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The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation

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Abstract

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation

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Objectives: To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of secondary hyperparathyroidism (SHPT) for people on dialysis due to end-stage renal disease (ESRD).

Data sources: Electronic databases were searched up to February 2006.

Review methods: Included randomised controlled trials (RCTs) on the clinical effectiveness of cinacalcet for SHPT in ESRD were critically appraised, had relevant data extracted and were summarised narratively. A Markov (state transition) model was developed that compared cinacalcet in addition to current standard treatment with phosphate binders and vitamin D to standard treatment alone. A simulated cohort of 1000 people aged 55 with SHPT was modelled until the whole cohort was dead. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analysis was undertaken as well as probabilistic sensitivity analysis.

Results: Seven trials comparing cinacalcet plus standard treatment with placebo plus standard treatment were included in the systematic review. A total of 846 people were randomised to receive cinacalcet. Cinacalcet was more effective at meeting parathyroid hormone (PTH) target levels (40% vs 5% in placebo, $p < 0.001$). In those patients meeting PTH targets, 90% also experienced a reduction in calcium–phosphate product levels, compared with 1% in placebo. Significantly fewer people treated with cinacalcet were hospitalised for cardiovascular events, although no difference was seen in all-cause hospitalisation or mortality. Significantly fewer fractures and parathyroidectomies were also seen with cinacalcet. Findings on all patient-based clinical outcomes were based on small numbers. The authors' economic model estimated that, compared to standard treatment alone, cinacalcet in addition to standard care costs an additional £21,167 and confers 0.34 QALYs (or 18 quality-adjusted weeks) per person. The incremental cost-effectiveness ratio (ICER) was £61,890/QALY. In most cases, even extreme adjustments to individual parameters did not result in an ICER below a willingness-to-pay threshold of £30,000/QALY with probabilistic analysis showing only 0.5% of simulations to be cost-effective at this threshold. Altering the assumptions in the model through using different data sources for the inputs produced a range of ICERs from £39,000 to £92,000/QALY.

Conclusions: Cinacalcet in addition to standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient-relevant clinical outcomes. Given the short follow-up in the trials, it is unclear how data should be extrapolated to the long term. Together with the high drug cost, this leads to cinacalcet being unlikely to be considered cost-effective. Recommendations for future research include obtaining accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long-term clinical outcomes.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Calciphylaxis Also known as calcific uraemic arteriolopathy, calciphylaxis is a type of extraskeletal calcification. It is characterised by small vessel mural calcification with or without endovascular fibrosis, extravascular calcification and vascular thrombosis, leading to tissue ischaemia.

Calcitriol Active vitamin D_3.

Dialysis vintage The length of time that someone has been receiving dialysis treatment.

Glomerular filtration rate (GFR) The glomeruli are renal capillary blood vessels actively involved in filtration. The GFR is a measure of the kidneys' ability to filter and remove waste products.

Hypercalcaemia High levels of serum calcium.

Hyperphosphataemia High levels of serum phosphate.

Hypocalcaemia Low levels of serum calcium.

Hypophosphataemia Low levels of serum phosphate.

Myocardium Heart muscle.

Osteoblast Cells associated with bone formation.

Osteoclast Cells responsible for bone breakdown.

Osteodystrophy Defective bone formation secondary to several pathological processes occurring in chronic kidney disease.

Osteitis fibrosa A complication of secondary hyperparathyroidism in which the bone becomes softened and deformed, and may develop cysts. May lead to bone pain and fractures.

Renal replacement therapy Dialysis or transplantation once renal function has deteriorated to an otherwise fatal extent.

Tetany Hyperexcitation of the nerves that may lead to muscle spasm and twitching, including of the vocal cords and epiglottis.

Uraemia Urea and other nitrogen-containing waste products found in the blood. Used to describe the constellation of symptoms of kidney failure including lethargy, depression, loss of appetite and oedema. Later symptoms include diarrhoea, anaemia, convulsions and coma.

List of abbreviations

AE	adverse event
BMD	bone mineral density
BNF	British National Formulary
Ca × P	calcium–phosphate product
CAPD	continuous ambulatory peritoneal dialysis
CCPD	continuous cycling peritoneal dialysis
CEAC	cost-effectiveness acceptability curve
CFE	cardiovascular event and fracture event
CFH	event free with previous fracture and cardiovascular event
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CRF	chronic renal failure
CV	cardiovascular
CVD	cardiovascular disease
CVE	cardiovascular event
CVH	event free with previous cardiovascular event
DOPPS	Dialysis Outcomes and Practice Patterns Study
EAG	expert advisory group
EQ-5D	EuroQol 5 Dimensions
ESRD	end-stage renal disease
EVF	event-free state
FCE	finished consultant episode
FDA	Food and Drug Administration
FRE	fracture event with hospitalisation
FRH	event free with previous fracture event
GFR	glomerular filtration rate
HD	haemodialysis
HES	Hospital Episode Statistics
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
iPTH	intact parathyroid hormone
IQR	interquartile range
IRMA	immunoradiometric assay
ITT	intention-to-treat
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQ	Kidney Disease Questionnaire
KDQoL	Kidney Disease – Quality of Life
LCHD	limited care haemodialysis
MCS	mental component score
MI	myocardial infarction
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NKF	National Kidney Foundation
NR	not reported
ns	not significant
NS	not stated

continued

List of abbreviations *continued*

NSRC	National Schedule of Reference Costs
OR	odds ratio
PCS	physical component score
PCT	primary care trust
PD	peritoneal dialysis
PSA	probabilistic sensitivity analysis
PTH	parathyroid hormone
PTx	parathyroidectomy
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form 36
SHPT	secondary hyperparathyroidism
SIP	Sickness Impact Profile
TTO	time trade-off
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The parathyroids are four small glands found in the neck, close to the thyroid. Normally, homeostatic control of serum calcium and phosphate levels is regulated within narrow bounds through parathyroid hormone (PTH) released by the parathyroids. Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD). It may develop early in chronic kidney disease (CKD) and progresses as renal function deteriorates. As it does so, the combined effects of reduced serum calcium, increased serum phosphate and decreased vitamin D activity lead to overactivity of the parathyroid glands as they try to maintain appropriate calcium levels. Eventually, the parathyroids may develop reduced expression of calcium and vitamin D receptors and so are less responsive to changes in serum levels that they should regulate.

There is an increased risk of vascular disease due to calcification in SHPT. SHPT is also the main cause of renal bone disease, which increases the risk of fracture. The relative impacts of calcium, phosphate and PTH, being complex, are unclear. Symptomatically, advanced SHPT can cause bone pain, muscle weakness and itching.

Current standard treatment for SHPT is based on reducing phosphate in the diet, use of phosphate binders (which contain calcium), vitamin D supplements and parathyroidectomy (surgical removal of the parathyroids). Currently, the Renal Registry reports that 72% of people meet target levels for PTH, 60% for phosphate and 63% for calcium.

Cinacalcet (Mimpara®; Amgen, Thousand Oaks, California, USA) is the first of a new class of calcimimetic drugs, which acts directly on parathyroid calcium receptors to increase their sensitivity to serum calcium. This suppresses overproduction of PTH which, in turn, reduces elevated serum calcium and phosphate levels.

Objectives

To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of SHPT for people on dialysis due to ESRD.

Methods

Systematic review

Electronic databases were searched for relevant published literature on the clinical effectiveness of cinacalcet for SHPT in ESRD. Updated searches were undertaken in February 2006. Included randomised controlled trials (RCTs) were critically appraised for internal and external validity. Relevant data were extracted and, as the largest trials were already pooled using patient-level data, a narrative synthesis was carried out.

Cost-effectiveness

Electronic databases were searched for relevant published literature on the cost-effectiveness of cinacalcet for SHPT in ESRD. No studies were identified. An economic evaluation was submitted by Amgen, the manufacturers of cinacalcet, to the National Institute for Health and Clinical Excellence as part of its appraisal of cinacalcet. This was critically appraised and compared with the authors' economic evaluation.

A Markov (state-transition) model was developed by the authors. The model compared cinacalcet in addition to current standard treatment with phosphate binders and vitamin D to standard treatment alone. A simulated cohort of 1000 people aged 55 years with SHPT was modelled until the whole cohort was dead. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analysis was undertaken as well as probabilistic sensitivity analysis.

Results

Number and quality of studies

Seven published reports of RCTs comparing cinacalcet plus standard treatment to placebo plus

standard treatment were identified. However, most of these papers related to just four Amgen trials which were more fully reported, including providing pooled data, in the medical review of cinacalcet by the US Food and Drug Administration. Therefore, this review was based on these four Amgen trials plus the three published papers that report on different trials. Details from a total of seven trials were therefore included in the systematic review, including a total of 846 people randomised to receive cinacalcet.

The trials were largely well designed. The primary outcome for all the trials was a measure of serum PTH reduction. Only one paper provided information about patient-based clinical outcomes. This used retrospective analysis of adverse effect data from the four main RCTs to assess the impact of cinacalcet on fracture, cardiovascular events, parathyroidectomy and mortality. However, most of these data were based on 6-month follow-up and it is unclear how the results should be extrapolated to the longer term. Some data came from people who agreed to take part in an extension study after the original 6-month deadline and it is not known whether their characteristics were the same as the originally randomised population. Methods used for censoring in the analysis were unclear. In addition, death rates in the trials were half that reported for a similar age group by the UK Renal Registry. It is therefore unclear whether the results are applicable to the routine clinical population.

Summary of risks and benefits

Cinacalcet in addition to standard treatment was more effective at meeting PTH target levels than placebo plus standard treatment (40% versus 5% in pooled analysis, $p < 0.001$). Of those patients meeting PTH targets, 90% also experienced a reduction in calcium–phosphate product levels compared with just 1% of those treated with placebo. Cinacalcet was more effective among those with moderately elevated PTH levels than those with very high levels of PTH, but in all cases was more effective than standard treatment at reaching target PTH levels (baseline PTH levels >32 to <53 pmol/l 60% versus 11%, >53 to <85 pmol/l 41% versus 2%, >85 pmol/l 12% versus 0).

One paper reported patient-based clinical outcomes using pooled adverse effect data from four RCTs. Significantly fewer people treated with cinacalcet were hospitalised for cardiovascular events [15.0 versus 19.7 cardiovascular events per 100 patient-years, relative risk (RR) 0.61, $p = 0.005$], although no difference was seen in all-cause hospitalisation or mortality. Significantly fewer fractures (3.2 versus 6.9 events per 100 patient-years, RR 0.46, $p = 0.04$) and parathyroidectomies (0.3 versus 4.1 events per 100 patient-years, RR = 0.07, $p = 0.00$) were also seen with cinacalcet, although these findings are based on small numbers. Given the short follow-up, it is not clear to what extent these results can be extrapolated to the longer term.

Withdrawal due to adverse effects was more common for those treated with cinacalcet than for those treated with placebo (15% versus 8%). Pooled incidence of serious adverse effects was not different between the study arms. However, there was significantly more nausea (31% versus 19%, $p < 0.001$) and vomiting (27% versus 15%, $p < 0.001$) among those treated with cinacalcet. Vomiting was related to the dose of cinacalcet received.

Summary of costs

The authors' cost–utility model estimates that the lifetime cost of standard treatment for SHPT is £6533 for a person with ESRD aged 55 years. The additional cost of cinacalcet is estimated at £21,167 (about £3800 annually). If the costs of dialysis are included in this assessment, standard care costs £81,523 and cinacalcet adds £25,423.

Summary of cost-effectiveness

Amgen submitted an estimate of cost–utility based on a Markov (state-transition) model, using data from the research report assessing the impact of cinacalcet on cardiovascular events, fractures, parathyroidectomies and mortality. This estimates the discounted incremental cost-effectiveness ratio (ICER) for cinacalcet in addition to standard care compared with standard care alone for people with SHPT as £35,600 per QALY.

The authors' model estimates that, compared with standard treatment alone, cinacalcet in addition to standard care costs an additional £21,167 and confers 0.34 QALYs (or 18 quality-adjusted weeks) per person. The ICER is £61,890 per QALY.

Analyses of uncertainty

One-way sensitivity analysis suggested that the model was particularly sensitive to a number of transition, utility and cost parameters. These were further investigated through threshold analyses. In most cases, even extreme adjustments to

individual parameters did not result in an ICER below a willingness-to-pay (WTP) threshold of £30,000 per QALY. An ICER of £30,000 per QALY was achieved if the cost of cinacalcet was reduced from 14.5p to 8p per mg. The ICER also fell below £30,000 in one-way threshold analysis if the relative risk of death associated with having 'very uncontrolled' PTH levels (>85 pmol/l) compared with meeting target levels of 32 pmol/l was raised to 2.2 (compared with 1.1814 in the base case).

In probabilistic analysis only 0.5% of simulations showed cinacalcet to be cost-effective at a WTP threshold of £30,000 per QALY. The cost-effectiveness acceptability curve shows that cinacalcet is only likely to be the most cost-effective treatment option above a WTP threshold of £62,000 per QALY.

The cost-effectiveness was evaluated of only treating those with moderately uncontrolled PTH (>32 <85 pmol/l). This reduced the ICER only slightly to £57,422 per QALY. Only treating those with very uncontrolled PTH levels (>85 pmol/l) increased the ICER to £81,479 per QALY.

The impact of altering the assumptions in the model by using different data sources for the inputs was also assessed. The range of ICERs for these analyses was £39,000 to £92,000 per QALY.

Discussion

The systematic review shows that cinacalcet is effective at reducing levels of PTH in people with SHPT. However, the identified studies have short follow-up and it remains unclear whether this impact will be maintained in the long term or what long-term impact will be seen on parathyroidectomy, fracture, cardiovascular events and mortality.

Although there is considerable uncertainty in many of the parameters used in the cost-effectiveness model, extensive sensitivity analysis shows that cinacalcet is unlikely to be considered cost-effective at usually acceptable levels of willingness to pay.

This assessment comprises a comprehensive assessment of the effectiveness and cost-effectiveness of cinacalcet for SHPT by an independent team through systematic review and economic modelling.

Better information about the relative impact of different biomarkers on clinical outcomes would allow a more precise estimation of the impact of cinacalcet. In addition, the assessment has been hampered by the lack of long-term follow-up data for people treated with cinacalcet compared with standard care.

Conclusions

Cinacalcet in addition to standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient-relevant clinical outcomes. Given the short follow-up in the trials, it is unclear how data should be extrapolated to the long term. Together with the high drug cost, this leads to cinacalcet being unlikely to be considered cost-effective.

Recommendations for research

The following topics are recommended for further research.

- Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long-term clinical outcomes are of paramount importance for future efforts to model the effectiveness of cinacalcet, or other similar agents.
- Longer term studies of the maintenance of PTH control in SHPT and of the clinical impact with cinacalcet are needed. Such studies should explicitly examine the impact of cinacalcet in subgroups based on age and diabetes.
- A better understanding of the epidemiology of fractures in SHPT is needed, including the pattern of fractures experienced in SHPT, and their consequences in terms of health service use, quality of life and mortality.
- The impact of fracture, cardiovascular events and very uncontrolled PTH levels on the quality of life of people with SHPT should be investigated.

Chapter 1

Aim

The aim of this health technology assessment was to establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of secondary hyperparathyroidism in people on dialysis due to end-stage renal failure (ESRD). The assessment was carried out to inform the appraisal of cinacalcet by the National Institute for Health and Clinical Excellence (NICE).

Chapter 2
Background

Description of underlying health problem

Chronic kidney disease (CKD) involves progressively decreasing kidney function. Recognised stages of CKD and commonly associated complications are shown in *Table 1*. Secondary hyperparathyroidism (SHPT) is a common complication of CKD.[3] It may develop in the early stages of CKD as a response to reduced serum calcium, typically as GFR falls to around 80–40 ml/min/1.73 m^2 (normal GFR for an adult is around 100 ml/min/1.73 m^2).[4] GFR is a measure of the kidneys' ability to filter and remove waste products, commonly indicated by clearance of creatinine (a muscle breakdown product).

SHPT is an adaptive response to the disrupted biochemistry in CKD, and the loss of normal physiological controls results in reduced vitamin D levels, excessive levels of phosphate and low levels of calcium.[5] Metabolic disturbances of vitamin D, calcium, phosphate and PTH level are thus common in CKD. SHPT progresses as renal function deteriorates and most people with ESRD (CKD stage 5) will have SHPT to varying degrees. At this stage, the kidneys are no longer able to excrete waste products effectively or to help regulate water and salts or the body's acidity. The kidneys also influence haemoglobin production, blood pressure regulation and bone turnover.[6]

Normal homeostatic control

There are four parathyroid glands, which are situated behind the thyroid gland in the neck. When they are functioning normally and producing appropriate amounts of PTH, calcium and phosphate serum levels are regulated within narrow bounds through the responses of the kidneys, gut and bone (*Figure 1*). A drop in serum

TABLE 1 *Stages of CKD*

Stage	Description	GFR (ml/min/1.73 m^2)	Common complications
1	Kidney damage with normal or increased GFR	≥90	Some hypertension
2	Kidney damage with mild reduction in GFR	60–89	Hypertension frequent Mild PTH elevation
3	Moderate reduction in GFR	30–59	Hypertension common Decreased Ca^{2+} absorption Reduced phosphate excretion More marked elevation of PTH Altered lipoprotein metabolism Reduced spontaneous protein intake Renal anaemia Left ventricular hypertrophy
4	Severe reduction in GFR	15–29	As above, more pronounced, plus: Metabolic acidosis Hyperkalaemia Decreased libido
5	Kidney failure (ESRD)	<15 or dialysis	All of the above, more severe, plus: Salt and water retention (heart failure) Anorexia Vomiting Pruritis

Adapted from UK Renal Association[1] and US Kidney Disease Outcomes Quality Initiative (KDOQI).[2]
GFR, glomerular filtration rate; PTH, parathyroid hormone.

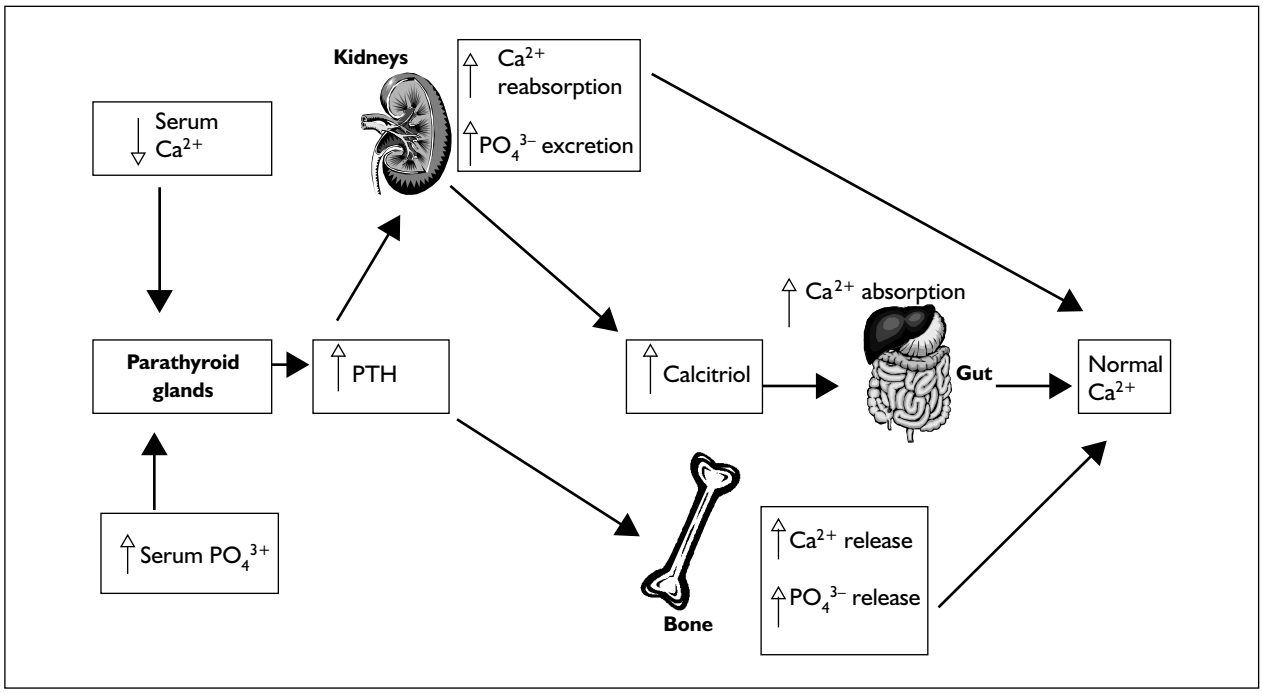

FIGURE 1 *Normal physiological response to a fall in serum calcium levels (hypocalcaemia) (adapted from Sexton, 2004[7])*

calcium levels causes increased levels of PTH to be released from the parathyroid glands. PTH acts on the bones (which release calcium and phosphate) and the kidneys (which reabsorb calcium but excrete phosphate). PTH also increases vitamin D activation in the kidney, stimulating increased calcium absorption from the gut.

Inactive vitamin D (cholecalciferol, vitamin D_3) is made when the skin is exposed to adequate sunlight and is also acquired through diet. These inactive forms are converted by the renal epithelial cells to the active form [calcitriol, $1,25(OH)_2D_3$]. In people with CKD, renal hydroxylation is impaired so that levels of serum calcitriol remain low and the specific nuclear binding proteins, vitamin D receptors, on the parathyroid glands are not sufficiently activated.[5,8] The amount of calcium that the gut absorbs also falls, resulting in less circulating serum calcium (hypocalcaemia). This is detected by the parathyroid glands, which respond with increased PTH production. As levels of calcitriol are reduced, these low levels of calcium fail to be properly compensated. PTH levels rise still further, resulting in SHPT.[7]

Phosphate is acquired from dietary sources such as dairy products, meat and nuts. As kidney function decreases, phosphate excretion is reduced, resulting in hyperphosphataemia. Hypocalcaemia may be caused when increased phosphate complexes with serum calcium. High concentrations of phosphate directly stimulate the parathyroid glands.[7]

Extracellular calcium (as Ca^{2+} ion) is the main regulator of PTH.[9] Low levels of serum calcium cause a reduction in the activity of calcium-sensing receptors on the parathyroid cell membrane, leading to greater PTH secretion. High serum calcium levels have the opposite effect, suppressing PTH secretion. In patients with CKD, increasingly high levels of PTH are needed to maintain appropriate calcium levels.[7]

In combination, the physiological demand for calcium, with excessive serum phosphate and low calcitriol, cause overactivity of the parathyroid glands and lead to SHPT. In advanced cases, parathyroid hyperplasia may give way to monoclonal proliferation, with rapid cell proliferation leading to vigorous nodular growth with reduced calcium receptor and vitamin D receptor expression, sometimes called tertiary hyperparathyroidism. At this stage the parathyroid glands become less responsive to serum levels of vitamin D and calcium and PTH becomes more difficult to control.[5]

Impact of the loss of homeostasis

An overview of the main morbidity and mortality risks with SHPT is given here, and described in

more detail in the section 'Prognosis' (p. 7). Increases in the risks of cardiovascular events and renal bone disease are the major effects of SHPT. Additional clinical consequences include soft-tissue calcification, hormonal disturbances, compromised immune system, neurobehavioural changes and altered red blood cell production.

