate	0.045	
Calcium acetate	0.051	
Sevelamer hydrochloride	0.043	
Lanthanum carbonate	0.040	
Constipation:		
Calcium carbonate	0.033	
Calcium acetate	0.023	
Sevelamer hydrochloride	0.002	
Lanthanum carbonate	0.050	
Nausea and vomiting:		
Calcium carbonate	0.106	
Calcium acetate	0.129	
Sevelamer hydrochloride	0.004	
Lanthanum carbonate	0.139	
Upper abdominal pain:		
Calcium carbonate	0.089	
Calcium acetate	0.010	
Sevelamer hydrochloride	0.021	
Lanthanum carbonate	0.025	
Health state utilities		
CKD stage 4	0.624	Gorodetskaya et al. show that HRQoL in CKD stage 4 is 10.4% better than in CKD stage 4 on dialysis; this estimate is used to raise the value from Liem et al. for CKD stage 5 on dialysis
CKD stage 5 on dialysis	0.565	Liem et al. 2008 meta-analysis of EQ-5D
After transplantation	0.809	

Parameter	Value	Source / notes
Event utilities		
Relative utility decrement associated with events:		
Cardiovascular event	78%	Block et al. (2004) found that congestive heart failure was the most common reason for cardiovascular-related admissions among people with ESRD. In a study investigating the impact of pharmacist interventions, Holland 2007 obtained health utility values for UK patients with congestive heart failure receiving standard medical management. The trial population utility was calculated to be 78% of that expected of the general UK population, adjusted for age and sex
Fracture	93%	Peasgood (2009) conducted a review of papers that reported utility values for people who suffered a fracture. Hip fractures were used as a proxy for "major fractures", and wrist fractures were used as a proxy for "minor fractures". It is assumed that: • the value represents the percentage reduction in utility that would be expected to occur as a result of a fracture compared with the general population of the same age and sex • a single value is used (rather than separate values for major and minor fractures) by assuming that minor fractures are approximately 9 times more prevalent than major fractures (as in the PenTAG cinacalcet model)
On the transplant waiting list	–	no decrement assumed
Transplantation event	87%	Hamidi V et al. Transplantation 2009 Mar 27:87(6) 831-8
Adverse events:		
Diarrhoea *** absolute decrement ***	-0.06	Szabo et al. 2008. Absolute decrement means that a person would have a reduction of 0.06 of a QALY if they had constipation, regardless of their underlying health state
Constipation	85%	Belsey 2010
Nausea/vomiting *** absolute decrement ***	-0.07	Szabo et al. 2008
Upper abdominal pain	73%	Latimer 2009. As a proxy for abdominal pain in CKD, utilities for patients with dyspepsia following treatment with non-steroidal anti-inflammatory drugs (NSAIDs) were used. This could be interpreted that a person with upper abdominal pain would have a utility 73% of that expected of the general UK population, adjusted for age and sex. See below for duration of health decrement

Parameter	Value	Source / notes
Duration of disutility (d)		
Cardiovascular event	Indefinite	
Fracture	1 year	
Transplantation event	1 month	
Adverse events:		
Diarrhoea	5 days	
Constipation	5 days	
Nausea/vomiting	5 days	
Upper abdominal pain	5 days	
Event costs		
Cardiovascular event	£1320.09	NHS reference costs 2011. Hospital procedures are coded to allow activity-based analysis of costs and resources. Using these codes, we can calculate an approximate cost to the NHS of a cardiovascular event to be used in the model. A weighted average of the following event codes was used: EB07H (Arrhythmia or Conduction Disorders with complications (CC)), PA23A (Cardiac Conditions with CC), EB01Z (Non interventional acquired cardiac conditions), EB05Z (Cardiac Arrest), EB06Z (Cardiac Valve Disorders), EB10Z (Actual or Suspected Myocardial Infarction), EB03H (Heart Failure or Shock with CC), AA22A (Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy with CC), DZ20Z (Pulmonary Oedema), QZ17A (Non-Surgical Peripheral Vascular Disease with Major CC), QZ17B (Non-Surgical Peripheral Vascular Disease with Intermediate CC) A weighted average of the cost of excess bed days associated with the above procedures was included
Fracture	£2711.61	NHS reference costs 2011. A weighted average of the following event codes were used: HD39A (Pathological Fractures with Major CC), HD39B (Pathological Fractures with CC
On the transplant waiting list	£0	No costs assumed for this event
Parathyroidectomy	£2532.55	NHS reference costs 2011. A weighted average of the following event codes were used: KA03A (Parathyroid Procedures with CC), KA03B (Parathyroid Procedures without CC)