There is little evidence to establish the relative impact of SHPT as a risk factor for vascular disease in ESRD.[10] Some evidence is available that links SHPT with valvular calcification, vascular calcification and calciphylaxis.[10] As high phosphate levels cause both SHPT and calcification, the relative impact of SHPT is unclear. Calcification of the coronary arteries, which may be measured using electron-beam tomography, has been shown to be more pronounced in those who are older, male, white and diabetic, who have been on dialysis for longer or who have higher calcium and phosphate levels.[11,12]

There is evidence that levels of PTH at least four times higher than normal increase the risk of significant bone disease.[10]

Hyperphosphataemia and/or hypercalcaemia are risk factors for vascular calcification, calcification of aortic and mitral valve rings and periarterial calcification.[10] However, it may be difficult to interpret the results of phosphate levels taken before dialysis, as they may mirror protein intake. Low phosphate may thus indicate malnutrition.[10] Studies from the USA have suggested that survival is best among those with moderately elevated phosphate levels, and patients who are thought to be fitter, well dialysed, more active and with good nutrition.[13]

While some studies have shown high levels of calcium (>3.0 mmol/l) to be associated with increased mortality, other studies have not shown such a link.[10] Some studies also show low calcium levels to be associated with mortality, ischaemic heart disease and cardiac failure.[10]

Hyperparathyroid bone disease

Bone disease in patients with ESRD is complex. It is affected not only by hypocalcaemia and lowered synthesis of vitamin D associated with hyperparathyroidism, but also by conditions that underlie ESRD, such as diabetes, as well as treatment modalities such as calcium supplements, phosphate binders and dialysate.[14] Renal osteodystrophy affects at least three-quarters of those with a GFR below 60 ml/min/1.73 m^2.[5] Two main types of renal bone disease are experienced with ESRD:

- high-turnover bone disease, caused by high PTH levels.
- low-turnover bone disease, caused by low PTH levels.

Mixed osteodystrophy can also occur.

High-turnover bone disease

PTH increases osteoclast activity and bone resorption, leading to high-turnover bone disease, which may include the typical features of osteitis fibrosa.[8] Up to three-quarters of patients with ESRD on dialysis have high-turnover bone disease.[5] Osteitis fibrosa can cause bone thinning, bowing and sometimes cysts, leading to bone pain (especially on exertion), painful joints, diminished vertebral height and fractures.[5,8]

Low-turnover bone disease

Low-turnover bone disease has two main forms: osteomalacia and adynamic bone disease. In osteomalacia, often related to aluminium levels, reduced osteoblast activity is accompanied by changes to the mineralisation process that increase osteoid (uncalcified bone matrix) formation.

Adynamic bone disease is increasing in prevalence and has been recorded in 23–50% of dialysis patients.[5] This condition involves diminished bone formation and reabsorption. It is thought to be the result of treatment choices for SHPT such as dialysis fluids high in calcium, calcium-based phosphate binders and vitamin D replacement,[5] and may be related to aluminium deposition. The resultant reduced uptake of calcium and phosphate leads to increased levels in the serum.[5] Such disorders can lead to bone deformities and spontaneous fractures, although the degree of impact on morbidity and mortality is unknown.

Measuring fracture risk

Bone mineral density (BMD) can be measured using dual-energy X-rays or computed tomographic (CT) scans to establish the amount of calcium compared with established norms. Results may be expressed as a *Z*-score, which compares BMD with an age- and gender-matched normal referent population. The World Health Organization (WHO) has established reference ranges for the general population. However, this only identifies the risk with osteoporosis, and the relation of BMD to fracture risk for those with renal osteodystrophy is less clear cut. The impact

of disordered biochemistry on fracture risk is discussed in the section 'Factors influencing risk of fracture' (p. 8).

Soft-tissue calcification

It has long been known that calcification of soft tissues is widespread among people with CKD.[12] This may be the result of hypercalcaemia or a high calcium–phosphate product (Ca × P) product. Calcification of the cardiac valves, aorta and coronary artery is associated with increased cardiovascular morbidity and mortality. Calcification may also be seen in lungs, eyes, joints and kidneys.[7]

High levels of serum phosphate may cause tissue calcification, both directly and indirectly.[12]

Epidemiology of CKD and ESRD

SHPT starts early in the course of CKD and is fairly ubiquitous in ESRD. The incidence of CKD may be estimated in population-based studies using serum creatinine concentration, which is a widely used, although insensitive, investigative test.[10] Such studies may underestimate actual CKD incidence.[10]

Two population studies in the UK have used serum creatinine concentration as a marker for CKD.[10] The first, based in Grampian, estimates a CKD incidence of 450 per million population (using a serum concentration of >300 µmol/l to indicate CKD).[15] The second, based in South West Hampshire Health Authority, found an annual CKD incidence of 1700 per million population [using serum creatinine concentrations of >150 µmol/l, 95% confidence interval (CI) 1562 to 1849] (source: Drey, 2000, quoted by the Renal Association[10]).

Two UK studies have estimated the annual incidence of ESRD based on creatinine concentrations of more than 500 µmol/l at 148 and 132 per million population (based on Feest, 1990, in Devon and the North-West, quoted by the Renal Association,[10] and Khan, 1994, based in Grampian,[15] respectively). Figures based on the Renal Registry in England suggest that 104 people per million population start renal replacement therapy (RRT) each year (about 6000 people), of whom 3% will receive a kidney transplant within 90 days, while the remainder receive dialysis.[16] The prevalent population receiving RRT in 2003 was 632 per million population (about 33,500 people). About half of these will have had a kidney transplant, while the remainder are receiving dialysis.[6]

Acceptance rates for RRT may also be used to estimate ESRD incidence, although these may also underestimate rates as they are influenced by detection, referral and acceptance levels.[16] The UK Renal Registry is estimated to cover 73% of the population of England and 100% of Wales. In 2003, 3556 patients were recorded as accepting RRT, giving a crude annual acceptance rate of 104 per million population.[16]

CKD is a disease of the elderly, with most of those affected in their seventies and eighties.[17] In a US study, two-thirds of the sampled population with grade 3–5 CKD were aged over 70 years and three-quarters had a history of hypertension.[18] Median age at acceptance of RRT is 65 years in the UK, although this is lower among ethnic minority populations, at 59 years.[16] This may relate to higher levels of diabetes among Indo-Asian populations and of hypertension in those of African and Afro-Caribbean origin,[10] although the age profile of these populations is generally younger than the white population. Sixty-two per cent of RRT patients are male,[13,16] an imbalance that is more pronounced in older populations.

CKD may be due to a number of different causes. Diabetes is the most common single underlying cause, present in 19% of patients according to the Renal Registry;[16] however, in many patients no underlying cause is identified.

Signs and symptoms associated with SHPT

Symptoms from rapid falls in calcium levels include tetany (hyperexcitation of the nerves that may lead to muscle spasm and twitching, including of the vocal cords and epiglottis), convulsions and cardiac arrhythmia.[7] However, these are rare in ESRD, where reductions to a low calcium level (hypocalcaemia) are usually more gradual. High levels of calcium (hypercalcaemia) are more common, and may cause symptoms of muscle weakness, nausea, thirst, confusion and constipation.[7] These may be iatrogenic from treatment with calcium-based phosphate-binders and vitamin D (as calcitriol).

High levels of phosphate can cause itching, nausea and resistance to erythropoietin (a hormone that regulates the production of red blood cells in the marrow).

SHPT can cause renal bone disease, leading to bone pain and a higher risk of fracture. A reduced response to epoetin (an amino acid glycopeptide that regulates red blood cell production) may result in anaemia. Cardiovascular calcification may involve the myocardium, the heart valves and arteries, and can cause increased mortality.[5] Calcification may also be seen elsewhere, in the lungs, kidneys, eyes and joints. Other symptoms may include muscle pain or stiffness, irritability, fatigue and poor sleep.

Prognosis

Untreated ESRD is inevitably fatal without treatment. The death rate among those treated with dialysis therapy remains high, at about 20% per year.[19] Abnormalities of mineral metabolism may cause significant bone disease and contribute to cardiovascular disease (CVD). Cardiovascular mortality is ten to 100 times greater in patients undergoing dialysis than in the general population (for patients aged 75–85 and 25–34 years, respectively).[4,5] Half of all deaths among dialysis patients are attributed to CVD.[20]

Factors influencing mortality risk

Age and the presence of co-morbidities influence survival in ESRD. The Renal Registry estimates only 39% of people starting RRT have no co-morbidity present. The five most frequent co-morbidities recorded are diabetes (26%), CVD (25%), angina (19%), smoking (18%) and peripheral vascular disease (14%).[16] Multivariate analysis on data held by the UK Renal Registry shows that the five co-morbidities with the strongest association with mortality are liver disease [hazard ratio (HR) 1.69, 95% CI 1.19 to 3.34), ischaemic/neuropathic ulcers (HR 1.75, 95% CI 1.23 to 2.49), malignancy (HR 1.69, 95% CI 1.32 to 2.15), diabetes (HR 1.65, 95% CI 1.35 to 2.02) and cerebrovascular disease (HR 1.39, 95% CI 1.09 to 1.78).[16]

The Renal Registry has classified risk groups for mortality based on age and presence of diabetes (*Table 2*).[10]

A UK study based on a hospital cohort of 292 people on dialysis (mean age 61 years) found that the severity of co-morbidity and functional status was a stronger predictor of mortality than age.[21] In addition, mortality is greater among those with low serum albumin and low cholesterol levels, associated with poor nutrition.[22]

Mortality risk is associated with levels of serum phosphate, possibly because of its effect on vascular calcification.[1] A US study of 40,538 patients on thrice-weekly dialysis assessed the impact of serum mineral levels on mortality over 18 months. Serum phosphate levels higher than 1.61 mmol/l (5.0 ml/dl) were associated with increased risk of death when adjustment was made for age, race or ethnicity, diabetes, time since initiation of dialysis and laboratory variables including parameters of mineral metabolism, nutritional status and haematological status.[19] Relative risk (RR) of death, compared with a reference population with phosphate serum concentrations of 1.29–1.61 mmol/l (4.0–5.0 mg/dl), is shown in *Table 3*.

The Renal Registry has also assessed relative mortality hazard for different levels of phosphate, calcium and Ca × P (derived by multiplying the values for phosphate and calcium) by mode of dialysis, haemodialysis and peritoneal dialysis.[13] The results are shown in Appendix 1. Numbers have been extracted from a graph and rounded to two decimal places, and so may be subject to inaccuracies. Data are not provided for higher serum levels, where risks may be highest.

Several small observational studies have found no association between serum calcium levels concentration and risk of mortality.[11,23,24] However, the study by Block and colleagues

TABLE 2 *Median survival of risk groups in the Renal Registry*

Risk classification	Population	Median survival (years)
Low risk	Non-diabetics aged <55 years	14.2
Medium risk	Non-diabetics aged 55–64 years Diabetics aged 15–54 years	7.4
High risk	Non-diabetics aged ≥65 years Diabetics aged >55 years	3.5

TABLE 3 *Relative risk of mortality with elevated phosphate levels*[19]

Serum phosphate level (mmol/l)	Serum phosphate level (mg/dl)	RR of mortality
1.61–1.94	5.0–6.0	1.07
1.94–2.26	6.0–7.0	1.25
2.26–2.58	7.0–8.0	1.43
2.58–2.91	8.0–9.0	1.67
≥2.91	≥9.0	2.02
Referent group phosphate levels = 1.29–1.61 mmol/l (4.0–5.0 mg/dl).		

TABLE 4 *Risk of cardiovascular hospitalisation by serum phosphate levels*[19]

Serum phosphate level (mmol/l)	Serum phosphate level (mg/dl)	Increased risk of cardiovascular hospitalisation (%)
1.61–1.94	5.0–6.0	10
1.94–2.26	6.0–7.0	15
2.26–2.58	7.0–8.0	29
2.58–2.91	8.0–9.0	28
≥2.91	≥9.0	38
Referent group phosphate levels = 1.29–1.61 mmol/l (4.0–5.0 mg/dl)		

(2004),[19] showed that raised calcium levels (adjusted for case-mix as before) were also associated with increased mortality compared with those within the reference range of 2.25–2.38 mmol/l (9.0–9.5 mg/dl). This was the case even when assessed within a narrow range of serum phosphate levels.

Finally, Block and colleagues (2004)[19] found that while high PTH concentrations greater than 63.6 pmol/l (600 pg/ml) were associated with increased risk of death in adjusted analysis, smaller increases of PTH, 31.8–63.6 pmol/l (300–600 pg/ml), were not. Levels of PTH were higher among younger patients, women, black people and those without diabetes.

Factors influencing risk of cardiovascular events

A recent review of studies examining the link between serum calcium, phosphorus, Ca × P and PTH in ESRD with coronary artery calcification found mixed results.[25] The importance of such biomarkers remains unclear.

Block and colleagues found that the risk of being hospitalised owing to cardiovascular events was associated with serum phosphate levels.[19] Increases in risk by serum phosphate levels compared with a reference group with phosphate levels of 1.29–1.61 mmol/l (4.0–5.0 mg/dl) are shown in *Table 4*. The same study found no association between cardiovascular hospitalisation and serum calcium levels. Levels of PTH greater than 63.6 pmol/l (600 pg/ml) were associated with greater risk (RR 1.17, 95% CI 1.06 to 1.29) than levels of 15.9–31.8 pmol/l (150–300 pg/ml). The authors suggest that this is largely due to high risk among those with very high levels of PTH, greater than 95.4 pmol/l (900 pg/ml), among whom the relative risk of cardiovascular hospitalisation was 1.26 (95% CI 1.12 to 1.42).[19]

Increased cardiovascular hospitalisation was also seen among patients who were male and/or white, had lower body weight or had diabetes.[19] In addition, it is suggested that some other traditional markers may be stronger indicators of cardiovascular risk than biomarkers even in the dialysis population, for example blood pressure, cholesterol, albumin and homocysteine levels.[13,26]

Factors influencing risk of fracture

A study of 101,039 patients with ESRD awaiting transplantation in the USA estimated the annual risk of hip fracture as 2.9 in 1000 patients.[27] PTH appears to be the most sensitive marker for disordered bone and mineral metabolism in CKD.[1,27] Elevated plasma PTH is negatively associated with measures of BMD.[1,28]

TABLE 5 *UK Renal Association standards for ESRD*

	Recommended serum values	Reference intervals[31]
PTH	< 4 times the upper limit of normal	0.9–5.4 pmol/l
Serum phosphate	<1.8 mmol/l	0.8–1.45 mmol/l
Serum calcium[a]	2.2–2.6 mmol/l	2.12–2.65 mmol/l

[a] Adjusted for albumin concentration in a predialysis sample.

Elevated PTH predicts the development of more severe hyperparathyroidism, which in turn is associated with increased skeletal and cardiovascular problems. However, detailed interpretation of the relationship of biomarkers with risk remains problematic. Block and colleagues found that phosphate concentration was significantly related to hospitalisation for fracture. The relative risk, per mg/dl increase in serum phosphate levels, was 1.12 (95% CI 1.03 to 1.22).[19] Patient characteristics associated with increased risk of fracture included age, being female, lower weight and longer time on dialysis. PTH levels were weakly associated with hospitalisation for fracture. No relationship was seen with calcium levels.

Current service provision

Haemodialysis is the usual therapy for people with ESRD. Four-hour dialysis sessions three times a week are typical.[6] Peritoneal dialysis is used by about 30% of UK patients as the initial treatment,[10] and involves dialysis fluid changes four or five times daily, or overnight.[6] However, most patients in the UK undergo haemodialysis and some patients on peritoneal dialysis may return to haemodialysis, especially in the last few months of life.[10] Studies comparing survival with different dialysis modalities are difficult to assess as patient groups are not usually comparable. However, a recent study of 1041 patients on dialysis followed for 7 years in the USA found no difference in survival for those on peritoneal dialysis compared with haemodialysis during the first year, but an increased risk was seen from the second year onwards (HR 2.34, 95% CI 1.19 to 4.59).[29]

Dialysis may also address calcium balance. In the past, high dialysate calcium concentration was used to allow calcium transport across the dialyser membrane. However, with increased use of calcium-containing phosphate binders and active vitamin D supplements which can lead to hypercalcaemia, lower concentrations are now recommended.[9]

While dialysis is life saving, at best it only replaces about 10% of normal renal function.[30] In addition to problems of SHPT, dialysis patients have other health problems such as water and salt retention, hypertension, anaemia, hyperlipidaemia and heart disease.[30] A change of diet and fluid intake is required for patients undergoing dialysis. Treatment (iron and epoetin) may also be needed to treat anaemia.

Transplant is a treatment option for those with ESRD, although the number treated is not large. In newly diagnosed ESRD, about 3% will receive a kidney transplant within the first 90 days.[16] In England for 2004/05, UK Transplant recorded a total of 1783 kidney transplants. Hospital Episode Statistics (HES) show that 63% of these were carried out in men at a mean age of 42 years (HES code M01). There has been a steady increase in transplants since 1998/99 (n = 1327), although the most recent figures are down 4% from 2003/04.

For patients on dialysis, a number of additional treatments may be used to try to maintain homeostasis. The Renal Association has set standards for the levels of serum minerals and hormones for patients with ESRD. These are shown in *Table 5*. The US National Kidney Foundation (NKF) has also produced clinical guidelines, the KDOQI for CKD,[2] and these are shown in *Table 6*. Conversion values from US units to UK units are shown in *Table 7*.

Some concerns about these targets have been noted, in particular the need for better clinical evidence to support any benefit of achieving these end-points.[19,32]

Accurate detection of PTH levels may be challenging. In kidney disease, fragments of PTH, which are biologically inactive, may build up in the body. Many commercial, so-called 'intact', PTH assays detect these fragments and may thus overestimate the degree of SHPT.[1] Some assays that detect only whole PTH ('bio-intact' hormone)

TABLE 6 *US National Kidney Foundation standards for CKD*[2]

CKD stage	Recommended serum values				
	GFR range (ml/min/1.73 m^2)	Phosphate (mg/dl)	Calcium[a] (mg/dl)	Ca × P (mg^2/m^2)	Intact PTH (pg/ml)
3	30–59	2.7–4.6	8.2–10.2	–	35–70
4	15–29	2.7–4.6	8.4–10.2	–	70–110
5	<15 or dialysis	3.5–5.5	8.4–9.5	<55	150–300
5 Converted to mmol/l		1.13–1.78	2.10–2.38	<4.4 $mmol^2/ml^2$	15.90–31.80

[a] Adjusted for albumin concentration in a predialysis sample.

TABLE 7 *Conversion values for grams to moles*

Serum biomarker	From	To	Conversion factor (×)
Parathyroid hormone	pg/ml	pmol/l	0.106
Calcium	mg/dl	mmol/l	0.25
Phosphate	mg/dl	mmol/l	0.3229
Ca × P	mg^2/dl^2	$mmol^2/l^2$	0.0807

are available, but there is wide variation in the use of different assays in the UK.[13] This is why there are no absolute levels given for circulating PTH. The Renal Association target (within four times the upper range of normal) allows for variation resulting from the use of different assays.

The Renal Registry records that 61% of dialysis patients in England and Wales in 2002 had phosphate levels controlled at the recommended level shown in *Table 5*. Phosphate control was found to be slightly better for patients on haemodialysis, although success in achieving targets varied between centres.[16]

The use of different methods to correct measured serum calcium for albumin concentration leads to difficulties in measuring the success of UK centres in meeting Renal Association calcium level targets. Furthermore, different methods may also be used to measure serum albumin. However, 63% of people are believed to have calcium levels within the target range based on local corrected results. The median reported corrected calcium level for all centres is about 2.4 mmol/l.[16]

Comparison of PTH levels across the centres that inform the Renal Registry is also difficult owing to the use of different assays. The median level for all dialysis patients is within the target, at about 19 pmol/l.[16] The Registry has tried to standardise the interpretation of data by using the median upper laboratory value from all assays used, and converting all measurements from grams to moles (giving a target of <32 pmol/l). Using this approach, about 66% of patients achieve the target, although there is wide variation between units.[16] Achievement of the target is similar on haemodialysis and peritoneal dialysis.

There is currently no Renal Association target for Ca × P. However, 67% of people meet KDOQI Ca × P targets of less than 4.4 $mmol^2/l^2$ (54.5 mg^2/ml^2). Again, there is a wide range across centres. Control of Ca × P levels is better with peritoneal dialysis than with haemodialysis.[16]

Current treatment for SHPT

The Department of Health published National Services Frameworks for renal services in 2004 and 2005.[6,18] Treatment of SHPT currently includes:

- reducing phosphate in the diet
- phosphate binders
- vitamin D supplements (in active forms such as calcitriol)
- parathyroidectomy.

Phosphate control

Reducing dietary phosphate may be difficult to achieve as some foodstuffs (e.g. fish, nuts and eggs), while high in phosphate, are also valuable protein sources. The Renal Registry suggests that dietitian support in collaboration with the prescribing team produces good results in ensuring that phosphate target levels are achieved.[16]

Phosphate binders reduce phosphate absorption in the gut through binding to phosphate in food. Tablets are taken during phosphate-rich meals. Three main types have been used:

- calcium-containing phosphate binders: these are cheap and may address hypocalcaemia, but carry an increased risk of hypercalcaemia owing to intestinal absorption of unbound calcium.[9,23] This risk is increased if activated vitamin D is also given
- aluminium-containing phosphate binders: these were used extensively in the past, but are used sparingly now despite the risk of aluminium toxicity being reduced since aluminium was removed from the water supply
- polymer binders (such as sevelamer): as an expensive phosphate binder, this is often reserved for second line treatment in the UK.

Vitamin D supplements

Vitamin D, in active form, may be given to patients with CKD and, if given early in the illness, may prevent progression to HPT.[18] Vitamin D therapy aims to reduce PTH secretion by increasing absorption of calcium through the gut and by a direct effect on PTH gene transcription. Treatment may lead to hypercalcaemia. Vitamin D analogues, especially if given in high doses intravenously, have been associated with increased Ca × P, which may increase vascular calcification.[32]

Parathyroidectomy

Advanced SHPT may be resistant to medical treatment. In these cases, the parathyroid glands may be surgically removed (parathyroidectomy). Renal Association guidelines recommend surgery if medical management cannot maintain PTH levels below four times the upper limit of normal, owing to an increased risk of significant bone disease at these levels.[10] In the USA, KDOQI guidelines reserve parathyroidectomy for patients with severe hyperparathyroidism (persistent serum levels of intact PTH >88.0 pmol/l) that is associated with hypercalcaemia and/or hyperphosphataemia that is refractory to medical therapy.

Incomplete excision of the parathyroid glands may mean that levels of calcium and PTH remain high. However, there is also a danger that low serum calcium levels resulting from a sudden removal of PTH may lead to an increased risk of bone disease.[33] There may therefore be a need for large calcium and vitamin D intake, and close monitoring at least in the short term.

Alternatively, subtotal parathyroidectomy or total parathyroidectomy with autograft of a small part of the gland in the arm, where it is accessible should further surgery be required, may be an option. Both latter methods are recommended by the KDOQI guidelines.

Parathyroidectomy may offer rapid improvement in quality of life for patients where very high PTH levels have led to symptoms such as bone pain, muscle weakness and itching.[34,35] Improvements in BMD have also been reported following parathyroidectomy.[36] However, persistent and recurrent SHPT is not uncommon, with 22% recurrence requiring medical or further surgical intervention reported over 5 years.[37]

A large cross-sectional study of over 17,000 dialysis patients in the USA, Europe and Japan showed differences between countries in parathyroidectomy rates of between 0.5 and 1.8 per 100 patient-years.[38] This study found a parathyroidectomy prevalence of 9.2% in the UK (1.5 per 100 patient-years).

In England for 2004/05 there were 2504 parathyroidectomies, 28% in men, among patients with a mean age of 59 years (HES code B14). This figure also includes treatment for primary hyperparathyroidism and tumours. There has been a steady increase in parathyroidectomies since 1998/99 (n = 1407).

One serious but uncommon complication of parathyroidectomy, with a rate of around 1/100, is vocal cord paralysis. Nerves serving the vocal cords run close to the parathyroid glands and can be damaged during surgery.

Limitations of current treatment

Currently, Renal Association targets for phosphate levels are met by 61% of the dialysis population, and targets for calcium and PTH are met by 63% and 67%, respectively.[16] Evidence from the USA shows only 5% of patients meeting all four KDOQI targets.[39]

Given the number of health problems that those on dialysis may have, such patients may take six to ten medicines daily.[30] Compliance is an issue. As many as 86% of dialysis patients are non-compliant with at least one aspect of their treatment.[30] Phosphate binders may have a poor taste, and may need to be taken in large quantities with each meal.[30] Non-compliance with dialysis has been shown to be associated with higher mortality.

Quality of life

Patients with ESRD on dialysis have significantly lower health-related quality of life (QoL) than the general healthy population. More severe grades of CKD have lower QoL with a higher prevalence of QoL impairments.[40]

QoL measures

Impairments in QoL in ESRD patients are wide ranging and relate to specific symptoms, reduced physical, psychological and social functioning, and change in employment status. Measures of QoL should therefore take each of these domains into account. Cagney and colleagues undertook a literature review of QoL instruments used in people with ESRD.[41] They identified 47 papers, published between 1975 and 1999, containing evidence of reliability and validity testing. Within this set, 53 QoL instruments were used, most generic (82%) and some disease specific (18%).

Generic measures of QoL

The Sickness Impact Profile (SIP, *Table 8*) was the most frequently used generic measure identified by Cagney and colleagues.[41] Both this and the Short Form 36 (SF-36) have been rigorously tested in the ESRD population and have reported striking differences in QoL compared with the general population. The SIP consists of 136 items, measuring 12 QoL dimensions. These are weighted by severity of dysfunction. Higher scores indicate greater dysfunction.

TABLE 8 *Dimensions of the generic SIP*

Physical	Psychosocial
Ambulation	Social interaction
Mobility	Communication
Body care	Alertness behaviour
Movement	Emotional behaviour
	Sleep and rest
	Eating
	Home management
	Recreation and pastimes
	Employment

A cross-sectional, multicentre Spanish study assessed 1013 randomly selected people who had been receiving dialysis for at least 3 months (age 53 ±15 years, 88% on haemodialysis).[42] Severe impairment in quality of life was seen in 26% of people assessed using the SIP, where a score of 20 or above indicates the need for substantial daily care. In the general population, average scores are about 5.

The SF-36 is scored from 0 to 100, with a higher score indicating a better perceived health status. Eight health domains are assessed: physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional and mental health. Another Spanish group published a number of studies using standardised SF-36 scores to investigate the impact of ESRD (n = 170) compared with an age- and gender-matched general population sample (n = 9151).[43] Better QoL than the general population is indicated by a score over zero, and a worse QoL relative to the general population is indicated by a score less than zero (*Table 9*).

The scores of those aged over 65 were closer to zero than those under 65, showing that older people with ESRD experience less QoL loss than their younger counterparts, compared with their peers. The standardised scores for patients under 65 were compared with those over 65. Significant differences were found in three domains (*Table 9*). Compared with a similarly aged general population, the impact of ESRD is greater in terms of general health in older patients, while

TABLE 9 *Standardised SF-36 scores comparing age <65 versus age >65 years in patients on chronic haemodialysis*

	Age <65 years (n = 71)	Age >65 years (n = 99)
Physical functioning **	–0.99 ± 1.07	–0.46 ± 0.87
Role – physical *	–0.53 ± 1.27	–0.09 ± 1.06
Bodily pain	–0.38 ± 1.01	–0.09 ± 0.98
General health **	–1.49 ± 0.93	–0.73 ± 0.85
Vitality	–0.53 ± 0.96	–0.25 ± 0.99
Social functioning	–0.35 ± 1.49	–0.11 ± 0.99
Role – emotional	–0.56 ± 1.47	–0.27 ± 1.3
Mental health	–0.18 ± 1.13	–0.11 ± 1.14

** p<0.01; * p<0.05 for people aged <65 versus >65 years on dialysis.

TABLE 10 *TTO values in ESRD*

Study	Sample	Age (years)	Dialysis type	Utility value (SD)
Churchill, 1984[44]	42	50	HD	0.58
	17	42	CAPD	0.66
Churchill, 1987[45]	60	NR	Hospital HD	0.43 (0.26)
	57	NR	Home HD	0.49 (0.23)
	52	NR	CAPD	0.56 (0.29)
Churchill, 1991[46]	47	60	HD	0.44 (0.28)
de Wit, 1998[47]	46	NR	HD	0.87 (0.2)
	23	NR	LCHD	0.93 (0.22)
	59	NR	CAPD	0.86 (0.23)
	37	NR	CCPD	0.93 (0.14)
de Wit, 2002[48]	69	60	HD	0.89 (0.15)
	66	55	PD	0.87 (0.21)
Hornberger, 1992[49]	58	53	NR	0.72 (NR)
Molzahn, 1996[50]	215	46	NR	0.39 (0.32)

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; HD, haemodialysis; LCHD, limited care haemodialysis; NR, not reported.

younger patients are more greatly affected in terms of physical role and physical functioning.

The time-trade off (TTO) technique is a preference-based method of evaluating QoL that has also been validated in the ESRD population. People are offered choices between living for a specified time in perfect health or living for a longer time with impaired health. A score of 0 is equivalent to death and 1 represents full health. Negative scores, indicating a health state worse than death, are also possible.

Six papers were identified that used TTO methods to obtain utility values among people with ESRD. These are summarised in *Table 10*. Utility estimates ranged from 0.39 to 0.93 (median = 0.69).

Disease-specific measures of QoL

Disease-specific questionnaires provide additional information related specifically to the condition and may be more responsive to clinical changes and treatment effects. The Kidney Disease Questionnaire (KDQ) and Kidney Disease – Quality of Life (KDQoL) (*Table 11*) have been adequately tested in the ESRD population.

The KDQoL Short Form (SF), one of the most widely used disease-specific measures, uses 43 disease-specific items, 36 generic items and an overall health-ranking item. Development of the KDQoL incorporated field-test data highlighting the thought processes of patients, what troubled them and the vocabulary they used to describe factors that affected their quality of life. Validity testing has involved correlating the KDQoL-SF with generic measures, such as EuroQoL, SF-36 and SIP, in patients with kidney disease.[51]

Factors associated with reduced QoL in ESRD

QoL relating to ESRD directly is difficult to measure as reduction in QoL is only partly related to kidney failure itself; treatment, complications of kidney disease, co-morbidity such as diabetes and CVD, and socio-demographic factors all have an impact on the perception of QoL. Poor QoL is associated with higher mortality.[52,53]

Impact of treatment on QoL

Among people on dialysis, the majority of studies looking at differences in QoL between haemodialysis and peritoneal dialysis report no significant difference in QoL.[54] Apparent differences in QoL between haemodialysis and peritoneal dialysis may be attributable to differences in effective renal replacement, reduced clinical complications, lifestyles afforded by these treatment modalities or case-mix differences in patient populations.[54]

Dialysis is an intrusive and time-consuming treatment that requires changes in people's lifestyle that may affect QoL. QoL outcomes may also have an impact on the dialysis regimen itself; almost 50% of withdrawals from dialysis are reported to be due to poor QoL.[55] Daily dialysis

TABLE 11 *Dimensions of the disease-specific KDQoL-SF questionnaire*

Generic	Disease specific
Physical functioning	Symptom/problem list (sore muscles, headaches, cramp, itchy skin, shortness of breath, dizziness, nausea)
General health	Effects of kidney disease (restrictions on fluid/dietary intake, impact on work, travel and lifting objects)
Pain	Burden of kidney disease (extent to which kidney disease causes frustration and interference with life)
Role – physical	Work status
Emotional well-being	Cognitive function
Role – emotional	Quality of social interaction (extent of irritability with other people/isolation from others)
Social function	Sexual function
Energy and fatigue	Sleep Social support Dialysis staff encouragement (extent to which person feels supported and encouraged by dialysis staff) Patient satisfaction (with overall care received) Overall health rating

TABLE 12 *Factors related to health-related QoL in dialysis patients*

Better QoL	Poorer QoL
Haematocrit/haemoglobin	Associated diseases (co-morbidity)
Socio-economic level	Diabetes
Educational level	Intermittent claudication
Dialysis schedule (daily dialysis, home haemodialysis, peritoneal dialysis)	Previous failed transplant
Black race	Female gender
Physical exercise	Depression
	Poor nutritional status
Adapted from Valderrabano *et al*. (2001).[54]	

appears to improve QoL.[56–58] Nocturnal short-term daily dialysis performed six to seven times weekly may have beneficial effects on QoL.[56,59] Improvements in metabolic control, cardiovascular morbidity and dialysis-related symptoms, as well as physical and social function, may be seen when dialysis is more frequent.

Other factors impacting on QoL

QoL may also be negatively affected by complications of CKD and co-morbid conditions, such as diabetes and CVD.[54] Nutrition is an important factor influencing the morbidity and mortality of patients with ESRD,[60] and anaemia has also been associated with poor QoL.[42] QoL and depression are closely linked and are also associated with increased co-morbidity, worse nutritional status, anaemia, low renal function and a high rate of peritonitis.[61] The prevalence of depression in people with ESRD varies depending on the measure used to detect it, but studies suggest that up to 70% of people on dialysis have some degree of depression.[61] People on dialysis are less active than the normal population and increased physical activity in this group is recommended.[62] The effects of physical activity on self-reported physical functioning may be of clinical importance because these scores have been shown to be highly predictive of outcomes such as hospitalisation and mortality in haemodialysis patients.[62] *Table 12* summarises elements associated with better and worse QoL in people on dialysis.

Description of the new intervention: cinacalcet

Licensing

Cinacalcet hydrochloride (trade name Mimpara®; Amgen) was licensed by the European Medicines

Agency (EMEA) in July 2004 for SHPT in people with ESRD on maintenance dialysis and for the reduction of hypercalcaemia in people with parathyroid carcinoma. The first of these indications is assessed here.

Dosage

Patients are initially given a dose of 30 mg per day, which is stepped up to a maximum of 180 mg per day if lower doses fail to control PTH levels. Blood levels need to be monitored every 2–4 weeks over the initial treatment phase to optimise the dose.

Costs

All costs are taken from the British National Formulary (BNF) number 50 (September 2005):[63]

- 30 mg, 28-tab pack = £126.28 (15p per mg)
- 60 mg, 28-tab pack = £232.96 (14p per mg)
- 90 mg, 28-tab pack = £349.4 (14p per mg).

Pharmacology

Cinacalcet is a calcimimetic agent: it acts on the calcium-sensing receptors on the parathyroid glands to increase their sensitivity to extracellular calcium.[30] This quickly suppresses the production of PTH, and in turn may reduce serum calcium and phosphate levels.[64]

Precautions

As cinacalcet may lower the amount of calcium in the blood and low calcium levels may increase the chance of seizures, blood calcium levels need to be monitored.

On-label precautions include:

- Patients should report the symptoms of low blood calcium immediately. Symptoms of low blood calcium include abnormal tingling sensations, muscle pain, cramping, spasms and seizures.
- Cinacalcet may cause adynamic bone disease if PTH levels drop too low.
- Patients with liver problems may need a lower dose of cinacalcet. Patients with liver problems should be monitored carefully during treatment.

Common adverse effects are:

- nausea and vomiting
- diarrhoea
- muscle pain
- dizziness
- high blood pressure
- weakness and tiredness
- loss of appetite.

Chapter 3

Systematic review of effectiveness

Research question

What is the effectiveness of cinacalcet compared to standard treatment for people on dialysis with hyperparathyroidism secondary to ESRD?

Review team and advisory group

This review was carried out by the Peninsula Technology Assessment Group (PenTAG), by Ruth Garside, Martin Pitt, Rob Anderson, Richard D'Souza, Stuart Mealing, Chris Roome, Ailsa Snaith, Karen Welch and Ken Stein.

An expert advisory group was formed for the project (see Appendix 2). This group was consulted during the assessment and provided comments on an early draft of the report. Members were Ms Caroline Ashley, Dr Henry Brown, Professor Terry Feest, Dr Jonathan Kwan, Professor Alison MacLeod, Dr Paul Roderick and Dr Robin Winney.

General methods

The review adopted the methodological approach published by the NHS Centre for Reviews and Dissemination (York) Report No. 4.[65] The study protocol is provided in Appendix 3.

Methods for systematic review of effectiveness

Inclusion criteria

- Intervention: cinacalcet HCI in licensed doses
- comparators:
  - placebo
  - 'standard care', which may include: phosphate binders, vitamin D and/or parathyroidectomy
- population: people with hyperparathyroidism secondary to ESRD on peritoneal dialysis or haemodialysis.
- study design: randomised controlled trials (RCTs) with at least 12 weeks' follow-up
- outcomes:
  - mortality
  - incidence of cardiovascular events
  - incidence of fractures
  - health-related QoL
  - symptoms related to hyperparathyroidism
  - serum PTH, calcium, phosphate and Ca × P product levels
  - parathyroidectomy
  - hospitalisation
  - adverse effects.

Exclusion criteria

- Population:
  - people with renal disease not on dialysis
  - primary hyperparathyroidism
- study design:
  - RCTs with less than 12 weeks' follow-up
  - study designs other than RCTs.

Search strategy

Electronic databases were searched for published systematic reviews, RCTs, economic evaluations and ongoing research in March 2005 and updated in February 2006. Appendix 4 shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant studies, and the US Food and Drug Administration (FDA) website was searched for relevant material.

Identification of studies

Relevant studies were identified in two stages. Abstracts returned by the search strategy were examined independently by two researchers (RG and KS) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (RG and KS) examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is illustrated in Appendix 5 and excluded studies are listed in Appendix 6.

Data extraction strategy

Data were independently extracted by two researchers (AS and CR). Disagreements were resolved by discussion. Actual numbers were extracted where possible. In some cases data had to be extracted from graphs and may be subject to inaccuracies. Such data are identified in the data extraction sheets. Data extraction forms for each included study are shown in Appendix 7.

Quality assessment strategy

Assessments of RCT quality were performed using the indicators shown below. Results were tabulated and these aspects described.

Internal validity

- Sample size
  - power calculation at design
- selection bias
  - explicit eligibility criteria
  - proper randomisation and allocation concealment
  - similarity of groups at baseline
- performance bias
  - similarity of treatment other than the intervention across groups
- attrition bias and intention-to-treat (ITT) analysis
  - all patients are accounted for
  - number of withdrawals specified and reasons described.
  - analysis undertaken on an ITT basis
- detection bias
  - blinding
  - objective outcome measures
  - appropriate data analysis.

Any potential conflict of interest was noted (for example, financial support provided to studies and/or authors by manufacturers of the interventions).

External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Study findings can only be effectively generalisable if they either describe a cohort that is representative of the affected population at large or present sufficient detail in their outcome data to allow the reader to extrapolate findings to a patient group with different characteristics.

Generalisability of included studies was assessed by examining the age, gender and race profile of the included patients, as well as their baseline mineral and PTH serum levels. Studies that were representative of the UK population with regard to these factors were judged to have high external validity.

Methods of analysis

Details of the methodology and results of included trials are tabulated and described in the text. Results from RCTs are presented in the same tables. Where calculated by the authors, χ^2 statistics were derived using the CHIDIST function of Microsoft Excel.

The results were not combined using meta-analysis in this review, because the major trials have already been reported in combination using patient-level data.

Most of the papers report outcome measure in metric units. These have been adjusted and are presented in standard units using the conversion factors shown in *Table 7* (p. 10).

Results of the systematic review: quantity of research available

Number and type of trials identified

Three Phase II RCTs with less than 12 weeks' follow-up were identified.[66–69] These were excluded from the main review.

Seven published reports of RCTs investigating cinacalcet for patients with ESRD on dialysis were identified (*Table 13*).[66,70–72,74–76] In addition, the FDA website contains its medical, statistical and pharmacological reviews of reports on four RCTs submitted by Amgen: trial numbers 20000172, 20000183, 20000188 and 20010141.[77] For simplicity, the remainder of the report refers to these trials by their last three digits only. These trials are summarised in *Table 14*.

TABLE 13 *Published RCTs of cinacalcet and their Amgen study numbers*

Publication	Amgen trial numbers	No. of patients
Block, 2004[70]	172 and 183	741
Cunningham, 2005[71]	Post-hoc analysis of patients in 172, 183, 188 and 141	1184
Lien, 2005[75]	Unclear: subgroup from 188 and 239	14
Lindberg, 2003[72]	990101 (no further details)	78
Lindberg, 2005[66]	188	395
Moe, 2005[76]	Combined data from 172, 183 and 188	1136
Quarles, 2003[74]	Study no. 730 (no further details)	71

Data from Amgen 172, 183, 188 and 141 appear to have been used for most of the identified publications. The paper by Block and colleagues[70] is based on Amgen 172 and 183, while Lindberg and colleagues (2005)[66] is based on Amgen 188. In addition, the paper by Moe and colleagues[76] reports combined data from Amgen 172, 183 and 188. Separate data from these publications are only reported where they are presented in a form not available in the FDA data (for example, the achievement of KDOQI guidelines). Similarly, the paper by Cunningham and colleagues[71] is a post hoc analysis of patients from all four Amgen trials (172, 183, 188 and 141) which looks at unique outcomes (such as fracture risk and mortality) and these data are reported here. This leaves three smaller RCTs, reported in publications by Lien and colleagues (n = 14),[75] Lindberg and colleagues (2003, n = 78)[72] and Quarles and colleagues (n = 71).[74] Lien and colleagues[75] report on a subgroup of patients from Amgen 188 and from another study. They provide information about BMD that is not reported in the main trial reports of Amgen 188. The other published reports are on based trials other than Amgen 172, 183, 188 and 141.

The authors have chosen to use the Amgen trial reports submitted to the FDA and reported on in their medical review as the primary source for the review. This is for several reasons. There is more detail, in terms both of methodology and outcomes, in the FDA medical review. For example, information about seizures is not reported in the published papers. In addition, many outcomes pooled across all three main trials are reported in the FDA medical review. As there are some small differences in the reported numbers between the Amgen trial data presented in the FDA medical review and the published reports, it was decided that only one source should be used.

Amgen trials reported by the FDA medical review

Amgen 172 (n = *410*), *Amgen 183* (n = *331*), *Amgen 188* (n = *395*)

Most of the evidence in the review comes from three, 6-month, randomised, double-blind, placebo-controlled Phase III trials of patients with SHPT on dialysis. Amgen 172 and 183 used a 12-week dose-titration period followed by a 14-week period of efficacy assessment and Amgen 188 had a 16-week dose titration and a 10-week efficacy assessment period. In total, 471 patients were randomised to placebo and 665 patients to cinacalcet across these three trials. Pooled data for these three trials were provided to the FDA.[77]

Amgen 141 (n = *48*)

This 52-week, multicentre, randomised, placebo-controlled, double-blind study was designed to evaluate the effects of cinacalcet on renal osteodystrophy (metabolic bone disease) in haemodialysis patients with secondary hyperparathyroidism. The study consisted of a 24-week dose-titration phase and a 28-week maintenance phase. In total, 48 patients were randomised in a 2:1 ratio to receive cinacalcet or placebo.

In all of the above trials, patients were treated with 30 mg once daily of cinacalcet or placebo. This dose could be increased to 50, 70, 90, 120 and 180 mg over the titration phase if lower doses failed to control PTH levels.

Dosing information

The FDA submission from Amgen reported that at the completion of the three Phase III trials 40% of patients were receiving 180 mg once daily of cinacalcet, while the remaining 60% of patients were equally divided among the 30, 60, 90 and 120 mg doses.[77]

Amgen 141 reported that at the end of the study (week 52) 19% of cinacalcet-treated patients were on the the 30 mg dose, 6% on the 50 mg dose, 9% on the 70 mg dose, 22% on the 90 mg dose, 13% on the 120 mg dose and 31% on the 180 mg dose.

Quarles and colleagues reported that 50% of the patients who completed the titration phase reached and sustained the 100 mg dose; that is, the maximum daily dose in this study.[74] Daily doses of 75 mg and 50 mg were reached in 41% of patients, whereas 9% of patients did not escalate above 25 mg; that is, the initial dose in this study.

Results of the systematic review: quality of included trials

The quality criteria for the included trials are summarised in *Table 15*.

Internal validity

Sample size

Amgen 172, 183, 188 and 141 were appropriately powered for the primary outcomes under consideration. With the exception of the study by Quarles and colleagues,[74] details of study power are lacking from the published trials.

TABLE 14 *Study characteristics*

Study	Study design	Sample size	Intervention	Comparator	Concurrent treatment	Setting	Length of treatment
Amgen 172	Phase III RCT	410	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 205)	Placebo (n = 205)	Vitamin D sterols Phosphate binders	Multiple centres (63) USA and Canada	26 weeks (12-week dose titration and 14-week efficacy assessment)
Amgen 183	Phase III RCT	331	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 m (n = 166)	Placebo (n = 165)	Vitamin D sterols Phosphate binders	Multiple centres (62) Europe and Australia	26 weeks (12-week dose titration and 14-week efficacy assessment)
Amgen 188	Phase III RCT	395	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 294)	Placebo (n = 101)	Vitamin D sterols Phosphate binders	Multiple centres (60) USA, Canada and Australia	26 weeks (16-week dose titration and 10-week efficacy assessment)
Amgen 141	Phase II RCT	48	Cinacalcet 30 mg with dose titration to 50, 90, 120 and 180 mg (n = 32)	Placebo (n = 16)	Vitamin D sterols Phosphate binders Calcium supplements	Multiple centres (17) USA and Europe	52 weeks (24-week dose titration and 28-week efficacy assessment)
Block, 2004[70]	Combined analysis of two Phase III RCTs (172 and 183)	741	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 371)	Placebo (n = 370)	Vitamin D sterols Phosphate binders	Multiple centres (125) North America, Europe and Australia	26 weeks (12-week dose titration and 14-week efficacy assessment)
Cunningham, 2005[71]	Combined analysis of four RCTs (172, 183, 188 and 141)	1184	Cinacalcet 20 or 30mg with dose titration to 180 mg (n = 679)	Placebo (n = 487)	Vitamin D sterols Phosphate binders	Multiple centres (202) USA, North America, Europe and Australia	Two trials: 26 weeks (12-week dose titration and 14-week efficacy assessment) One trial: 26 weeks (16-week titration and 10-week efficacy assessment) One trial: 52 weeks (24-week dose titration and 28-week efficacy assessment)
Lien, 2005[75]	Subgroup from RCT	14	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 8)	Placebo (n = 6)	Vitamin D sterols Phosphate binders	Single centre (USA)	26 weeks (12-week dose titration and 14-week efficacy assessment) for haemodialysis subjects 18 weeks for predialysis subjects

continued

TABLE 14 *Study characteristics (cont'd)*

Study	Study design	Sample size	Intervention	Comparator	Concurrent treatment	Setting	Length of treatment
Lindberg, 2003[72]	RCT	78	Cinacalcet 20 mg with dose titration to 30, 40 and 50 mg (n = 39)	Placebo (n = 39)	Vitamin D sterols Phosphate binders	Multiple centres (25) USA and Canada	18 weeks (12-week dose titration and 6-week efficacy assessment)
Lindberg, 2005[66]	RCT	395	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 294)	Placebo (n = 101)		Multiple centres (60) USA, Canada and Australia	26 weeks (16-week dose titration and 10-week efficacy assessment)
Moe, 2005[76]	Combined analysis of three phase III RCTs (172, 183 and 188)	1136	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180 mg (n = 665)	Placebo (n = 471)	Vitamin D sterols Phosphate binder	Multiple centres (182) USA, Canada, Europe and Australia	26 weeks Two trials (12-week dose titration and 14-week efficacy assessment) One trial (16-week dose titration and 10-week efficacy assessment)
Quarles, 2003[74]		71	Cinacalcet 25 mg with dose titration to 50, 75 and 100 mg (n = 36)	Placebo (n = 35)	Vitamin D sterols Phosphate binders		18 weeks (12-week dose titration and 6-week efficacy assessment)

Selection bias

Randomisation

Randomisation methods are generally not detailed in either the FDA medical review of the Amgen trials or the published trials. The exception is Quarles and colleagues,[74] which describes randomisation using an interactive voice response system. Amgen 172, 183 and 188 state that dose titration bottle numbers were provided by 'the IVRS', without further explanation. It therefore seems likely that an interactive voice response system was used for all these trials. Such a method of central allocation is sound.