Parameter	Value	Source / notes
Transplantation	£22558.09	NHS reference costs 2011. A weighted average of the following event codes were used: LA01A (Kidney Transplant 19 years and over from Cadaver non-Heart beating donor), LA02A (Kidney Transplant 19 years and over from Cadaver Heart beating donor), LA03A (Kidney Transplant 19 years and over from Live donor). Additional drug costs (recommended doses in BNF 63, assuming a 70 kg adult): • All patients receive postoperative basiliximab (as per NICE technology appraisal 85); 2 vials per person • 75% of people receive tacrolimus immunotherapy; 17.5 mg/kg/d for first 15 days • 25% of people receive ciclosporin immunotherapy; 12.5 mg/kg/d for first 15 days See below for maintenance immunotherapy costs
Adverse events:		
Diarrhoea	£36.00	Each assumed to incur 1 GP appointment (see below)
Constipation	£36.00	
Nausea/vomiting	£36.00	
Upper abdominal pain	£36.00	
Calculation of costs:		
Unit costs:		
GP appointment	£36.00	Personal and Social Services Research Unit 2011
Resource use:		
GP appointments:		
Diarrhoea	1	Developers' assumption, validated by GDG
Constipation	1	
Nausea/vomiting	1	
Upper abdominal pain	1	
Intervention costs		
Cost per quarter:		
Calcium carbonate	£62.28	Calculated as below

Parameter	Value	Source / notes
Calcium acetate	£187.61	
Sevelamer hydrochloride	£476.25	
Lanthanum carbonate	£398.22	
Unit cost (per g)		
Calcium carbonate	£0.07	Costs per pack from BNF 63 Cost per gram is calculated by dividing grams per unit dose by number of unit doses per pack Calcichew is used for base-case calcium carbonate cost/gram PhosLo is used for base-case calcium acetate cost/gram Other preparations are explored in the sensitivity analysis Lanthanum tablets are supplied in different strength formulations, which result in a different cost per gram (lanthanum 500 mg tablet: £2.54/gram, 750 mg tablet: £2.25/gram, 1000 mg tablet £1.79/gram). The cost/gram of the lanthanum 750 mg tablet is used in the model.
Calcium acetate	£0.11	
Sevelamer hydrochloride	£0.82	
Lanthanum carbonate	£2.25	
Assumed dose (g/d):		
Calcium carbonate	3.66	Pooled evidence from effectiveness evidence base (that is, the average dose at which each binder was delivered)
Calcium acetate	4.82	
Sevelamer hydrochloride	6.37	
Lanthanum carbonate	1.93	
State costs per quarter		
CKD stage 5 on dialysis	£25.00	Excluding dialysis costs
After transplantation (maintenance per quarter)	£639.17	Calculated using recommended doses in BNF 63, assuming a 70 kg adult: • 75% of people receive tacrolimus immunotherapy; 6 mg/kg/d as maintenance • 25% of people receive ciclosporin immunotherapy; 4 mg/kg/d as maintenance
Unit costs		
PTH test	£10.00	NHS reference costs 2011. cost of ‘other’ biochemistry test
Calcium test	£1.00	NHS reference costs 2011 cost of ‘standard’ biochemistry test

Parameter	Value	Source / notes
Phosphorus test	£1.00	NHS reference costs 2011 cost of 'standard' biochemistry test
Dialysis cost per session:		
Adults:		
Home haemodialysis	£122.85	NHS reference costs 2011
Hospital haemodialysis	£159.77	NHS reference costs 2011
Satellite haemodialysis	£158.25	NHS reference costs 2011
Continuous ambulatory PD	£51.36	NHS reference costs 2011
Automated PD	£57.16	NHS reference costs 2011
Post-transplantation immunosuppressants:		
Basiliximab (per 20 mg vial)	£842.38	BNF 63
Ciclosporin (per mg)	£0.03	BNF 63
Tacrolimus (per mg)	£1.61	BNF
Resource use per quarter		
PTH test	1.000	Assumed that all patients would receive quarterly PTH, phosphate and calcium testing. GDG validated.
Calcium test	1.000	
Phosphate test	1.000	
Dialysis:		
Proportion of adults receiving home HD	0.025	UK Renal Registry 2010
Proportion of adults receiving hospital HD	0.398	
Proportion of adults receiving satellite HD	0.421	
Proportion of adults receiving continuous ambulatory PD	0.086	
Proportion of adults receiving automated PD	0.069	
Number of sessions per week:		
Home HD	4	Assumption of number of sessions per week on average needed for each method of dialysis. Validated by the GDG
Hospital HD	3	
Satellite HD	3	
Continuous ambulatory PD	7	
Automated PD	7	

Parameter	Value	Source / notes
Post-transplantation immunosuppressants:		
Ciclosporin:		
Dose per kg (mg, initial 15 days)	12.5	BNF 63 (used in calculating costs/quarter above)
Dose per kg (mg, maintenance)	4	
Tacrolimus		
Dose per kg (mg, initial month)	17.5	British National Formulary No. 63 (used in calculating costs/quarter above)
Dose per kg (mg, maintenance)	6	
Basiliximab		
Number of vials per person	2	British National Formulary No. 63 (used in calculating costs/quarter above)
Per quarter costs		
Vitamin D	£13.00	Assumption that vitamin D dosing costs on average £1 per week (as in PenTAG cinacalcet model)
Dialysis	£6006.73	Overall total derived from assumptions above
Post-transplantation costs:		
Tacrolimus (maintenance, per cycle)	£879.86	Overall totals derived from assumptions above
Ciclosporin (maintenance, per cycle)	£639.17	
Tacrolimus (additional perioperative cost)	£562.13	
Ciclosporin (additional perioperative cost)	£223.13	
Proportion of people on tacrolimus compared with ciclosporin	75.0%	Developers' assumption, validated by the GDG
Basiliximab (perioperative only)	£1684.76	Overall total derived from assumptions above