Lien and colleagues analysed BMD data for RCT 'completers' at one study centre. It is not clear whether all completers were included in this analysis, thus a potential source of selection bias cannot be ruled out.[75]

Similarity of groups at baseline

Individually, the studied groups in Amgen 172, 183, 188 and 141 appear well matched at baseline. However, in the pooled analysis by Cunningham and colleagues[71] there are significant differences in terms of age, ethnicity and dialysis modality at baseline. Presumably this is due to small differences in these individual trials being compounded when they are combined. A significantly higher proportion of people in the cinacalcet group were aged below 65 years and younger mean age at randomisation was also reported. In addition, there were more black patients in the cinacalcet group. While lower age may bias in favour of cinacalcet, different racial mix may bias against cinacalcet. Prevalence of diabetes, a potential confounder for the impact of race, was similar. There were more patients on peritoneal dialysis among those receiving cinacalcet.

Small differences in baseline characteristics were also noted in other trials, but their impact on biochemical results is unknown. In Amgen 141, the proportion of diabetic patients was almost twice as great in the placebo group as in the cinacalcet group, although this difference (44% versus 25%) was not statistically significant. The study by Quarles and colleagues had more men in the control than in the treatment arm.[74]

Performance bias

Similar proportions of both arms were initially receiving vitamin D sterols and phosphate binders in Amgen trials 141, 172, 183 and 188 as well as in Lindberg (2003)[72] and Quarles.[74]

Lindberg and colleagues (2003)[72] reported similar levels of vitamin D sterol and phosphate binder use in both in cinacalcet and placebo arms during the study.

Subgroup analyses by the numbered Amgen trials and Quarles and colleagues[74] reported that greater percentage reductions from baseline in PTH were observed in the cinacalcet group regardless of whether they had an increase, decrease or no change in vitamin D sterol dose from baseline.

Protocol violations were well described for Amgen trials 172, 183 and 188, and although numerous, were not considered likely to bias the results.

The published trials provided little or no information on protocol violations.

Attrition bias and ITT analysis

Different rates of attrition between active and control groups were observed in the trials, particularly study 183, where 80% of the placebo group completed the study compared with 64% of the cinacalcet study ($p = 0.002$, calculated by PenTAG).

In contrast to the other trials, the withdrawal rates from the trial by Quarles and colleagues[74] were higher in the placebo group. This paper does not report reasons for withdrawal. Although stated as an ITT analysis, this data set is not defined and there is no detail on how missing data points were handled.

Detection bias

Allocation concealment

Most trials report that numbered bottles were used and that the trials were 'double blind', but further details are not provided. Only Quarles and colleagues[74] report that placebo and active tablets were identical. In addition, given that biochemical measures generally deviated between cinacalcet and placebo groups early in therapy, it is questionable whether concealment of allocation was maintained throughout the study.

Analysis

The study by Cunningham and colleagues[71] is a retrospective, post hoc analysis of Amgen 172, 183, 188 and 141. Data for mortality, fracture, parathyroidectomy and cardiovascular events based on safety monitoring in the original trials were synthesised. Most of these data are based on trials with 6-month follow-up, with only between 268 and 305 patients remaining at risk in the study at week 38 (from the original 1184 included). Most of these are people participating

TABLE 15 *Summary of quality criteria for included RCTs*

Study	Power calculation	Randomisation method	Allocation concealment	Assessors blinded?	Groups similar at baseline	ITT	Protocol violations specified	Missing value treatment	Attrition	All patients accounted for
Amgen 172 (n = 410)	Yes	1:1 stratified by baseline PTH and Ca × P. Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	'Double blind'; no details given	Yes	Yes	Specified, numerous, but if anything would underestimate the efficacy of cinacalcet	Adequate: three analyses undertaken yielding similar results: 1. count as non-responders. 2. exclude 3. LOCF	Similar proportions (77% placebo vs 71% cinacalcet) completed the trial	Yes
Amgen 183 (n = 331)	Yes	1:1 stratified by baseline PTH and Ca × P Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	'Double blind'; no details given	Yes	Yes	Specified, numerous evenly distributed between treatments	Adequate: three analyses undertaken yielding similar results: 1. count as non-responders 2. exclude 3. LOCF	Significantly more patients receiving placebo completed the trial (80% vs 64%, $p = 0.002^a$) Main reason is AEs, 23% vs 5%	Yes; withdrawal reasons specified
Amgen 188 (n = 395)	Yes	3:1 stratified by baseline PTH and dialysis modality Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	'Double blind'; no details given	Yes	Yes	Specified and evenly distributed between treatments	Adequate: three analyses undertaken yielding similar results: 1. count as non-responders 2. exclude 3. LOCF	About three-quarters of each group completed the study	Yes; withdrawal reasons specified

continued

TABLE 15 *Summary of quality criteria for included RCTs (cont'd)*

Study	Power calculation	Randomisation method	Allocation concealment	Assessors blinded?	Groups similar at baseline	ITT	Protocol violations specified	Missing value treatment	Attrition	All patients accounted for
Amgen 141 (n = 48)	Yes	2:1 Methods not stated	Unclear	'Double blind'; no details given	Generally yes, but incidence of diabetes higher in the placebo group (44% vs 25%)	Yes	Specified and evenly distributed between treatments	Not stated	Withdrawals twice as frequent in cinacalcet group (38% vs 19%, ns[a])	Yes; withdrawal reasons specified
Cunningham, 2005[71] (n = 1184)	Not stated	Study pools patients from numbered trials 141, 172, 183 and 188	Numbered bottles but no further details given	'Double blind'; but no details given	Yes, but significant differences in proportion of patients aged < 65 years (77% vs 71%), age at randomisation (53 vs 54.7 years), ethnicity, and dialysis modality	Yes	Not stated	Not clear in survival analyses. For subjective measures 238 patients provided no efficacy data and were excluded, 22 provided no baseline data and were excluded	Not clear	Not detailed
Lien, 2005[75] (n = 14)	No	Included 14 patients who completed numbered trials 188[b] (n = 10) and 239[c] (n = 4) at one centre	No details	'Double blind'; no details given	More males in the placebo group	No	Yes	No. Analysis on completers only	Not relevant as analysis is on completers only	Yes

continued

TABLE 15 *Summary of quality criteria for included RCTs (cont'd)*

Study	Power calculation	Randomisation method	Allocation concealment	Assessors blinded?	Groups similar at baseline	ITT	Protocol violations specified	Missing value treatment	Attrition	All patients accounted for
Lindberg, 2003[72] (n = 78)	Not stated	1:1 Method not stated	No details given	'Double blind'; no details given	Yes	Yes	None specified	Not clear, but for the primary outcome variable missing values would be classed as non-responders	Similar proportions of patients completed the study (87% and 82%)	Yes, but reasons for withdrawal not stated
Moe, 2005[76] (n = 1136)	Not stated	Pooled reanalysis of results from numbered trials 172, 183 and 188	No details given	'Double blind'; no details given	Yes	No	None specified	Not described	Not detailed but 74% overall completed the trials	No
Quarles, 2003[74] (n = 71)	Yes	1:1 Interactive voice response system	Identical tablets; no further details given	'Double blind'; no details given	More women in placebo group (51% vs 25%, p = 0.04[a])	Yes	None stated	Not detailed	5.5% withdrew from cinacalcet group vs 11.4% from placebo group (ns[a]). No reasons given	No: data at week 18 suggest that one cinacalcet and three placebo group patients are unaccounted for

AE, adverse event; IVRS, interactive voice response system; LOCF, last observation carried forward; ns, not significant.
[a] Calculated by PenTAG.
[b] There is a discrepancy between the designs of the FDA study number 20000188 and that described in the methods section of Lien.[75]
[c] FDA study number 20010239 was conducted in patients not receiving dialysis and is excluded from this review.

in a study extension, and it is not reported how these patients were selected, or whether they are representative of the originally randomised population. Baseline characteristics already differed, with significantly more people aged under 65 years, fewer white people and more people on peritoneal dialysis in the cinacalcet arm. No adjustment is made in the analysis for these potential confounders. By the end of the analysis, around 21% of the originally randomised population were still providing data. The titration phase of the trials appears to contribute more than half of the total patient-weeks of exposure.

There is a lack of transparency about censoring the survival analysis carried out by Cunningham and colleagues.[71] Depending on the outcome reported, different numbers of patients are reported at risk at the same time-point and there is no explanation for this.

To enable comparison of event rates between cinacalcet and placebo groups, the number of events was expressed as the event rate per 100 patient-years. Using this way of presenting data, a patient exposed to a drug for 1 year contributes as much data as, for example, four patients exposed for 13 weeks each. The following formula was used to calculate the event rate per 100 patient-years:

$$\text{Event rate per 100 years} = \frac{\text{Events}}{\text{Duration of exposure in the group}} \times 100$$

Total exposure is expressed as patient-years, and is a crude rate, unmodified for any potential covariates. The duration of exposure in the cinacalcet group was 1.27 times the duration of exposure in the placebo group. However, 1.44 times more patients were originally randomised to cinacalcet owing to asymmetric randomisation in the trials. The relatively reduced exposure for those receiving cinacalcet is due to more withdrawals. This reduces the numbers of people at risk of adverse events proportionally more for those receiving cinacalcet compared with those receiving standard treatment. Only around 28% of those receiving standard treatment and 18% of those receiving cinacalcet provided data at 52 weeks. The results at 1 year are thus based on a very small proportion of the original study population.

The difference in the number of parathyroidectomies needed in each group and the associated very small p-value ($p = 0.009$) would appear convincing. The reduction in risk indicates that one parathyroidectomy would be prevented for every 26 patients treated with cinacalcet rather than placebo [= 1/(0.041–0.003)]. However, data are sparse, with only one parathyroidectomy recorded in the cinacalcet group and 12 in the control group. A reduction in parathyroidectomy rate is biologically plausible, as one of the key determinants driving the decision to proceed to parathyroidectomy would be biochemical measures. However, it is unclear, given the short follow-up and small numbers, whether it is possible to extrapolate these results to the longer term.

There were significantly fewer fractures among those treated with cinacalcet. The curves for placebo and cinacalcet diverge early in treatment (by week 12 of the titration phase).

Although significantly fewer cardiovascular-related hospitalisations were reported with cinacalcet, no difference was seen in hospitalisation for all causes. In the cinacalcet arm, the survival curves show no events between weeks 28 and 40. This is not in keeping with the trend observed through earlier and later time-points, where events appear to be recorded at regular intervals. The plateau period coincides with the time of greatest attrition: 61% in the placebo arm and 68% in the cinacalcet arm. This difference in attrition may affect the results of the comparison if these patients are excluded from analysis. The rate of events after this plateau period appears faster than before, an effect of many patients being censored during weeks 28–40.

Despite apparent differences in fracture and cardiovascular events, no significant difference was observed in all-cause hospitalisation or all-cause mortality in this study. Again, this may indicate that short-term follow-up is insufficient to identify clinically important differences.

External validity

Biochemical markers were used as the primary outcome in Amgen 172, 183 and 188, and by Lindberg and colleagues (2003)[72] and Moe and colleagues (2005)[76] (reanalysis of pooled data from Amgen 172, 183 and 188). While the maintenance of these markers within defined ranges is a treatment goal, the impact of this on important clinical outcomes, such as cardiovascular events and mortality, and fractures, is still uncertain.

The main outcome measures for the trials relate to achieving PTH levels below targets (e.g. ≤26.5 pmol/l) or minimum reductions of a certain level (at least 30%). However, oversuppression of

PTH may also be problematic, potentially leading to adynamic bone disease at levels below 10.6 pmol/l. Limited information about this is presented in the FDA medical review, but none is reported in the published trials.

Although, in general, study groups were well matched in the trials, some contained a higher number of black participants than may be expected in a UK population being considered for treatment. Data from the UK Renal Registry suggest that 3.2% of the UK dialysis population are black, whereas in Amgen trials 172, 188 and 141 the proportions of black participants were 58%, 65% and 37% respectively. It is known that black patients tend to have a higher parathyroid gland mass, predisposing them towards more severe SHPT which may be treatment resistant.[78] However, stratified analysis showed no indication that the response to treatment varies with ethnicity.[70]

The assay used to measure PTH values in the trials was the Nichols intact immunoradiometric assay (IRMA). Other assays may report PTH values higher or lower than this. For example, the Nichols Advantage intact PTH assay reports values 30–50% higher than those recorded by the IRMA, meaning that undetected oversuppression of PTH is a possibility.[77]

Lien reports BMD measurements in a small group of patients participating in other trials.[75] There appears to be an inconsistency in the reporting of lumbar spine measures. The BMD was observed to decrease in both groups, yet an improvement in T-score is reported, which is not logical. The relevance of the findings of this small study is therefore not clear.

Amgen 172 and 183 restricted the proportion of recruited people who had very high levels of PTH (>800 pg/ml, 85 pmol/l) to 20%. In Amgen 188 there was no such restriction and 40% of those recruited to the trial had levels of PTH above 85 pmol/l. However, as trial data are reported by subgroup, extrapolation of the results to the appropriate patient group remains possible.

The analysis of clinical outcomes by Cunningham and colleagues[71] reports mortality rates of 5.2 per 100 patient-years for those treated with cinacalcet and 7.4 per 100 patient-years for those receiving standard treatment. This is much lower than the rates reported in by the UK Renal Registry, where overall mortality rates are 15.0 per 100 patient-years for the prevalent dialysis population (16.0 per 100 patient-years in those aged 55–64 years).[16] This suggests that the population recruited into Amgen 172, 183, 188 and 141 was much fitter than the general clinical population in the UK.

All trials were supported by Amgen, and employees of the company are co-authors on all of the trials apart from the published report by Lien.[75]

Summary of study quality

A summary of study quality is given in Box 1 on p. 28.

Results of included trials

The following outcomes reported in the RCTs are summarised in this section:

- percentage of patients achieving a mean PTH level of 26.5 pmol/l or below
  - subgroup analysis of patients achieving a mean PTH level of 26.5 pmol/l or below, according to: baseline PTH level, baseline calcium level, baseline phosphate level, baseline Ca × P level and duration of dialysis (dialysis vintage)
- reduction in mean PTH levels by at least 30% in all patients
  - subgroup analyses of the reduction in mean PTH levels by at least 30% according to: baseline PTH level, baseline calcium level, baseline phosphate level, baseline Ca × P level and duration of dialysis (dialysis vintage)
- percentage change in mean PTH from baseline
- percentage change in mean serum calcium from baseline
- percentage change in mean serum phosphate from baseline
- percentage change in mean Ca × P from baseline
- percentage of patients with mean PTH level of 26.5 pmol/l or below and a reduction from baseline in Ca × P.
  - subgroup analyses of the percentage of patients with mean PTH level of 26.5 pmol/l or below and a reduction from baseline in Ca × P by: baseline intact parathyroid hormone (iPTH) level and baseline calcium level
- percentage of patients achieving the KDOQI targets for serum PTH, calcium, phosphate and Ca × P
- BMD in the femur and lumbar spine
- clinical outcomes: number of parathyroidectomies, hospitalisations for cardiovascular events, hospitalisations for all causes and fractures, and mortality
- quality of life
- adverse effects.

BOX 1 *Summary of quality of included trials*

- There are seven published reports of RCTs of cinacalcet compared with placebo. However, five of these were based on the results of three Phase III RCTs (Amgen 172, 183 and 188) and one Phase II RCT (Amgen 141). As these numbered trials were reported more fully in the US FDA medical review of the Amgen submission for approval, this source was used for the present review. Data from published journal articles were reported where they provided new information.
- The RCTs appear to be well designed with appropriate sample sizes. In total, 846 patients were randomised to receive cinacalcet.
- Patient characteristics among individual trials were similar across the cinacalcet and placebo arms. However, pooled analysis showed significant differences in age, ethnicity and dialysis modality.
- Patients appear to have been randomised centrally in the main RCTs. Although it is not clear whether allocation concealment could have been maintained given the very different responses between cinacalcet and placebo arms, the objective nature of outcome measures should minimise any threat to validity.
- For all trials, the primary outcome was decrease in the levels of serum PTH. One report provides a retrospective analysis of pooled trial data to identify the relevant clinical outcomes of parathyroidectomy, cardiovascular event, fracture and mortality. However, as most trials provide only 6-month follow-up, it is unclear whether differences in these outcomes can be extrapolated to long-term use, particularly where absolute numbers of events are small.
- When pooled for analysis of clinical outcomes, there are baseline differences in age, race and mode of dialysis between the placebo and cinacalcet arms. No adjustment is made for this in the analysis. Further, data for 12 months are based on data from a small, planned RCT and those from the 6-month RCTs who agreed to an extension. Details of this population are not supplied.
- Details of censoring in survival analysis are not given, and reported numbers of patients at risk are different depending on the outcome analysed.
- The trials contain a greater percentage of black patients than would be found in a UK population. Some studies suggest that there is a predisposition to more severe SHPT among black people. Treatment response in the trials showed no relation to ethnicity.
- All trials were supported by the manufacturers of cinacalcet.

Percentage of all patients achieving a mean intact PTH level of <26.5 pmol/l or below

Three Phase III trials (Amgen 172, 183, 188) measured the proportion of people achieving the target of a mean PTH value of 26.5 pmol/l or below during the efficacy assessment phase as the primary outcome of interest.

All three trials demonstrated that significantly more people treated with cinacalcet achieved target mean PTH levels during the efficacy assessment phase [pooled analysis 40% versus 5%, $p < 0.001$; odds ratio (OR) 12.33, 95% CI 7.96 to 19.09].

The smaller Amgen 141 reported that 53% of people treated with cinacalcet, compared with 6% of those treated with placebo, achieved target mean PTH levels.

Of the published trials, only Quarles and colleagues[74] reported this outcome, finding that overall, significantly more people treated with cinacalcet achieved the target than those treated with placebo ($p = 0.029$).

The FDA medical review reports oversuppression of PTH (below 10.6 pmol/l) in Amgen 141, 172, 183 and 188.[77] Of those reported as reaching the target levels, about half in each trial had PTH levels below 10.6 pmol/l (ranging from 6% to 17% of the total population). It is noted that at several weeks during the trial 25% of people had such levels of PTH. Other PTH assays used in clinical practice may report values 30–50% higher than the assay used in these clinical trials.

Subgroup analysis of percentage of patients achieving a mean PTH level of 26.5 pmol/l or below by baseline PTH

Pooled analysis of three trials (Amgen 172, 183, 188) showed that more people treated with cinacalcet with lowest baseline PTH achieved target mean PTH levels compared with patients in the higher baseline PTH strata. However, the absolute risk difference between cinacalcet and placebo reduces with higher baseline PTH levels. The confidence intervals associated with the odds ratios for these subgroups are very wide and overlap (*Table 16*).

Subgroup analysis of achievement of a mean PTH level of 26.5 pmol/l or below by baseline Ca × P, calcium and phosphate levels and dialysis vintage

Tables 17–20 show no significant effects in subgroup analyses according to baseline calcium, phosphate, Ca × P or dialysis vintage.

TABLE 16 *Achievement of PTH levels ≤26.5 pmol/l by baseline PTH levels and dialysis mode*

	All (%)		Baseline PTH >31.8 and <53 pmol/l (%)		Baseline PTH >53.0 and <84.8 pmol/l (%)		Baseline PTH >84.8 pmol/l (%)		Patients on peritoneal dialysis (%)	
	Cinacalcet	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**
Amgen 172 (*n* = 410)	41***	4	52	5	41	4	15	0	NA	NA
Amgen 183 (*n* = 331)	46***	7	65	14	44	2	9	0	NA	NA
Amgen 188 (*n* = 395)	35***	6	65	24	39	0	10	0	38	0
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	40***	5	60	11	41	2	12	0	NR	NR
Pooled data OR (95% CI)	12.33 (7.96 to 19.09)		10.85 (6.36 to 18.49)		23.83 (8.28 to 68.58)		10.85 (2.01 to 58.50)		NR	NR
Amgen141 (*n* = 48)	53	6	NR	NR	NR	NR	NR	NR	NR	NR
Quarles, 2003[74] (*n* = 71)	44¶	20	NR	NR	NR	NR	NR	NR	NR	NR

NA, not applicable; NR, not reported.
*** $p < 0.001$, ¶ $p = 0.029$ (both versus placebo).

TABLE 17 *Percentage of people achieving a mean PTH <26.5 pmol/l according to baseline serum Ca × P value*

	Achievement of PTH level ≤26.5 pmol/l					
	All subjects (%)		Baseline Ca × P <5.65 mmol²/l² (%)		Baseline Ca × P >5.65 mmol²/l² (%)	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Amgen 172 (*n* = 410)	41***	4	43	5	37	2
Amgen 183 (*n* = 331)	46***	7	49	9	37	0
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	40***	5	43	7	30	1
OR (95% CI)	12.33 (7.96 to 19.09)		10.41 (6.57 to 16.49)		29.84 (7.09 to 126)	

*** $p < 0.001$ versus placebo.

TABLE 18 *Achievement of mean PTH <26.5 pmol/l according to baseline serum calcium value*

	Achievement of PTH level ≤26.5 pmol/l					
	All subjects		Baseline serum calcium <2.75 mmol/l		Baseline serum calcium >2.75 mmol/l	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	40***	5	41	6	23	0
OR (95% CI)	12.33 (7.96 to 19.09)		11.86 (7.63 to 18.44)		10.33 (1.81 to 59.06)	

*** $p < 0.001$ versus placebo.

Achievement of a reduction in mean PTH levels from baseline of at least 30%

Pooled analysis of Amgen 172, 183 and 188, Amgen 141, Lindberg and colleagues (2003)[72] and Quarles and colleagues[74] found that significantly more people treated with cinacalcet achieved a reduction of at least 30% in mean PTH compared with of placebo-treated patients[77] (*Table 21*).

Subgroup analysis of the achievement of a reduction in mean PTH levels of at least 30% by baseline iPTH, Ca × P, calcium and phosphate levels

The response rate for people treated with cinacalcet who achieved at least a 30% reduction in PTH was similar among all subgroups of baseline severity in the pooled analysis of three Amgen trials (172, 183, 188) in the FDA medical review. The published papers did not report such subgroup analysis. Odds ratios for higher baseline Ca × P (>5.65 mmol²/l²) suggest that such levels may be associated with greater mean PTH reduction in people treated with cinacalcet. However, given the number of subgroup analyses carried out on the data set, this finding may be a type I error and should be viewed with caution. For baseline calcium and phosphate levels, 95% confidence intervals are very wide and overlap between the groups. (*Tables 22–24*).

The impact of dialysis vintage was also explored (*Table 25*). In this case too, the confidence intervals are very wide and overlap between the three categories of dialysis duration.

It should be noted that the reported reductions in patients with high baseline levels of PTH may still leave these patients with high PTH levels.

Percentage change in mean PTH from baseline

Pooled analysis of the three main Amgen trials (172, 183, 188) shows that treatment with cinacalcet resulted in a significantly greater

TABLE 19 *Achievement of mean PTH ≤26.5 pmol/l according to baseline serum phosphate value*

	Achievement of PTH level ≤26.5 pmol/l					
	All subjects		Baseline serum phosphate <2.10 mmol/l		Baseline serum phosphate ≥2.10 mmol/l	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (n = 1136)	40***	5	44	8	33	2
OR (95% CI)	12.33 (7.96 to 19.09)		8.93 (5.50 to 14.52)		30.95 (10.32 to 92.87)	

*** $p < 0.001$ versus placebo.

TABLE 20 *Achievement of mean PTH ≤26.5 pmol/l during efficacy assessment according to duration of dialysis*

	Achievement of PTH level ≤26.5 pmol/l							
	All subjects		Duration of dialysis >0–1 year		Duration of dialysis >1–5 years		Duration of dialysis >5 years	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (n = 1136)	40***	5	51	10	44	4	31	5
OR (95% CI)	12.33 (7.96 to 19.09)		11.70 (3.94 to 34.73)		19.98 (10.12 to 39.47)		7.47 (3.71 to 15.06)	

*** $p < 0.001$ versus placebo.

decrease from baseline in mean PTH ($p < 0.001$) compared with placebo (*Table 26*).[77] The same was true for the trials reported by Lindberg and colleagues (2003) and Quarles and colleagues ($p < 0.001$ for both).[72,74]

Trial 141 reported that, at the end of the study, mean plasma PTH concentrations were reduced by 54% in the cinacalcet group compared with an increase of 36% in the placebo group.[77]

Both Lindberg and colleagues (2003)[72] and Quarles and colleagues[74] reported significantly greater decreases in mean PTH levels with cinacalcet compared with placebo ($p < 0.001$).

Percentage change in serum Ca^{2+} from baseline

Pooled analysis of the three Amgen trials (172, 183, 188) shows that mean serum calcium concentration was reduced by 6.7% in the cinacalcet group, compared with an increase of 0.5% in the placebo group ($p < 0.001$).[77] Trial 141 reports that mean serum calcium concentration was reduced by 5% in the cinacalcet group compared with an increase of 2% in the placebo group.[77] The FDA review of these trials notes that changes in calcium levels were not correlated with changes in PTH.[77]

Lindberg and colleagues (2003) report that mean serum calcium levels decreased by 4.7% in the cinacalcet arm compared with no change in the placebo arm. This was a significant difference ($p < 0.001$).[72] Similarly, a significant difference was found by Quarles and colleagues (*Table 26*).[74]

Percentage change in serum phosphate from baseline

Pooled analysis of Amgen 172, 183 and 188 showed that mean serum phosphate concentration was reduced by 7.8% in the cinacalcet group, compared with a 0.3% reduction in the placebo group ($p < 0.001$).[77]

Trial 141 reported that mean serum phosphate concentration was reduced by 10% in the cinacalcet group, compared with a decrease of 14% in the placebo group.[77]

The FDA medical review of the Amgen trials notes that changes in serum phosphate levels were not correlated with changes in PTH.

TABLE 21 *Percentage of people achieving a reduction in mean PTH of ≥30% from baseline according to baseline PTH value*

	Achievement of a reduction in PTH level of ≥30%									
	All subjects		**Baseline PTH ≥31.8 and <53 pmol/l**		**Baseline PTH >53.0 and <84.8 pmol/l**		**Baseline PTH >84.8 pmol/l**		**Subjects on PD**	
	Cinacalcet	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**
Amgen 172 (n = 410)	61***	11	58	8	64	18	65	8	NA	NA
Amgen 183 (n = 331)	68***	12	67	NR	73	NR	61	NR	NA	NA
Amgen 188 (n = 395)	59***	10	65	24	63	7	51	6	62	0
Pooled data, Amgen 172, 183, 188 (n = 1136)	62[¶]	11	62	12	68	13	56	6	NR	NR
Pooled data OR (95% CI)	NR		10.79 (6.46 to 18.04)		14.75 (8.37 to 25.98)		21.44 (9.25 to 49.68)		NR	
Lindberg, 2003[72] (n = 78)	38*	8	NR	NR	NR	NR	NR	NR	NR	NR
Quarles, 2003[74] (n = 71)	53[‡]	23	NR	NR	NR	NR	NR	NR	NR	NR

*** $p < 0.001$, * $p = 0.001$, [‡] $p = 0.009$, [¶] $p = 0.029$ (all versus placebo).

TABLE 22 *Achievement of a reduction in mean PTH of ≥30% from baseline according to baseline Ca × P value*

	Achievement of a reduction in PTH level of ≥30%					
	All subjects		Baseline Ca × P ≤5.65 mmol²/l²		Baseline Ca × P >5.65 mmol²/l²	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Amgen 172 (*n* = 410)	61***	11	60	14	65	5
Amgen 183 (*n* = 331)	68***	12	66	NR	76	NR
Amgen 188 (*n* = 395)	59***	10	NR	NR	NR	NR
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	62***	11	62	14	63	4
Pooled data, OR (95% CI)	NR		10.38 (7.19 to 14.97)		46.59 (18.23 to 119)	

*** $p < 0.001$ versus placebo.

TABLE 23 *Achievement of a reduction in mean PTH of ≥30% according to baseline calcium value*

	Achievement of a reduction in PTH level of ≥30%					
	All subjects		Baseline calcium <2.75 mmol/l		Baseline calcium ≥2.75 mmol/l	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	62***	11	62	12	62	4
Pooled data, OR (95% CI)	NR		13.14 (9.29 to 18.59)		25.15 (6.37 to 99.28)	

*** $p < 0.001$ versus placebo.

TABLE 24 *Achievement of a reduction in mean PTH of ≥30% according to baseline serum phosphate value*

	Achievement of a reduction in PTH level of ≥30%					
	All subjects		Baseline phosphate <2.10 mmol/l		Baseline phosphate ≥2.10 mmol/l	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (*n* = 1136)	62***	11	63	13	62	8
Pooled data, OR (95% CI)	NR		11.31 (7.47 to 17.12)		20.08 (11.17 to 36.08)	

*** $p < 0.001$ versus placebo.

Significant differences were also shown by Lindberg and colleagues and Quarles and colleagues, with reductions in the cinacalcet arm and increases in the placebo arms (*Table 26*).[72,74]

Percentage change from baseline in serum Ca × P

In the pooled analysis of Amgen 172, 183 and 188, mean serum Ca × P concentration was reduced by 13.8% in the cinacalcet group,

TABLE 25 *Achievement of a reduction in mean PTH of ≥30% according to duration of dialysis*

	Achievement of a reduction in PTH level of ≥30%							
	All subjects		Dialysis duration 0–1 year		Dialysis duration >1–5 years		Dialysis duration >5 years	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data, Amgen 172, 183, 188 (n = 1136)	62***	11	66	20	61	10	60	10
Pooled data, OR (95% CI)	NR		8.38 (3.41 to 20.59)		16.70 (10.09 to 27.64)		13.08 (7.57 to 22.59)	

*** $p < 0.001$ versus placebo.

TABLE 26 *Percentage change in mean serum levels of iPTH, calcium, phosphate and Ca × P*

	% Change mean PTH		% Change mean calcium		% Change mean phosphate		% Change mean Ca × P	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Amgen 172 (n = 410)	–38.4***	+9.5	–6.3***	+0.5	–7.1***	+1.1	–13.0***	+1.5
Amgen 183 (n = 331)	–47.5***	+8.8	–7.6***	+0.4	–9.9***	–0.9	–16.7***	–0.7
Amgen 188 (n = 395)	–40.3***	+4.1	–6.5***	+0.9	–7.2***	–2.2	–12.9***	–1.4
Pooled data, Amgen 172, 183, 188 (n = 1136)	–41.5**	+8.1	–6.7**	+0.5	–7.8	–0.3	–13.8***	+0.1
Amgen 141 (n = 48)	–54	+36	–5	+2	–10	–14	NR	NR
Lindberg, 2003[72] (n = 78)	–26***	+22	–4.7***	0	–7.5[†]	+10.9	–11.9***	+10.9
Quarles, 2003[74] (n = 71)	–32.5***	+3.0	–4.6***	+2.6	–2.6[¶]	+7.0	–7.9[§]	+11.0

*** $p < 0.001$, ** nominal $p < 0.001$, [†] $p < 0.003$, [¶] $p = 0.217$ (all versus placebo), [§] $p = 0.013$.

compared with an increase of 0.1% in the placebo group ($p < 0.001$).[77]

Similarly, significant differences were found by both Lindberg and colleagues (2003) and Quarles and colleagues.[72,74] (*Table 26*).

Achievement of mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P

Amgen 172 and 183 reported the percentage of people who showed both a mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P. Amgen 173 found that 36% of the cinacalcet-treated patients compared with 1% of patients in the placebo group achieved both of these targets ($p < 0.001$) (*Table 27*). Since 41% of cinacalcet-treated patients had a mean PTH of 26.5 pmol/l or below, approximately 90% of patients who achieved a PTH of 26.5 pmol/l also had reductions in Ca × P.[77]

In trial 183, 42% of the cinacalcet group compared with 5% in the placebo group had both a mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P during the efficacy assessment phase ($p < 0.001$). As 46% of patients had a mean PTH of 26.5 pmol/l or below, approximately 91% of patients who achieved a PTH of 26.5 pmol/l or below, also had reductions in Ca × P.[77]

TABLE 27 *Achievement of mean PTH ≤26.5 pmol/l and a reduction from baseline in Ca × P*

	PTH ≤26.5 pmol/l and a reduction from baseline in serum Ca × P (% subjects)	
	Cinacalcet	**Placebo**
Amgen 172 (*n* = 410)	36***	1
Amgen 183 (*n* = 331)	42***	5

*** $p < 0.001$ versus placebo.

TABLE 28 *Achievement of KDOQI standards (Moe and colleagues, 2005)*[73]

	% Patients achieving KDOQI targets (pooled data)		
	Placebo (*n* = 409)	**Cinacalcet (*n* = 547)**	***p***
Mean PTH < 31.8 pmol/l			
Baseline	<1	<1	
Maintenance phase	10	56	<0.001
Mean serum calcium 2.10–2.37 mmol/l			
Baseline	33	32	
Maintenance phase	24	49	<0.001
Mean serum phosphate 1.13–1.78 mmol/l			
Baseline	31	33	
Maintenance phase	33	46	<0.001
Mean Ca × P <4.44 $mmol^2/l^2$			
Baseline	34	37	
Maintenance phase	36	65	<0.001
Mean PTH <31.8 pmol/l and Ca × P <4.44 $mmol^2/l^2$			
Baseline	0	0	
Maintenance phase	6	41	<0.001

Subgroup analysis by baseline PTH

In trial 172, results from those achieving both a mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P were analysed by baseline PTH. Forty-five per cent of cinacalcet-treated patients with PTH levels between 32 and 53 pmol/l achieved this end-point, compared with 37% of those with PTH levels between 53 and 85 pmol/l and 15% of those with PTH levels of above 85 pmol/l.[77]

Subgroup analysis by baseline Ca × P

Details of people achieving both a mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P were also analysed according to baseline Ca × P level in the 172 trial. Similar proportions of people treated with cinacalcet in each baseline Ca × P stratum achieved a mean PTH of 26.5 pmol/l or below and a reduction from baseline in Ca × P (35% of those with Ca × P <5.65 $mmol^2/l^2$ and 39% of those >5.65 $mmol^2/l^2$). For patients who received placebo, the proportions who achieved the end-point in each baseline stratum ranged from 0% to 5%.[77]

Achievement of KDOQI targets for serum levels

The study by Moe and colleagues combines data from Amgen 172, 188 and 183 to identify the proportion of patients achieving the KDOQI guidelines for mineral and PTH serum levels [as shown in *Table 6* in (p. 10); Renal Association targets are shown in *Table 5* (p. 10)].[73] Significantly more patients treated with cinacalcet achieved these targets than those receiving placebo ($p < 0.001$) see (*Table 28*).

Impact of cinacalcet on BMD

The trial by Lien and colleagues (2005) reports on a small subgroup of 14 patients from Amgen 188 and Amgen trial 239.[75] Changes in BMD between baseline and 6 months are reported. On cinacalcet, a significant increase in femoral

TABLE 29 *Changes in BMD (Lien and colleagues, 2005)*[75]

	Placebo (n = 6)		Cinacalcet (n = 8)	
	Baseline (mean ± SD)	End of study (mean ± SD)	Baseline (mean ± SD)	End of study (mean ± SD)
Femur BMD (g/cm^2)	0.921 ± 0.250	0.904 ± 0.244*	0.945 ± 0.169	0.961 ± 0.174*
Femur T-score	–1.03 ± 1.56	–1.30 ± 1.70	–0.76 ± 1.10	–0.65 ± 1.16*
Lumbar spine BMD (g/cm^2)	1.156 ± 0.276	1.149 ± 0.288	1.283 ± 0.219	1.269 ± 0.221
Lumbar spine T-score	–0.72 ± 2.31	–0.63 ± 2.23	–0.52 ±1.69	–0.39 ± 1.69

* $p < 0.05$ vs baseline.

TABLE 30 *Impact of cinacalcet on the risk of fracture, cardiovascular event, parathyroidectomy and mortality: pooled adverse event data*

	Event count		Events per 100 patient-years			
	Placebo (n = 487)	Cinacalcet (n = 697)	Placebo	Cinacalcet	RR (95% CI)	p
Mortality	NR	NR	7.4	5.2	0.81 (0.45 to 1.45)	0.47
Cardiovascular hospitalisation	77	72	19.7	15.0	0.61 (0.43 to 0.86)	0.005
All-cause hospitalisation	NR	NR	71.0	67.0	1.03 (0.87 to 1.22)	0.74
Fracture	20	12	6.9	3.2	0.46 (0.22 to 0.95)	0.04
Parathyroidectomy	12	1	4.1	0.3	0.07 (0.01 to 0.55)	0.009

BMD was shown, compared with a significant decrease with placebo. Changes in lumbar BMD were not significant (*Table 29*). Analysis of differences between groups was not reported.

Impact of cinacalcet on cardiovascular events, fracture, parathyroidectomy and death

The study by Cunningham and colleagues uses adverse event data from the Amgen 172, 183, 188 and 141 to assess the impact of cinacalcet on fracture, cardiovascular events, hospitalisation and mortality.[71] Results are shown in *Table 30*. No significant difference was seen in overall mortality or all-cause hospitalisation. However, significant differences were seen at 6–12-month follow-up in cardiovascular hospitalisation, fracture and parathyroidectomy (*Table 30*).

Quality of life

Cunningham and colleagues also report QoL from combined data from Amgen 172, 183 and 188.[71] No significant differences in the change over time were found for most of the domains measured by the SF-36. There was a significant difference in the change in scores for people treated with cinacalcet compared with placebo in the physical component score (0.5 versus –0.8, $p = 0.01$), the bodily pain score (0.6 versus –1.0, $p = 0.03$) and the general health score (0.2 versus –1.0, $p = 0.02$). There was no difference overall between the study arms in self-assessed decline in physical status. However, more people in the cinacalcet arm reported an increase of 5 points or more (26% versus 20%, $p = 0.03$).

Adverse effects

Full details of reported adverse effects are shown in the extraction tables (Appendix 7). Adverse effects were reported in different ways across the trials. Only three published trials[66,70,73] included adverse events, reporting only a selection of those in the FDA medical review.

Deaths

All deaths that occurred on-study and within 30 days of discontinuation, withdrawal or completion of the study were recorded by Amgen 172, 183 and 188.[77] There was no significant difference between study arms. Fifteen patients (3%) randomised to receive placebo and 14 (2%) randomised to cinacalcet died during these core 6-month trials. The causes of death in the cinacalcet-treated patients were not unusual for this population.

Trial 141 reported three deaths (9%) in the cinacalcet group and 2 (13%) in the placebo group. Two patients receiving cinacalcet died of cardiac arrest. One subject receiving cinacalcet died of sepsis. In the placebo group one subject died of intracranial haemorrhage and one of pulmonary embolism.[77]

Serious adverse events

The FDA medical review of cinacalcet considered a serious adverse event (SAE) or reaction to be any untoward medical occurrence that at any dose resulted in death, was life-threatening, required or prolonged hospitalisation, resulted in significant disability, or was a congenital anomaly or birth defect.[77]

The pooled incidence of SAEs from Amgen 172, 183 and 188 was 31% in the placebo group and 29% in the cinacalcet group. No individual SAE occurred in more than 2% of patients. The most common SAEs included (placebo, cinacalcet), vascular access thrombosis (2%, 2%), pneumonia (2%, 2%), sepsis (2%, 2%) and non-cardiac chest pain (<1%, 2%). SAEs of cardiac arrest occurred in 1% of patients in each treatment group (six placebo, nine cinacalcet). Cardiac arrest was fatal in ten patients [three (<1%) placebo and eight (1%) cinacalcet].[77]

Withdrawal due to adverse events

Withdrawals due to adverse events in the pooled data for Amgen 172, 183 and 188 occurred in 8% of patients receiving placebo compared with 15% ($p = 0.005$, calculated by PenTAG) of patients receiving cinacalcet. The most common individual events leading to withdrawal were (placebo, cinacalcet) nausea (1%, 5%, $p = 0.001$), vomiting (<1%, 4%), diarrhoea (<1%, 2%) and abdominal pain (<1%, 2%).[77]

Trial 141 reported that four patients (13%) in the cinacalcet group and none in the placebo group withdrew because of adverse events. Adverse events that most commonly resulted in withdrawal involved the gastrointestinal system, with one subject each who withdrew owing to dyspepsia, nausea and vomiting.

All adverse events

Pooled data for Amgen 172, 183 and 188 were not reported. Adverse event rates of 90%, 93% and 91% were reported in the cinacalcet-treated groups of the individual trials, respectively, compared with similar values (95%, 93% and 93%) in the placebo groups.

Ninety-seven per cent of patients in the cinacalcet arm of Amgen 141 and 100% of patients in the placebo group reported at least one adverse event during the study. The most common adverse events were (cinacalcet, placebo) nausea (44%, 44%), abdominal pain (44%, 19%), and vomiting (41%, 31%). These differences were not significant (as calculated by PenTAG).

Specific adverse events

As cinacalcet may cause calcium levels to fall and low calcium is associated with seizures, pack advice states that such serum levels should be closely monitored. In addition, recognised common adverse effects include nausea and vomiting, diarrhoea, muscle pain, dizziness, high blood pressure, weakness, tiredness and loss of appetite.

Nausea and vomiting

Nausea and vomiting were the two most commonly reported adverse events and the most frequent reasons for premature withdrawal from the trials.

The incidence of nausea in the cinacalcet groups in the pooled data for Amgen 172, 183 and 188 was higher than in the placebo groups (31% versus 19%, $p < 0.001$, calculated by PenTAG). Similarly, the incidence of vomiting was significantly higher in the cinacalcet group (27% versus 15%, $p < 0.001$, calculated by PenTAG). Vomiting was dose related, whereas nausea was not.

In the smaller Amgen 141, the incidence of nausea in both the cinacalcet and placebo groups was 44%. Forty-one per cent of patients in the cinacalcet group experienced vomiting, compared with 31% of the placebo-group (not significant, as calculated by PenTAG).

Hypocalcaemia

Approximately 25% of people receiving placebo and 65% of people receiving cinacalcet in the pooled trials developed at least one serum calcium level below 2.1 mmol/l. A similar pattern of hypocalcaemia in drug- versus placebo-treated patients was noted in analyses stratified by baseline PTH levels and Ca × P products.

In Amgen 141, three adverse events of asymptomatic hypocalcaemia (two cinacalcet, one placebo) were reported.

Seizures

Five per cent of patients in the cinacalcet and placebo groups reported having a history of seizures at baseline across the three pooled trials

(172, 183 and 188). Eleven (2%) of the cinacalcet patients experienced at least one seizure, five of whom had a history of seizures. Two (0.4%) of those receiving placebo had at least one seizure during the trials, both of whom had a history of seizures ($p = 0.054$). It is not known whether this represents a true risk attributable to the drug through hypocalcaemia.

No seizures were reported in Amgen 141.

BOX 2 *Summary of results from the systematic review*

Biochemical outcomes

- All included trials show that cinacalcet is significantly more effective than placebo at reducing PTH levels to target levels of 26.5 pmol/l or below (40% versus 5% in pooled analysis).
- Of people achieving target levels for PTH, 91% also had reductions in Ca × P levels.
- More patients treated with cinacalcet achieved a reduction of at least 30% in mean PTH level compared with placebo (62% versus 11% in pooled analysis).
- Patients treated with cinacalcet showed significantly greater percentage changes from baseline in mean levels of calcium (–6.7% versus +0.5%), phosphate (–7.8% versus +0.3%) and Ca × P product (–13.8% versus +0.1%) compared with those treated with placebo.
- A large number of subgroup analyses was undertaken on biochemical outcomes according to severity of biochemical derangement and dialysis duration. Most of these were not significant and the trends in results are difficult to interpret. There is some suggestion that cinacalcet may be more effective in less advanced disease. These findings should be treated with caution due to the risk of type I error.

Clinical outcomes

- One trial provided results on important patient-based outcomes (parathyroidectomy, cardiovascular event, fracture and mortality) using pooled data from four RCTs. However, trial follow-up was only for 6–12 months and it is not known whether extrapolation of these results to the long term is valid.
- Significantly fewer patients treated with cinacalcet were hospitalised for cardiovascular events (RR 0.61, $p = 0.005$), although no significant difference was seen in all-cause hospitalisation or mortality.
- There were significantly fewer fractures (RR 0.46, $p = 0.04$) and parathyroidectomies (RR 0.07, $p = 0.009$) in the cinacalcet arm than in the placebo arm. However, this finding is based on small numbers.

Adverse events

- Withdrawal due to adverse effects was reported in more cinacalcet patients than those receiving placebo (15% versus 8%), most commonly for gastrointestinal disturbances.
- Significantly more people treated with cinacalcet experienced nausea (31% versus 19%) and vomiting (27% versus 15%).
- Eleven (2%) of cinacalcet patients experienced seizures, compared with two (0.4%) of those treated with placebo ($p = 0.0054$).

Chapter 4

Cost-effectiveness

Aim of the economic evaluation

To establish, based on available data, the cost–utility of cinacalcet for treating hyperparathyroidism secondary to ESRD in dialysis patients compared with standard treatment.

Research question

What is the cost-effectiveness of cinacalcet for treating hyperparathyroidism secondary to ESRD in people on dialysis compared with standard treatment?

Systematic review of cost-effectiveness studies

Methods

Search strategy and critical appraisal methods

Electronic databases were searched using the strategy shown in Appendix 4.

Inclusion and exclusion criteria

Studies were included if they were cost–utility analyses of cinacalcet compared with standard treatment for people with ESRD on dialysis with SHPT.

Published cost-effectiveness studies

No cost–utility studies in the relevant populations were identified.

Cost-effectiveness study provided by industry

One cost–utility study was submitted to the NICE appraisal process by Amgen.

Economic evaluation of cinacalcet submitted by Amgen

Design

Cost-effectiveness was estimated using a decision model: a state transition (Markov) model of the lifetime progression of SHPT in patients with ESRD. The main features of the model were as follows.

Starting cohort(s)

Adult patients (≥18 years old) with refractory SHPT and ESRD being treated by haemodialysis or peritoneal dialysis. 'Refractory' is defined as not controlled by high-dose vitamin D analogues and phosphate binders. SHPT is defined as having PTH levels of 31.6 pmol/l or higher and calcium levels above 2.1 mmol/l.

Interventions compared

- Cinacalcet in addition to standard treatment (vitamin D and phosphate binders)
- standard treatment with vitamin D and phosphate binders.

Model structure

The eight health states in the Markov model represent the status of people in relation to their history of the main adverse events of interest: cardiovascular events, major fractures and parathyroidectomies. For each preparathyroidectomy health state, there is an equivalent postparathyroidectomy state, as illustrated in *Figure 2*.

Main outcomes simulated

Cardiovascular events, fractures (both major and minor), parathyroidectomies and mortality are the main outcomes simulated. The first cardiovascular event or major fracture leads to a change of health state, as does parathyroidectomy. Subsequent major fractures or cardiovascular events do not lead to a change in health state. Only one of these three types of clinical event can occur in any 6-month period. Minor fractures incur a cost but no change in health state or QoL (utility).

Quality-adjusted life-years (QALYs) were calculated by applying a background utility value for people with ESRD on dialysis (0.681), together with utility decrements following either cardiovascular events (–0.09) or fracture events (–0.09). If both complications were experienced, the decrements were combined (–0.18).

Assumed benefit of cinacalcet

People receiving cinacalcet were assumed to suffer different rates of the main outcomes from those receiving standard treatment (i.e. lower rates of death, cardiovascular events and fractures, and substantially lower rates of parathyroidectomies). These were calculated from the relative risks reported by Cunningham and colleagues.[71]

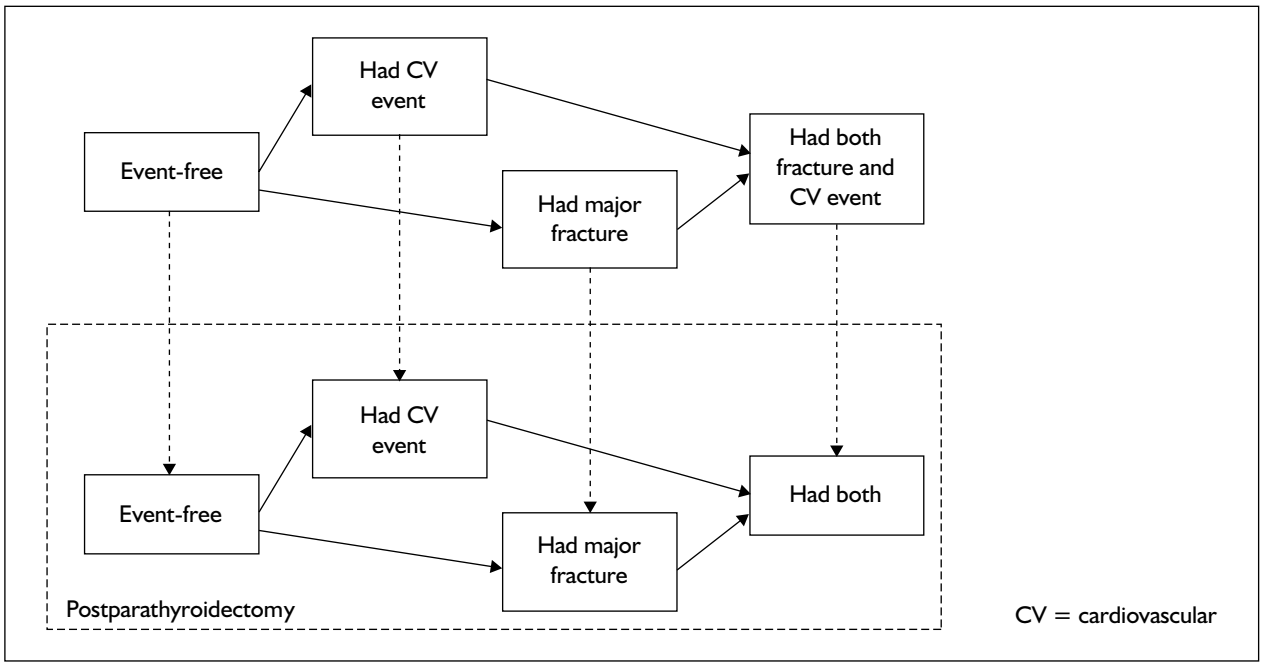

FIGURE 2 *Flow diagram of the Amgen Markov model.*

Data sources
Most parameters in the model were drawn from the pooled results of four clinical trials of cinacalcet, as reported by Cunningham and colleagues.[71] The main utility values for health states defined in the model were from a systematic review of the relevant literature carried out for the submission to NICE. Costing was conducted from a UK NHS perspective.

Subgroup analyses
Separate analyses are reported for those with moderate or severe SHPT, defined as those with PTH levels of 300–800 pg/ml (32–64 pmol/l) and over 800 pg/ml (>64 pmol/l), respectively.

The key trade-offs in the Amgen model are therefore:

- the increased cost of treatment with cinacalcet
- the decreased risk of cardiovascular events, major and minor fractures, and lower rates of parathyroidectomy with cinacalcet associated with
  - consequent reduction in the cost of managing those events and a delay in the timing of those events
  - averted reductions in QoL due to these events.

Conducted by
The industry submission on the cost-effectiveness of cinacalcet (Mimpara) was conducted by Amgen. Appendix 7 of this submission was a commissioned systematic review of the literature on preference-based health state and utility values among people with ESRD.

Summary of Amgen cost–utility results
The main (deterministic) results of the Amgen comparison of cinacalcet with standard care for SHPT are shown in *Table 31*. Their probabilistic sensitivity analysis (PSA) also showed that cinacalcet had a more than 50% chance of being cost-effective only when the maximum willingness to pay (WTP) per QALY exceeded approximately £37,000, and that even at £100,000 per QALY gained there was a greater than one in four chance that cinacalcet is not cost-effective.

Overall appraisal
The economic evaluation of Mimpara submitted by Amgen appears to be a well-conducted analysis of the main relevant cost and health consequences of the decision problem specified in the NICE scope. The methods and results are described with commendable clarity, and an appropriate selection of sensitivity analyses is presented, including a probabilistic sensitivity analysis.

The cost–consequence analysis, in which they examine the cost per person achieving control of PTH levels, is appropriately reported separately from the reference case. This cost–utility analysis relied on additional assumptions about lower required doses of vitamin D and phosphate

TABLE 31 *Amgen base-case cost–utility analysis by initial severity of SHPT (discounted results)*

	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£ per QALY)
All patients					
Standard care	3,000		2.87		
Cinacalcet plus standard care	21,900	19,000	3.40	0.53	35,600
Patients with moderate[a] SHPT:					
Standard care	2,600		2.88		
Cinacalcet plus standard care	18,900	16,300	3.42	0.54	30,400
Patients with severe[b] SHPT:					
Standard care	4,000		2.83		
Cinacalcet plus standard care	29,200	25,300	3.36	0.52	48,300

Source: Amgen industry submission, Table 7 p. 32.
[a] PTH >31.6 and <84.2 pmol/l (>300 and ≤800 pg/ml).
[b] PTH >84.2 pmol/l (>800 pg/ml).
ICER, incremental cost-effectiveness ratio.

binders for those treated with cinacalcet, based on data from the OPTIMA trial (currently unpublished).

The reviewers' main concern with the Amgen analysis is with the reliance on a single study, the validity of which is difficult to judge as a source for most of the key input parameters. Furthermore, the validity of extrapolating these short-term effectiveness findings to the remaining lifetime of people with ESRD is uncertain.

Major weaknesses of the industry analysis

Reliance on and extrapolation of Cunningham study results

The main weakness of the industry analysis is its reliance on the study by Cunningham and colleagues[71] as the sole source for effectiveness data, particularly the relative risk rates for cardiovascular events, and major and minor fractures, and the extrapolation of these short-term risk reductions to the remaining time on cinacalcet. Cunningham and colleagues pooled the results of four trials, which were designed for the primary purpose of estimating differences in biochemical markers; followed patients for a short period; experienced high rates of censoring, which is not fully explained; and may not be representative of the UK ESRD population (they experience half the mortality of the same age group reported in the UK's Renal Registry).

Other limitations

The utility decrements for experiencing cardiovascular events or major fractures that resulted in hospitalisation were assumed to apply from the time of the first event onwards. Although there is evidence suggesting some lasting utility decrement due to such events, attributing the same utility decrement for both the period (6 months) in which the event occurred and all years thereafter seems to be an unrealistic assumption. This could bias in favour of cinacalcet.

The assumed 'background' mortality for those with ESRD, sourced directly from UK Renal Registry data, is likely to be underestimated in the industry analysis, because people with ESRD suffering SHPT are a more severely ill minority (33%) of all patients with ESRD. This will favour the effectiveness of cinacalcet, since death is a competing risk with the other adverse clinical events which drive the differences in quality-adjusted life expectancy.

It appears that minor fractures are assumed to lead to hospitalisation in many cases, as 44% attract the average unit cost for inpatient treatment [Healthcare Resource Group (HRG) H45 'Minor fractures or dislocations']. It is not clear how this figure is derived or whether the case-mix of minor fractures incurred by people with SHPT includes the same types of fracture as HRG H45 (i.e. mostly fractures of the wrist, fingers, thumb and toes). Neither is it clear whether, in an NHS setting, people with ESRD having minor fractures would be treated as inpatients.

The NHS unit costs of different cardiovascular events and fracture events used in the Amgen analysis were those for elective inpatient episodes. We believe that these would almost certainly be

non-elective episodes. This means that the Amgen analysis has overestimated the cost of each CVD hospitalisation by £530 (£1817–1287), underestimated the cost of each major fracture by £953 (£4767–3814) and overestimated the cost of treating each minor fracture by £502.[79] However, taken together, we do not believe that these errors have made a substantial impact on the cost-effectiveness results.

Another potentially important omission from the industry analysis is the ongoing cost of dialysis. If cinacalcet leads to survival gains, there will be significant cost implications for the NHS owing to the need for dialysis during those added months or years of life. Current methodological conventions recommend that medical costs that are "related to the intervention" be included.[80,81]

The analysis also excluded other standard treatment costs such as vitamin D and phosphate binders.

While stating that the model uses a time-horizon of 35 years their results are, in fact, from a simulation of only 15 years (by which time 8.7% of the cinacalcet cohort and 4.7% of the 'standard care' cohort are still alive). Rerunning the analysis for 35 years (when over 99.9% of both cohorts are dead) reduces the base-case ICER to £33,000 per QALY.

PenTAG cost–utility model

The systematic review of cinacalcet found that most existing trials of cinacalcet provide short-term data (6–12 months' follow-up) using biomarkers as outcomes, whereas the crucial data to establish both long-term effectiveness and cost-effectiveness of cinacalcet are patient-based clinical outcomes such as cardiovascular events, fractures and mortality. One paper, by Cunningham and colleagues,[71] does report these outcomes for short-term follow-up. However, as we were uncertain how to extrapolate these data, we have explored them in a scenario analysis. The approach for the base case is to use evidence from the RCTs of cinacalcet about impact on levels of PTH and then use data from large cohort studies about the consequent risk of important outcomes contingent on biochemical levels.

A major challenge to modelling the effect of cinacalcet in the long term is the need to account for the combined impact of changes in the different biochemical markers. Only one study was identified, based on routine data in a Canadian population, that has examined the relationship between calcium, phosphate, PTH and dialysis duration in combination on mortality.[82] The study population was 515 British Columbian patients (69% on haemodialysis), followed from 2000 to 2002. The analysis demonstrates the complexity of the relationship, with significant interactions between biochemical measures and dialysis duration. We considered using the results of this study as the basis for modelling the cost-effectiveness of cinacalcet, but rejected this approach for two main reasons. First, the study was based on routine data which, while reflecting the quality of care in the British Columbian setting, may not be applicable to the UK. Secondly, only mortality was reported and the objectives of this review included the estimation of the impact of cinacalcet on morbidity. In addition, only very limited data are available from the cinacalcet trials about the impact on combined biomarkers.

We therefore modelled the impact of biochemical factors individually on outcomes. The base case looks at the impact of PTH control. Additional scenario analysis looks at PTH and Ca × P control with cinacalcet. These analyses are rendered somewhat speculative by their univariate nature and the paucity of available data. This is currently an unavoidable limitation on modelling in this condition, which cannot be addressed without appropriate multivariate analysis of large cohorts of people in ESRD. The likely impact on conclusions, in terms of direction and size of bias, is unclear.

Summary description of the PenTAG model

A Markov (state transition) model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The structure of the model was informed by current literature and expert opinion on the progression of SHPT in patients with ESRD and its treatment.

The model estimates the incremental cost–utility of adding cinacalcet to the current standard treatment of SHPT in ESRD. Cost–utility provides an estimate of the costs (in pounds) and benefits (in QALYs) of treatments. The incremental analysis shows the difference in cost and benefits between the two treatments.

The population is those with ESRD on dialysis with SHPT. The treatments compared are cinacalcet as an addition to standard treatment and standard treatment alone. In the base case a

hypothetical cohort of 1000 ESRD patients with SHPT is modelled until the whole cohort has died. The initial starting age for the cohort is 55 years old, based on the mean age of participants in Amgen RCTs 172 and 183 and reported by Block and colleagues.[70] Other trials do not supply mean age, but report the percentage of their sample under or over 65 years of age. The model uses a cycle length of 3 months to capture the possibility of multiple adverse effects such as cardiovascular events and fractures.

Where possible, estimates for the model were taken from the literature. Where no published information was available, the expert advisory group was consulted. Individuals were sent lists of questions independently. Where there was consensus this value was used. Where different responses were supplied these were used to inform the uncertainty in probabilistic analyses.

In the main, costs from 2004 are used as these are the most recent available data for many standard sources. The exceptions are drug and dialysis costs, where currently available 2005 costs are used. An inflation factor was not applied for two reasons: first, inflated costs are based on assumptions and so may be subject to inaccuracies and, secondly, current inflation rates are low, minimising the necessity of inflating subsequent year costs particular for only one year, as would be the case here.

Structure of the model

Figure 3 is a summary diagram of the model presented as a decision tree. The square junction represents a decision node; in this case, clinicians may decide to treat with standard care alone or with standard care plus cinacalcet. The circular junctions are chance nodes: the proportions of people experiencing different events at these chance nodes are based on probabilities drawn from the literature. Initial treatment for one cycle (3 months) of either standard treatment alone or standard treatment plus cinacalcet is followed by patients being stratified into three levels of PTH control reflecting findings after the titration period from pooled analysis of Amgen 172, 183 and 188. *Figure 4* presents a more detailed influence diagram of the model.

People are considered 'controlled' if they have a PTH level of 32 pmol/l or less, in accordance with Renal Association standards. They are defined as 'uncontrolled' if they have a PTH of between 33 and 84 pmol/l, and 'very uncontrolled' if they have a PTH level of 85 pmol/l or more based on definitions in the cinacalcet trials. Those with 'very uncontrolled' PTH are further subdivided into patients who are eligible or ineligible for parathyroidectomy. Two 'postsurgical' outcomes are modelled, for patients with or without adverse surgical effects. Parathyroidectomy only occurs in patients with 'very uncontrolled' levels of PTH.

PTH levels that are not controlled result in a greater risk of cardiovascular events or fractures, which are in turn associated with greater risk of mortality. In each cycle, stratified by degree of biochemical control, people can experience the following events:

- no fracture or cardiovascular event (event free)
- cardiovascular event
- fracture
- death from cardiovascular causes
- death from other causes.

The chance of having a subsequent cardiovascular or fracture event is increased after an initial event of that type. Patients may die from any health state from either cardiovascular or other causes.

The influence diagram for the model is shown in *Figure 4*. Health states are shown as white boxes (e.g. 'Event free' or 'CV event') and possible movements between these states are shown as arrows. The different degrees of control over PTH levels are shown as the different shaded strata in the diagram (e.g. 'controlled' or 'uncontrolled' PTH levels). Surgical status (pre- or postparathyroidectomy) is also presented as different, shaded strata. *Table 32* contains a list of health states used in the model.

People in both cinacalcet and standard treatment arms enter the initial treatment phase, during which those on cinacalcet go through the titration phase to establish the appropriate controlling dose. Based on pooled trial data from the systematic review, 7% of people treated with cinacalcet withdraw from treatment due to adverse effects at this stage. These people are simulated in the same way as those in the cohort not treated with cinacalcet and they accumulate the risks, costs and benefits associated with standard treatment. These costs and benefits for patients withdrawing from cinacalcet treatment continue to be counted within the cinacalcet arm.

The cohort modelled in the standard treatment arm receive alterations to their treatment to attempt to bring the PTH level under control during this initial treatment phase. After the

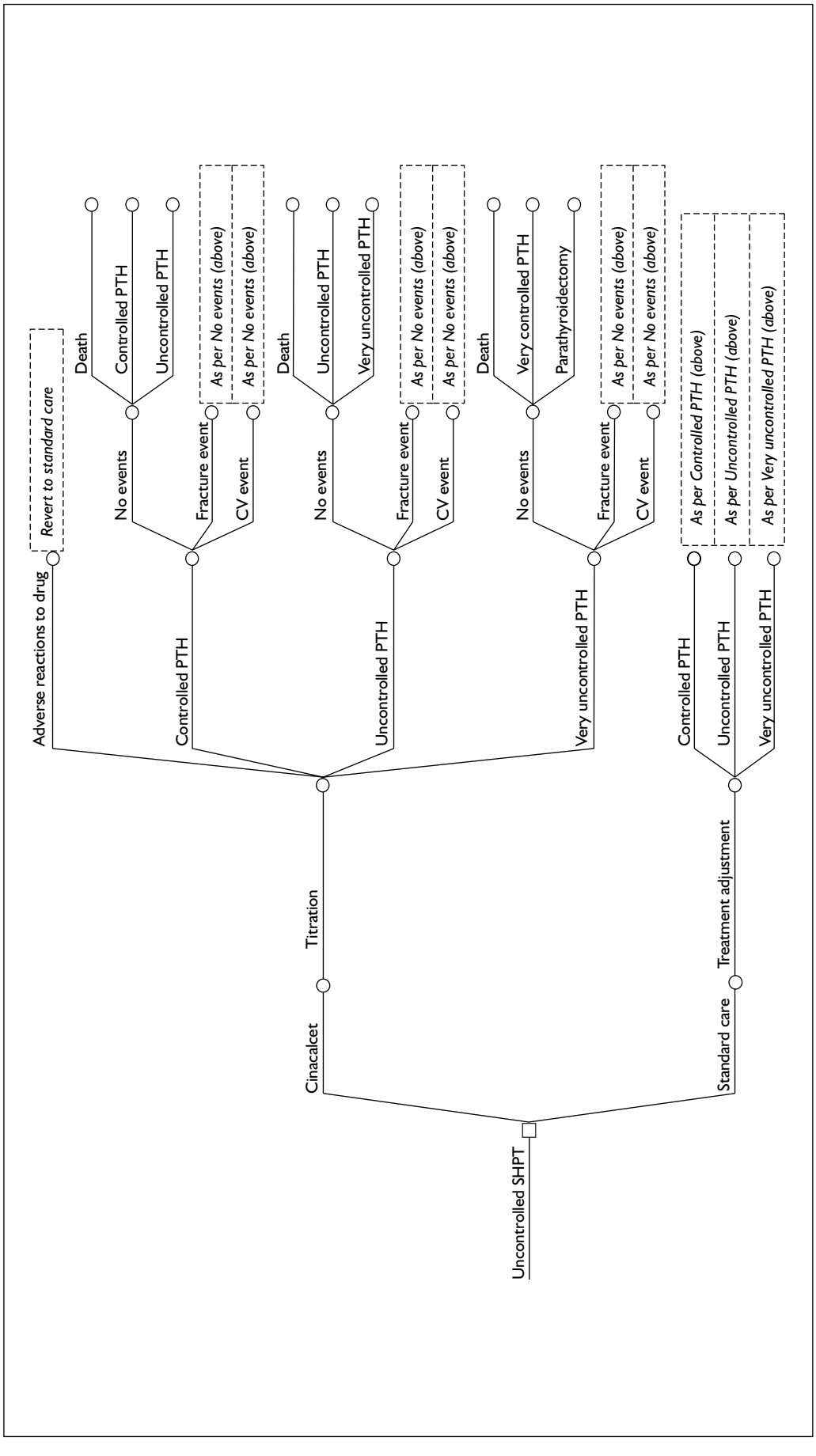

FIGURE 3 *Decision tree for PenTAG economic model*

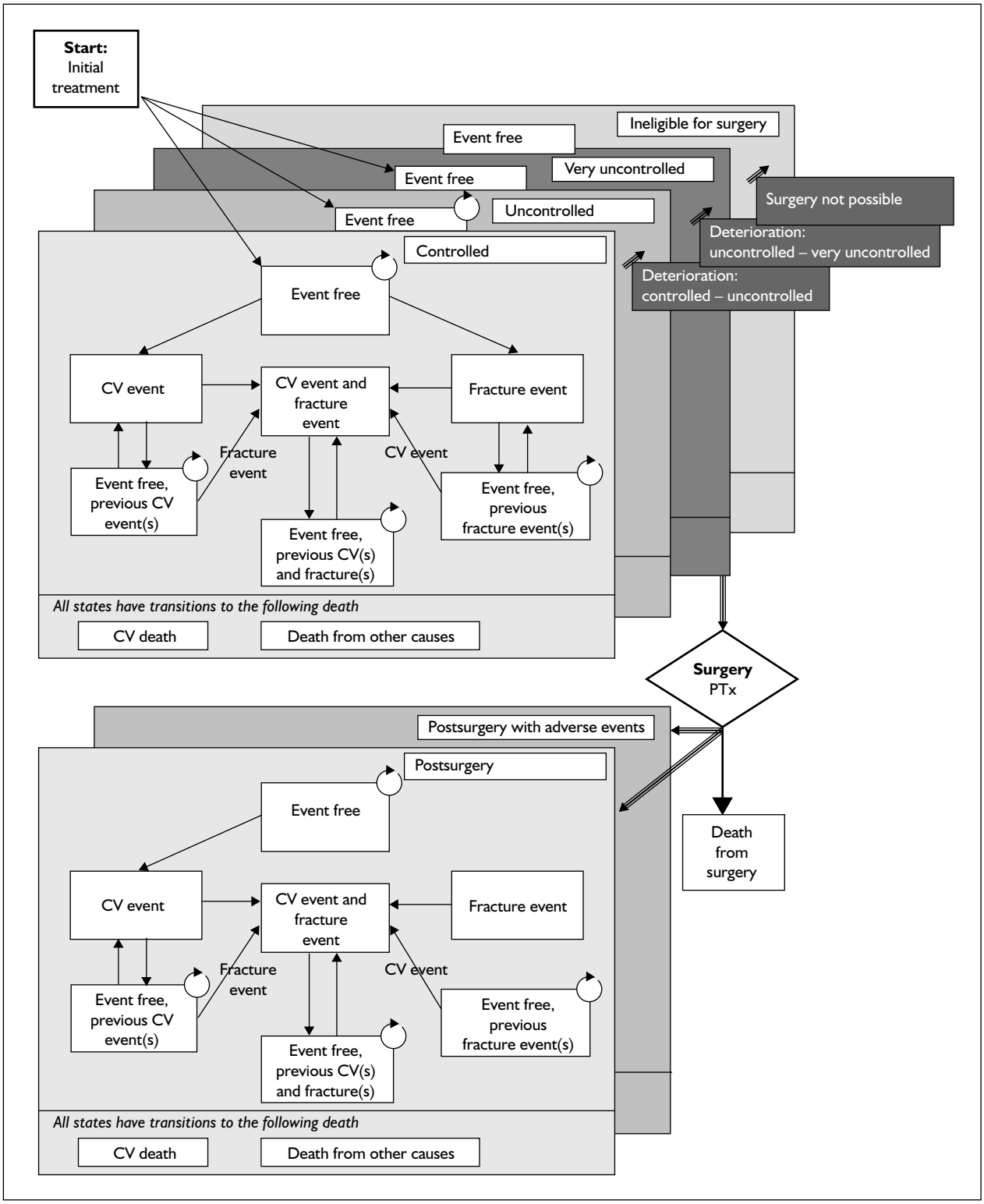

FIGURE 4 *Influence diagram for cost–utility model. PTx, parathyroidectomy.*

initial treatment phase, PTH levels in both arms will be controlled, uncontrolled or very uncontrolled, based on the data from the systematic review, and people enter the corresponding strata of the model.

The seven health states visible with controlled PTH levels in *Figure 4* are replicated for all degrees of PTH control and the two postparathyroidectomy strata. Thus, each of the model strata (PTH uncontrolled, very

TABLE 32 *Description of health states used in the economic model*

Disease state	Description
Event free	Patient has never had either a CV event or a fracture serious enough to require hospitalisation
CV event	Patient has a CV event requiring hospitalisation Patient has never had a major fracture
Fracture event	Patient has a fracture event Patient has never had a CV event serious enough to require hospitalisation
Event free; history of CV event	Patient has previously had at least one CV event requiring hospitalisation Patient has never had a major fracture Patient experiences no new adverse event in the current cycle
Event free; history of fracture	Patient has previously had at least one fracture Patient has never had a CV event serious enough to require hospitalisation Patient experiences no new adverse event in the current cycle
CV and fracture event	Patient has either: a fracture event and has previously had at least one CV event requiring hospitalisation or a CV event requiring hospitalisation and has previously had at least one fracture event
Event free; CV and fracture history	Patient has had at least one CV event and at least one fracture event Patient experiences no new event in the current cycle
CV death	Patient dies from cardiac causes
Non-CV death	Patient dies from non-surgically related, non-cardiac causes
Surgical death	Patient dies from surgically related causes

uncontrolled, etc.) duplicates the health states and structure shown for controlled PTH levels in the model. The thin arrows between boxes represent possible transitions experienced by the cohort within each of the strata, with transitions permitted in the direction of the arrows and circular arrows representing staying in the same health state for another model cycle or cycles.

In addition, patients in the standard treatment arm can move to progressively more uncontrolled states representing loss of PTH control over time. This is shown by the thicker, double arrows representing movement between model strata in *Figure 4*. Surgery itself is modelled as a transition (rather than a health state) that is applied to eligible patients with very uncontrolled PTH levels. This is because the cost and benefits of surgery are much shorter than the cycle length. Patients pick up benefits as a result of surgery due to falling PTH levels almost immediately and this is best captured through the relevant model stratum for this PTH level.

Within a Markov state transition model, patients reside in one of a number of discrete health states. At regular time intervals (the model cycle) people make at most one transition between states. A 3-month cycle was felt appropriate to capture accurately the clinical pathways for SHP. Before and after each cycle, all patients must be in one of the health states in the model. This means that, for example, a patient currently in the event-free state (EVF) can move to either the fracture state (FRE) or cardiovascular event state (CVE), or remain in the event-free state. People remaining in a particular health state are represented on the influence diagram (*Figure 4*) by circular arrows. The possible transitions between states are identical in all of the different model strata. The probabilities attached to each transition during each model cycle are based, where possible, on published data and, where no data were available, on expert opinion (see next section). The impact of changes in these probabilities on the final cost–utility value is explored using sensitivity analyses.

During each cycle people may experience no serious event, a major fracture or a cardiovascular event. In addition, there may be deterioration in the control of PTH levels with people moving to a

more severe degree of hyperparathyroidism, for example, becoming 'uncontrolled' having had 'controlled' PTH. Members of the cohort move to a state that reflects their previous event history, but at a more severe degree of HPT. It is possible both to move between strata and to experience an event in the same cycle.

On reaching very uncontrolled levels of PTH, people become candidates for parathyroidectomy. Those who have successful parathyroidectomy enter one of the postsurgical states where they remain until they die. People who are deemed ineligible for surgery remain with the risks associated with very uncontrolled levels of PTH until they die. This is also the case for those for whom surgery is unsuccessful at controlling PTH.

Differences in costs and benefits between the arms of the model are based on the different proportions of people who have controlled, uncontrolled or very uncontrolled levels of PTH after standard treatment alone or with cinacalcet. Relative risks of having a fracture or cardiovascular event or of mortality depend on the PTH level and are taken from the literature. Patients with controlled PTH levels have been taken as the baseline throughout, with the risk of an event occurring with more uncontrolled PTH levels being relative to this baseline group. This may overestimate the risk for people with more uncontrolled PTH and so bias the model in favour of cinacalcet. However, Renal Registry data show that 66% of the UK renal replacement therapy (RRT) population under current treatment regimens have controlled PTH levels.[13] The impact of different relative risks is explored in sensitivity analysis.

Death may occur from any of the health states. The death rate is assumed to be dependent on age, and is therefore modelled as a time-dependent variable. Death from cardiovascular causes and death from other causes are possible in all of the model strata. In addition, there is a small risk of death as a complication of parathyroidectomy.

Unless otherwise specified, all references to people with very uncontrolled levels of PTH refer to both those eligible and those ineligible for surgery.

A half-cycle correction was not added to the model, as the cycle length was felt to be sufficiently short for this not to be necessary. This is unlikely to have a significant impact on the results.

Sources of estimates used in the PenTAG cost-effectiveness models

Transitions between health states

Effectiveness of standard treatment alone and plus cinacalcet in reducing PTH levels

Table 33 shows the distribution across the model strata of each of the cohorts at the start of each model. The systematic review shows how many people had controlled PTH levels after the titration phase with standard treatment alone or with cinacalcet. It was assumed that the impact of standard treatment plus placebo reported in the trials will be the same as for standard treatment alone in clinical practice.

The proportions that were uncontrolled or very uncontrolled were not reported in the cinacalcet trials. Data supplied by the Renal Registry showed that, of those who did not have PTH levels below the target level, 70% had PTH levels between 32 and 85 pmol/l and 30% had PTH levels of more than 85 pmol/l (Ansell D: personal communication, February 2006). These data were used to distribute those without controlled PTH between these two degrees of control.

Progression of hyperparathyroidism over time

Control of serum PTH levels tends to worsen over time for people on dialysis. This may be due to a number of factors such as gradual worsening of disease or lack of compliance with treatment, which is known to be important. The model takes this into account by allowing deterioration of control so that people receiving standard treatment can move from having controlled PTH to being uncontrolled, and from having uncontrolled PTH levels to having very uncontrolled levels. Advice from the clinical advisory group was sought to establish the extent of such deterioration. However, as opinion varied and no published data were available, an assumption was made based on the range of information supplied by the clinical experts (*Table 34*). The impact of this assumption was explored in extensive sensitivity analysis.

It is unclear how the effectiveness of cinacalcet should be extrapolated beyond the length of the trials as it is not known whether consistent control is more or less likely with cinacalcet compared with standard treatment. Compliance could be an issue with cinacalcet in clinical practice as it adds to the burden of medication and may cause adverse

TABLE 33 *Effectiveness of cinacalcet and standard treatment in controlling PTH levels*

Variable	Value	Source	Comments
Differential percentage of withdrawals in each arm of the model	0.07	Pooled RCT data	15% withdrawal from treatment arm and 8% placebo from main RCT data pooled
Proportion of the standard treatment cohort having 'controlled' PTH levels on completion of the titration phase	0.05	Pooled RCT data	Table 9 shows proportion of each cohort with PTH ≤32 pmol/l after titration
Proportion of the standard treatment cohort having 'uncontrolled' PTH levels on completion of the titration phase	0.665	Assumption based on pooled RCT data and Renal Registry	95% of those receiving standard treatment do not achieve target PTH levels. Of those that are not controlled, assume 70% are 'uncontrolled'
Proportion of the standard treatment cohort having 'very uncontrolled' PTH levels on completion of the titration phase	0.285	Assumption based on pooled RCT data and Renal Registry	95% of those receiving standard treatment do not achieve target PTH levels. Of those that are not controlled, assume 30% remain 'very uncontrolled'
Proportion of the cinacalcet cohort entering the 'controlled' subpopulation on completion of the titration phase	0.4	Pooled RCT data	Table 16 shows proportion of each cohort with PTH ≤26.5 pmol/l after treatment
Proportion of the cinacalcet cohort having 'uncontrolled' PTH levels on completion of the titration phase	0.42	Assumption based on pooled RCT data and Renal Registry	60% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled, assume 70% are 'uncontrolled'
Proportion of the cinacalcet cohort having 'very uncontrolled' PTH levels on completion of the titration phase	0.18	Assumption based on pooled RCT data and Renal Registry	60% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled, assume 30% are 'very uncontrolled'

TABLE 34 *Loss of control of PTH over time (deterioration)*

Variable	Value	Source	Comments
Proportion of people with 'controlled' PTH levels that become 'uncontrolled' each cycle in the standard treatment arm (per year)	0.1	Assumption	No published data available. Information from EAG varied
Proportion of people with 'uncontrolled' PTH levels that become 'very uncontrolled' each cycle in the standard treatment arm (per year)	0.2	Assumption	No published data available. Information from EAG varied
Proportion of people with 'controlled' PTH levels that become 'uncontrolled' each cycle in the cinacalcet arm (per year)	0	Assumption	No published data available. Information from EAG varied
Proportion of people with 'uncontrolled' PTH levels that become 'very uncontrolled' each cycle in the cinacalcet arm (per year)	0	Assumption	No published data available. Information from EAG varied

EAG, expert advisory group.

effects such as nausea. However, in the absence of relevant data, it was assumed that there was no loss of control over time with cinacalcet. The impact of this assumption was explored in sensitivity analysis.

Mortality

Background death rates are derived from the cumulative average survival probabilities after the initial 90 days on dialysis reported in the Renal Registry for 10-year age bands.[13] The initial

TABLE 35 *Cumulative 1-year probability of death due to all causes*

Age group (years)	1-year mortality	Source
45–54	0.083	Renal Registry
55–64	0.150	Renal Registry
65–74	0.213	Renal Registry
75–84	0.276	Renal Registry
≥85	0.354	Renal Registry

90 days of dialysis carry higher mortality as people may have acute health problems. The probability of death at the start and end of these 10-year categories is likely to be different. Therefore, death rates were interpolated for individual ages using the methods described in Appendix 8. Illustrative values are shown in *Table 35*.

Relative mortality risk based on PTH levels

Having established the overall mortality rate by age, the impact of PTH levels was estimated using a large US cohort study by Block and colleagues.[19] This study, although based in the USA, was felt to be the most appropriate as it was by far the largest identified and contained information about both cardiovascular risk and mortality, as well as including relative risk data about the impact of other biomarkers, such as Ca × P. The paper assessed the impact of various biochemical markers on the risk of adverse events occurring. PTH levels were divided into six ranges (<150, 150–300, 300–600, 600–900, 900–1200 and ≥1200 pg/ml). (These are equivalent to values of <16, 16–32, 32–64, 64–95, 95–127 and ≥127 pmol/l.) The relative risk of mortality occurring in each of these PTH ranges was reported. Relative risks for the ranges used in the model for those with 'controlled', 'uncontrolled' and 'very uncontrolled' PTH were derived using the methods described in Appendix 9. *Table 36* summarises the relative risk values used in the model. These are applied to the age-dependent probabilities of all-cause death to obtain the required cycle probability of death in each of the model strata.

Surgical mortality is described in the section 'Surgical mortality' (p. 54).

Cardiovascular-related transition probabilities

The rate at which initial, non-fatal cardiovascular events occur has been assumed to be constant. The risk of having a subsequent cardiovascular event is assumed to be higher once an event has previously occurred.

Death from cardiovascular causes

Three different causes of mortality are modelled: cardiovascular death, death from other causes and surgical deaths (which accounts for the small proportion of those patients who die as a result of parathyroidectomy). Death from other causes represents a relatively stable background level of mortality within the model that varies slightly depending on the level of PTH control, but which is consistent for all the health states at a given degree of PTH control. Cardiovascular death is the main source of differential death rates between the states at each degree of SHPT severity. To derive the cardiovascular death transition probabilities for each health state in the model, two types of data have been combined. First, the overall proportion of the death rate for the population known to be attributable to cardiovascular causes and, secondly, the relative risk of cardiovascular death for each health state compared to the event-free state. These two types of data have been obtained from a range of sources and combined to derive the values for

TABLE 36 *Relative risk modifiers for all-cause mortality for different degrees of PTH control*

Degree of PTH control	Value	Source	Justification/comments
'Controlled'	1.0	Block, 2004[19]	US data based on 40,538 dialysis patients. Baseline range used in all calculations is 150–300 pg/ml (16–32 pmol/l), therefore RR is 1
'Uncontrolled'	1.0613	Block, 2004[19]	US data based on 40,538 dialysis patients. Paper reports RRs for six different PTH ranges. Plot of RRs against PTH shows a linear relationship. Value imputed using a PTH level of 550 pg/ml (58 pmol/l)
'Very uncontrolled'	1.1824	Block, 2004[19]	US data based on 40,538 dialysis patients. Paper reports RRs for six different PTH ranges. Plot of RRs against PTH shows a linear relationship. Value imputed using a PTH level of 1200 pg/ml (127 pmol/l)

TABLE 37 *Relative risk of cardiovascular death in different health states compared with the 'event-free' health state*

Health state	Value	Source	Justification
Death from CV event (CVE)	13.20	Herzog, 1998[83]	Derived from reported mortality for dialysis patients hospitalised due to CV event (0.26)
Event free, previous CV event (CVH)	2.9	Renal Registry[16]	Mortality with CV disease for England and Wales
Fracture event with hospitalisation (FRE)	1.84	Mittalhenkle, 2004[84]	See section 'Cardiovascular-related transition probabilities' (p. 49)
Event free with previous fracture event (FRH)	1.84	Mittalhenkle, 2004[84]	See section 'Cardiovascular-related transition probabilities' (p. 49)
CV event and fracture event experience (CFE)	1.91	Mittalhenkle, 2004[84]	See section 'Cardiovascular-related transition probabilities' (p. 49)
Event free with previous fracture and CV event (CFH)	1.91	Mittalhenkle, 2004[84]	See section 'Cardiovascular-related transition probabilities' (p. 49)

cardiovascular death transition probabilities for each modelled health state, as described in Appendix 10.

The transition probabilities relating to death from cardiovascular causes for each health state in the model are calculated from the standard treatment arm of the model. These probabilities are then applied equally to the cinacalcet arm of the model. Reduced cardiovascular mortality in the cinacalcet arm can arise in two ways: first, through more of the population having controlled PTH levels and so having a lower overall death probability and, secondly, through a lower proportion of the population at all levels of PTH control occupying health states related to cardiovascular events and fractures which carry higher risk. For example, if cardiovascular events are reduced with cinacalcet then the associated state occupancy of this high-risk state will be reduced and the number of cardiovascular deaths will be lower.

Variation of cardiovascular death risk between health states

The risk of cardiovascular death for people who have a cardiovascular event is likely to be higher than for those who have not had a cardiovascular event. In the model, this means a greater risk of cardiovascular death for people occupying health states 'cardiovascular event' or 'post-cardiovascular event' compared with those occupying the event-free health state. In addition, the risk of cardiovascular death is greater for patients with uncontrolled or very uncontrolled levels of PTH compared with those with controlled levels. Finally, the risk of dying from a subsequent cardiovascular event increases if people have a history of either cardiovascular events or major fractures. This means that different transition probabilities for cardiovascular death are needed both for the different strata of the model and for the different health states within each strata.

Determining the cardiovascular death risk during cardiovascular hospitalisation

In a US-based study of 34,189 patients on long-term dialysis, Herzog and colleagues describe long-term survival after an acute myocardial infarction (MI).[83] In-hospital mortality for patients suffering from MI was 26%. Therefore, it was assumed that the probability of cardiovascular death for patients hospitalised for a cardiovascular event is on average 0.26 across the strata. This is the probability of death from cardiovascular causes from the model health state 'cardiovascular event requiring hospitalisation'.

Determining the cardiovascular death risk during and after fractures

Mittalhenkle and colleagues[84] explored the risk of mortality over 5 years associated with hip fracture in ESRD patients in the USA. The study included 7636 patients with a hip fracture and 22,896 matched controls. In people with no history of cardiovascular disease, a hip fracture led to an 84% increase in the risk of cardiovascular mortality compared with people with no history of fracture. In those with a history of cardiovascular disease, a hip fracture led to a 91% increased risk of cardiovascular-related death compared with a similar person with no fracture. It was assumed that the increased risk of cardiovascular death following all major fractures is not significantly different from that for hip fracture. Therefore, the relative risk of cardiovascular death after having had a major fracture requiring hospitalisation is 1.84. This is applied to the health states 'fracture event requiring hospitalisation' and 'event free

TABLE 38 *Relative risk of cardiovascular event according to levels of PTH control*

Degree of PTH control	Value	Source	Justification/comments
Controlled	1.0	Block, 2004[19]	US data based on 40,538 dialysis patients. Baseline range used in all calculations is 16–32 pmol/l. Paper only reports statistically significant RRs for PTH >64, therefore RR is 1
Uncontrolled	1.17	Block, 2004[19]	US data based on 40,538 dialysis patients. It is assumed that the RR for PTH >64 pmol/l represents those with 'uncontrolled' PTH in the model
Very uncontrolled	1.26	Block, 2004[19]	US data based on 40,538 dialysis patients. It is assumed that the RR for PTH >95 pmol/l represents those with 'very uncontrolled' PTH in the model
Postsurgical	1.26	Modeller assumption	Assumption has been made that CV calcification is irreversible, and therefore after surgery the risk of a CV event is the same as for those with very uncontrolled PTH
Postsurgical with adverse events	1.26	Modeller assumption	Assumption has been made that CV calcification is irreversible, and therefore after surgery the risk of a CV event is the same as for those with very uncontrolled PTH

TABLE 39 *Cycle probability of an initial cardiovascular event by extent of PTH control*

	PTH levels			
	Controlled	Uncontrolled	Very uncontrolled	Postsurgery
Event probability	0.02662	0.03114	0.03354	0.03354

with a history of fracture'. For patients who have had both a non-fatal cardiovascular event and a previous fracture (occupying the 'event free with previous cardiovascular and fracture events' health state), the relative risk of death is 1.91 compared with those who have had neither of these events (the 'event-free' health state in the model). Again, these values have been assumed to apply regardless of the level of control of PTH levels.

Determining the cardiovascular death risk for patients with cardiovascular and fracture history

Table 37 summarises the relative risk modifiers for people who have had fractures or cardiovascular events compared with the risk of cardiovascular-related death for people who have no history of cardiovascular event or fracture. The risk of cardiovascular-related death for those who have a history of both a fracture and a cardiovascular event is lower than for those with a previous cardiovascular event only, based on data from Mittalhenkle and colleagues,[84] but since few people enter this health state in the model, the impact on the model results is unlikely to be significant.

First cardiovascular hospitalisation

In a study of 40,538 people on dialysis, Block and colleagues[19] report 5876 cardiovascular hospitalisations over the 12–18-month follow-up period, based on International Classification of Diseases-9 (ICD-9) codes. This gives a rate of 0.1023 events per patient-year. The corresponding baseline cycle probability of a cardiovascular event is therefore 0.02662.

Block and colleagues[19] also report the relative risk of cardiovascular hospitalisation for people with PTH levels of 600 pg/ml (64 pmol/l) or above, or 900 pg/ml or above (95 pmol/l), compared with those with PTH levels of 150–300 pg/dl (16–32 pmol/l). The relative risks are shown in *Table 38*. These values have been used to represent the relative risks for patients in the model with 'uncontrolled' and 'very uncontrolled' PTH levels. Derived values used in the model are shown in *Table 39*.

Subsequent cardiovascular events

A subsequent cardiovascular event is defined as hospitalisation due to cardiovascular problems in

people with a history of hospitalisation for a cardiovascular event. It is assumed that the probability of having a subsequent cardiovascular event serious enough to require hospitalisation increases once one has already occurred. As assuming the modelled population was all cardiovascular event naive would underestimate the risk of cardiovascular events, it was assumed that some of the starting cohort already have a history of cardiovascular event. Based on data from the Renal Registry, 15.7% of people in the model enter the 'previous cardiovascular event' health state in the first cycle after the initial treatment phase. The available data only provide estimates of the risk of a subsequent heart failure event after an initial admission for heart failure. It is unclear how representative this is of the subsequent risk of other cardiovascular events and this is a potential limitation of the model. This value was used because a large US cohort study of dialysis patients (n = 40,538) showed that heart failure is the most common cardiovascular cause of hospitalisation, accounting for 3.3% of admissions.[19] Other frequent causes were chest pain (3%), cardiac arrest (0.9%), acute MI (0.8%) and angina pectoris (0.8%).

In a retrospective cohort study of 1995 US dialysis patients, Trespalacios and colleagues examined the risk factors associated with both initial and subsequent hospitalisations for people with and without prior congestive heart failure (CHF).[85] *Table 40* shows the numbers of people in this study hospitalised for heart failure who had a history of CHF.

The risk ratio for hospitalisation in people with a history of CHF compared with people with no history of CHF is (103/1031)/(188/846) = 2.224 (95% CI 1.781 to 2.778). The probability of a subsequent admission for CHF is the transition probability for an initial cardiovascular event multiplied by this value (*Table 41*).

Fracture-related transition probabilities

We were unable to identify any published information about the epidemiology of fractures specifically in the ESRD population. Hip/femur fractures were used as the identifier for major fractures due to renal osteodystrophy. Within the model, each hip fracture also incurs the cost and reduction in utility due to fractures at other sites based on the distribution of fractures in the general population.[86] Major fractures are modelled explicitly through patient movement to the relevant health state, with associated costs, a reduction in quality of life (utility) and increased risk of mortality. For the associated minor fracture, the impact on utility value and cost is modelled for one cycle.

We assumed that the pattern of fractures in renal osteodystrophy is the same as in the general population. This is a limitation but no data about the pattern of fracture in ESRD were identified. Neither osteoporosis data, based mostly on older women, nor general population data provide an ideal match for this population. Although osteoporotic fractures may be more similar to those due to renal osteodystrophy than the general population, there are differences in these groups. Moreover, there are no straightforward definitions of osteoporotic fractures. Previous technology assessments about osteoporosis have used general population studies, and assumed that those at specific sites are osteoporotic.[87]

TABLE 40 *Calculation of risk modifier for subsequent cardiovascular event given a previous event*[85]

	Hospitalised for CHF	Not hospitalised for CHF	Totals
No prior history of CHF	103	928	1031
Prior history of CHF	188	658	846
Totals	291	1586	1877

TABLE 41 *Cycle probability of a subsequent cardiovascular event occurring by degree of PTH control*

	PTH levels			
	Controlled	Uncontrolled	Very uncontrolled	Postsurgery
Probability of a subsequent CV event	0.05920	0.06927	0.07459	0.07459

The risk of having an initial fracture is based on constant risk and is not time dependent, which may underestimate the number of fractures experienced. After having the first fracture, the risk of having subsequent fractures is higher. The rate at which first fractures occur depends on PTH levels.

Initial fractures

A US-based study of over 100,000 people awaiting kidney transplantation reported a hip fracture rate of 2.9 events per 1000 patient-years.[27] In the general population of England and Wales hip fractures represent 10.35% of all reported fractures (24,934 out of 240,857 fractures).[86]

As was the case with mortality, it is necessary to modify this baseline rate of hip fractures to reflect the risk of an event occurring at each level of PTH control. Only one relevant study, by Kim and colleagues, was identified.[88] This study is only available in abstract form and included 10,018 patients on dialysis in the USA. It reports the hazard ratio for fracture by different PTH levels. The risk of fractures for those with PTH levels of more than 85 pmol/l was increased by 94% compared with those with PTH levels of 16–32 pmol/l.

The study by Kim and colleagues[88] reports hazard ratios separately for people with PTH levels of 32–53 and 53–85 pmol/l. Kim and colleagues report that those with PTH levels of 32–53 pmol/l have a reduced risk of fracture compared with the reference population (16–32 pmol/l), which seems counterintuitive. The hazard ratios for both PTH categories have 95% confidence intervals that include 1. In order not to bias against cinacalcet in the base case, the hazard ratio reported by Kim and colleagues for patients with PTH levels of 53–85 pmol/l was used for those with uncontrolled PTH. The impact of this assumption has been explored through sensitivity analysis. *Table 42* shows the hazard ratios used in the PenTAG model to estimate the probability of fracture depending on the degree of PTH control.

Applying these values to the baseline annual rate and adjusting for cycle length leads to the transition probabilities shown in *Table 43*. These probabilities are only applied to transitions from health states where the patient has no history of a fracture (e.g. from EVF, CVE or CVH) to states where a fracture occurs (FRE and CFE).

Second and subsequent fractures

Based on a meta-analysis of studies assessing the increased risk of subsequent fracture after initial fracture in osteoporosis, Stevenson and colleagues report that the relative risk of a subsequent hip fracture after initial hip fracture is 2.3.[89] This value was applied to all of the model strata. Multiplying the probabilities of initial fracture in each of the model strata by this value gives the probability of a subsequent fracture depending on the degree of PTH control (*Table 43*). These probabilities are applied to transitions from health states where a patient has a history of a fracture.

Parathyroidectomy transition probabilities

The model only allows parathyroidectomy for patients whose levels of PTH are very uncontrolled. Input from clinicians in the EAG suggested that use of parathyroidectomy is variable. A 10% annual rate of parathyroidectomy for those with very uncontrolled levels of PTH has been used. For the modelled cohort, a constant

TABLE 42 *Modifiers for initial fractures at different levels of PTH control*

PTH levels	Value	Source	Justification/comments
Controlled	1.0	Kim, 2004[88]	Base case for HRs published in the abstract. US study of 10,018 dialysis patients
Uncontrolled	1.12	Kim, 2004[88]	HR of fracture for patients with PTH levels of 500–800 pg/ml (53–85 pmol/l). US study of 10,018 dialysis patients
Very uncontrolled	1.94	Kim, 2004[88]	Weighted average of the HRs published in the abstract. US study of 10,018 dialysis patients
Postsurgical	1.0	Kim, 2004[88]	Postsurgical risk of fracture assumed the same as in the controlled group
Postsurgical with adverse events	1.0	Kim, 2004[88]	Postsurgical risk of fracture assumed the same as in the controlled group

TABLE 43 *Cycle probability of an initial and a subsequent fracture by level of PTH control*

	PTH levels			
	Controlled	**Uncontrolled**	**Very uncontrolled**	**Postsurgery**
Initial fracture probability	0.000726	0.00081	0.00141	0.000726
Subsequent fracture probability	0.00167	0.00187	0.00324	0.00167

TABLE 44 *Proportion of parathyroidectomies that fail to control PTH*

Variable	Value	Source	Comments
Proportion of operations that are unsuccessful in controlling patients' biomarkers	0.08	Jofre, 2003[90]	12/148 PTx required reoperation or retained PTH levels over 97.5 pmol/l
		Kim, 1994[91]	5/60 persistent or recurrent hyperparathyroidism

transition probability has been used. In addition, the EAG suggested that about 15% of people aged 55 years would be unsuitable for surgery, rising to 25% for those aged 75 years. This has been assumed to increase at a linear rate.

The number of people in the cohort with very uncontrolled PTH levels at the start is based on the numbers from the pooled data of the RCTs included in the systematic review (see *Table 33*).

People having a successful parathyroidectomy are assumed to have the same risk of a fracture event as people with controlled PTH levels (i.e. RR = 1). It has been assumed that cardiovascular calcification is irreversible, meaning that the risk of a cardiovascular event postsurgery stays the same as it was presurgery for those with very uncontrolled PTH levels.

The model does not assume that surgery is always successful. Two studies of people undergoing parathyroidectomy, one in 60 people in the USA and one in 148 people in Spain, both report an 8% failure rate, resulting in continued hyperparathyroidism or reoperation.[90,91] In the model, 8% of people return to having very uncontrolled PTH after surgery (*Table 44*). Those that do have a successful operation no longer suffer from SHPT and do not require a repeat operation. Potentially, this is a limitation of the model as it may overestimate effectiveness and underestimate the total number of parathyroidectomies.

In addition, 1% of those receiving parathyroidectomy experience an SAE, such as vocal cord damage. These people enter the 'postparathyroidectomy, adverse effects' stratum of the model. Here, they attract the same risks and benefits as those with very uncontrolled levels of PTH.

Given the assumptions made in the calculation of this value, the uncertainties in its derivation are explored in sensitivity analysis.

Surgical mortality

Surgical mortality data were taken from a matched cohort study by Kestenbaum and colleagues.[92] People with ESRD (n = 4558) who underwent an initial parathyroidectomy were matched with those not undergoing surgery based on age, race, gender, cause of ESRD, dialysis duration and dialysis modality. Postparathyroidectomy, the risk of death is initially increased in the first 90 days postsurgery (RR 1.84), but subsequently mortality is reduced (RR 0.87). In the model, the relative risk of death after surgery applied relative to those with very uncontrolled PTH. *Table 45* shows the relative risk data used in the first and subsequent model cycles postsurgery.

Utilities

Utility values assigned by general population samples were searched for, as a societal perspective is preferred by NICE. We also wanted to identify sources that had used a preference-based method for measuring utility. The TTO method has been established as being adequately tested in an ESRD population.[41]

Utility values for ESRD

A search for utility values in ESRD was undertaken using the strategy described in Appendix 4. Only one paper, by de Wit and colleagues, identified societal values for people with ESRD on dialysis.[47]

TABLE 45 *Relative risk of mortality related to parathyroidectomy*

Variable	Value	Source	Comments
Postsurgical (first 90 days)	3.356	Kestenbaum, 2004[92]	Short-term increase in the risk of death compared with patients who did not have surgery. Value represents an 84% increase in risk compared with those with very uncontrolled PTH
Postsurgical with adverse events (first 90 days)	3.356	Kestenbaum, 2004[92]	Short-term increase in the risk of death compared with patients who did not have surgery. Value represents an 84% increase in risk compared with those with very uncontrolled PTH
Postsurgical (after 90 days)	1.029	Kestenbaum, 2004[92]	Long-term reduction in the risk of death compared with patients who did not have surgery. Value represents a 13% reduction in risk compared with those with very uncontrolled PTH
Postsurgical with adverse events (after 90 days)	1.029	Kestenbaum, 2004[92]	Long-term reduction in the risk of death compared with patients who did not have surgery. Value represents a 13% reduction in risk compared with those with very uncontrolled PTH

TABLE 46 *Utility values for dialysis given by a general population sample*

Study	Dialysis type	Utility value (SD)
de Wit, 1998[47]	HD	0.66 (0.29)
	LCHD	0.81 (0.24)
	CAPD	0.71 (0.29)
	CCPD	0.81 (0.19)

In this case, Dutch people with ESRD completed the EuroQol 5 Dimensions (EQ-5D) and these results were translated by de Wit and colleagues using the preference-based scores obtained by Dolan for EQ-5D states from a representative sample of the UK population.[93] Utility values are shown in *Table 46*. In the UK, 73% of dialysis patients receive haemodialysis and 27% peritoneal dialysis, so the model used a weighted average for the utility value of 0.6735.[13]

Impact of PTH level on utility

No papers were identified that reported utility value by PTH level, and only one paper looked at any measure of QoL in relation to this measure. Knight and colleagues[52] measured the physical and mental health components of the SF-36 in 14,815 people with ESRD in the USA. They did not find any significant association with PTH levels and either physical or mental health, although there was a trend towards higher mean PTH levels in groups with worsening QoL scores. However, it should be noted that levels of PTH are not particularly high in this study.[52] In addition, bone pain and pruritus are common symptoms of hyperparathyroidism and studies have reported an increase in QoL after parathyroidectomy as a result of these resolving. Advice from clinical experts suggested that there was not likely to be an impact on QoL with uncontrolled compared with controlled PTH, but that people with very uncontrolled PTH levels would be adversely affected. The model therefore incorporates a scaled reduction of 15% in utility for those in the event-free health state who have very uncontrolled PTH.

Utility values for cardiovascular events

No studies were identified that provided utility values for people with ESRD after experiencing a cardiac event. Two relevant studies were identified, by Nease and colleagues[94] and Martin and colleagues.[95] However, in both cases, these papers report the impact of ongoing symptoms as having relatively high utility scores of 0.96 and 0.98, respectively. It was assumed that the reduction in utility will be ongoing after people have recovered from hospitalisation due to a cardiovascular event. This ongoing scaled health reduction is calculated by multiplying the value for ESRD by the value for angina.

Values were also sought assessing the impact of acute cardiovascular events requiring hospitalisation, such as MI, and this was applied to a single cycle (3 months). The Harvard Cost-Effectiveness Analysis (CEA)[96] database of health state utility values gives a value of 0.71 for CHF based on a community rating using the TTO method (taken from Beaver Dam Health) (*Table 47*).

TABLE 47 *Scaled reduction in utility value for cardiovascular events*

Single health state	Value	Source	Justification
CHF	0.71	Harvard CEA database[96]	CHF the most common reason for CV hospitalisation for patients with ESRD.[19] Value used in model is this multiplied by value for ESRD for one cycle
Chronic CVD	0.97	Nease, 1995[94] Martin, 1999[95]	Weighted mean of values for angina or dyspnoea symptoms. Applied to people with ESRD after CV event cycle

TABLE 48 *Scaled reduction in utility values for fractures*

Single health state	Value	Source	Justification
Hip fracture (first cycle)	0.797	Brazier, 2002[97]	Reference case based on recent SR of osteoporosis literature
Hip fracture (subsequent cycles)	0.8985	Brazier, 2002[97]	Reference case for subsequent impact of hip fracture in SR based on author experience
Proximal humerus fracture (one cycle)	0.981	Brazier, 2002[97]	Reference case based on recent SR of osteoporosis literature

SR, systematic review.

CHF is the most common cardiovascular reason for hospitalisation among those with ESRD, accounting for 3.3% of hospitalisations, while cardiac arrest and acute MI account for 0.9% and 0.8%, respectively.[19]

Utility values for fracture

No studies were found that assessed the QoL impact of fractures in people with ESRD. Fracture studies tend to be either in the general population or in those with osteoporosis. Extrapolating data from either of these populations to those with ESRD is not ideal. General population data are likely to contain more young, very active people, whereas osteoporosis studies tend to be in elderly women. However, because osteoporosis fractures are more likely to follow a similar pattern to fractures due to bone disease in ESRD than the general population, this was felt to be a more relevant source of utility estimates.

Brazier and colleagues[97] recently conducted a systematic review of utility values for osteoporosis-related conditions. They recommend a set of values as a reference case for economic models of osteoporosis which they suggest should be applied in the first year to population norms for the relevant populations. These are based on EQ-5D values. For subsequent years, Brazier and colleagues suggest that a value of half the initial impact should be used for major fractures, but no impact for minor fractures. The hip fracture value was used as a proxy for all major fracture events, and humerus fracture values for minor fractures (*Table 48*).

Utility values and parathyroidectomy

People who have a successful parathyroidectomy are assumed to gain control of PTH levels and have the same values for all health states as for a person whose PTH is 'controlled'. People who have adverse effects due to parathyroidectomy are assumed not to benefit from this surgery in terms of QoL gains, and so keep the same utility values as people with very uncontrolled PTH levels. As the impact of surgery itself was assumed to be short, no utility decrement was modelled.

The utility values used in the economic model are summarised in *Table 49*.

Identification and measurement of resource use

Perspective and costing principles

Costing was conducted using a variety of data sources to determine the amount and valuation (unit costs) of resources used. An NHS perspective was used.

TABLE 49 *Summary of utility values used in the economic model*

Disease state	Value	Source	Justification
Event-free survival	0.6735	de Wit, 1998[47]	European study using societal values of utility found HD 0.66 and PD 0.71. Weighted value based on 73% HD and 27% PD in the UK[13]
CV event (with hospitalisation)	0.4782	Harvard CEA database[96]	CHF the most common reason for CV hospitalisation for patients with ESRD (utility 0.71).[19] Value used in model is this multiplied by value for ESRD for one cycle
Event free, previous CV event	0.6533	Nease, 1995;[94] Martin, 1999[95]	Weighted mean of values for angina or dyspnoea symptoms (utility 0.97). Applied as an ongoing scaled reduction to ESRD patients after CV event
Fracture event (with hospitalisation)	0.5368	Brazier, 2002[97]	Reference case based on recent SR of osteoporosis literature for hip fracture (utility 0.797). Applied as reduction for one cycle
Event free, previous fracture	0.6051	Brazier, 2002[97]	Reference case for subsequent impact of hip fracture in SR based on author experience (utility 0.8985). Applied as ongoing scaled reduction to ESRD patients after fracture event
CV event and fracture experience	0.3811	See above	Assume that the impact of these is compound
Event free, previous CV and fracture events	0.5870	See above	Assume that the impact of these reductions is compound. Applied to subsequent states
Impact of having uncontrolled PTH levels	× 1	Author assumption	Assume that there is no impact on QoL of PTH of 33–84 pmol/l for patients whose PTH levels are uncontrolled compared with patients who have controlled PTH
Impact of having very uncontrolled PTH levels	× 0.85	Author assumption	Assume that a scaled reduction of 15% is applied to all health states for patients whose PTH levels are very uncontrolled compared with patients who have controlled PTH
Postparathyroidectomy	As for people with 'controlled' PTH levels	Author assumption	Assume that after successful surgery, patients have controlled PTH levels
Postparathyroidectomy with adverse effects	As for people with 'very uncontrolled' PTH levels	Author assumption	Assume that after surgery patients with adverse effects have the same QoL as those with very uncontrolled PTH levels

The types of NHS resource use initially intended for inclusion in the analysis were:

- resources that are consumed at different rates during or after treatment with cinacalcet, compared with during or after standard treatment
- resources related to treatments, procedures, service contacts, adverse events or other potentially cost-inducing events that may differ between those treated with cinacalcet and standard treatment (either because of trial or other evidence suggesting that they actually differ, or because there may be differences in survival between intervention and comparator)
- resources for which there is a probable opportunity cost (i.e. those that would, in all likelihood, otherwise be used for some other purpose or patients within the NHS).

Resource use included in the analysis

Ultimately, the following types of resource use were included in the base-case analysis (*Table 50*):

- cinacalcet (during initial treatment phase and maintenance)
- annual cost of standard care for SHPT (vitamin D and phosphate binders) for people with ESRD on dialysis

TABLE 50 *Types of resource use consumed by comparator*

Type of resource use	Cinacalcet	Control	Justification for inclusion
Cinacalcet (drug) during maintenance phase	✓	×	Integral to taking cinacalcet
Cinacalcet (drug) during titration phase	✓	×	Integral to taking cinacalcet
Cost of vitamin D and phosphate binders	✓	✓	May differ between cinacalcet and standard treatment arm
CV-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on cinacalcet
Major fracture-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on cinacalcet
Minor fracture-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on cinacalcet
Parathyroidectomies	✓	✓	Trial evidence that these occur at a different rate in those on cinacalcet
Tests for PTH, calcium and phosphate levels	✓	✓	Regular testing in those on and not on cinacalcet, and increased frequency of some tests in period following parathyroidectomy

- hospital resources to treat those cardiovascular-related adverse events that lead to hospitalisation
- hospital resources to treat major fractures that lead to hospitalisation
- hospital resources to treat minor fractures that lead to hospitalisation
- hospital resources to conduct parathyroidectomies
- regular blood tests for PTH, calcium and phosphate levels.

Costs not included in the analysis

The following costs, initially considered for possible inclusion, were not included in the analysis for the reasons described.

Dialysis costs

In the base-case analysis, the background cost of dialysis was not included for all patients in both arms of the model. This is likely to bias the analysis in favour of cinacalcet. If cinacalcet leads to survival gains, there will be significant cost implications for the NHS due to the need for dialysis during those added years of life. The handling of healthcare costs in added years of life due to an intervention is a methodological issue of considerable controversy.[80,81] Current conventions recommend that medical costs that are 'related to the intervention' should be included in cost-effectiveness analysis. It could be debated to what extent dialysis is related to SHPT as opposed to being related to the broader underlying condition of ESRD. In addition, dialysis is a very expensive treatment that has already been accepted as standard for this population, although it may not be deemed cost-effective. The impact of including dialysis costs was assessed in sensitivity analysis.

Amount of different resources used

The amount of different resources used is dependent on either the amount of time spent in a particular disease state or the incidence of particular events (such as treatments or hospitalisations). *Table 51* lists the amount of resources used and the source.

It is unclear how much prescriptions of vitamin D and phosphate binders may change with the addition of cinacalcet. The dosage included in the cinacalcet trials was largely fixed by study protocol. The EAG felt that cinacalcet might reduce the need for phosphate binders and, in particular, might result in less use of expensive drugs such as sevelamer, which may be used more commonly when cheaper drugs appear not to be working.

There is no published evidence on this issue, so in the base case equal levels of consumption of phosphate binders and vitamin D were assumed in both arms of the model. On the basis of expert clinical opinion, however, it was assumed that the more expensive phosphate binder, sevelamer, would be reserved for patients with very uncontrolled PTH levels. Therefore, because cinacalcet influences how many patients' PTH

TABLE 51 *Mean quantities of resources used with uncertainty and data source*

Resource type	Amount	Unit	SD	Source
Cinacalcet dose during maintenance phase (for patients with initial PTH >32 pmol/l)	94.4	mg per day	±46.0	Cunningham, 2005,[71] as cited in Appendix 2 of Amgen industry submission
Cinacalcet dose during titration phase (for patients with initial PTH >32 pmol/l)	81.6	mg per day	±35.3	Cunningham, 2005,[71] as cited in Appendix 2 of Amgen industry submission
Phosphate binders	16% taking none 38%[a] or 86% taking calcium carbonate 11% taking calcium acetate 48%[a] or 0% taking sevelamer	Mean dose: 6 tabs per day 3 tabs per day 12 tabs per day	NA NA NA NA	Audit of 510 SHPT patients being treated in Belfast City Hospital, Northern Ireland (Brown H: personal communication, February 2006) Mean doses not supplied, so assumed (expert advice)
Vitamin D	37.3% taking none 62.7% taking vitamin D	Patient-specific data (median 250 ng per day, range 36–2143 ng per day)	NA	Audit of 510 SHPT patients being treated in Belfast City Hospital, Northern Ireland (Brown H: personal communication, February 2006)
CV-related hospitalisations	CV event incidence rates according to level of PTH control. See section 'Cardiovascular-related transition probabilities' (p. 49)			
Major fracture-related hospitalisations	Major fracture event incidence rates according to level of PTH control. See section 'Fracture-related transition probabilities' (p. 52)			
Minor fracture-related hospitalisations	Determined as a multiple (approx. ×9) of the incidence of major fracture-related hospitalisations (which varies according to both level of PTH control and whether there has been a previous major fracture). See section 'Fracture-related transition probabilities'			
Parathyroidectomies	See section on transition probabilities			
Frequency of PTH tests (for people in both with cinacalcet and standard treatment arms)	1	Per quarter	0.5–2.0	EAG
Frequency of calcium and phosphate tests (for people in both with cinacalcet and standard treatment arms), except:	1	Per month	0.5–2.0	EAG
higher frequency of calcium test in 3 months following parathyroidectomy (for people in both with cinacalcet and standard treatment arms)	1	Per week	0.5–2.0	EAG

[a] Sevelamer only taken when PTH is very uncontrolled. With controlled and uncontrolled PTH it is assumed that the sevelamer 48% would be on calcium carbonate instead.

levels become very uncontrolled, this may lead to fewer patients on cinacalcet consuming sevelamer.

Unit costs used in the model

The main unit costs, their base-case values and ranges for sensitivity analysis, and their justification for use are described in *Table 52*. A more detailed description of sources and justification can be found in the following sections.

Dialysis costs are not used in the base case, but are used for sensitivity analysis. Methods of

TABLE 52 *Unit costs (2005 prices)*

Resource	Unit cost (£)	Unit	Lower value (£)	Upper value (£)	Source (justification)
Cinacalcet	0.145	per mg	NA	NA	List price of Mimpara® from BNF No. 50,[63,71] mean price per mg of 30-mg (15.03p) and 60-mg (13.87p) 28-tab packs
Calcium carbonate (phosphate binder)	0.0933	per 1250 mg	NA	NA	List price of Calcichew® from BNF No. 50[63,71]
Calcium acetate (phosphate binder)	0.1099	per 1000 mg	NA	NA	List price of Phosex® from BNF No. 50[63,71]
Sevelamer (phosphate binder)	0.682	per 800 mg	NA	NA	List price of Renagel® from BNF No. 50[63,71]
Aluminium hydroxide (phosphate binder)	0.0313	per 475 mg	NA	NA	List price of Alu-Cap® from BNF No. 50[63,71]
Vitamin D	0.1953	per 250 ng	NA	NA	List price of Alfacalcidol® from BNF No. 50[63,71]
	0.3203	per 500 ng			
	0.4883	per1000 ng			
CV-related hospitalisation	1287	per FCE	881	2021	Weighted average of average unit cost for HRGs E29, E37, E18, A22, E22, E11, D37, Q17 and E42; from NHS NSRC 2004[79] table for non-elective inpatient episodes, in NHS Trusts and PCTs. See *Table 53* for calculation
Major fracture-related hospitalisation	4620	per FCE	3184	5824	Weighted average of average unit cost for HRGs H84, H82, H36 and H39; from NHS NSRC 2004[79] table for non-elective inpatient episodes, in NHS trusts and PCTs. See *Table 54* for calculation
Minor fracture-related hospitalisation	917	per FCE	519	1184	44% of average unit cost for HRG H45, as no other available data; from NHS NSRC 2004[79] table for non-elective inpatient episodes, in NHS trusts and PCTs
Parathyroidectomy	1998	per FCE	1470	2428	Average unit cost for HRG K02; from NHS NSRC 2004[79] table for elective inpatient episodes, in NHS trusts and PCTs
PTH level tests	19	per test	10	30	Amgen industry submission
Calcium level test	4	per test	2	6	Laboratory Manager, Department of Clinical Chemistry, RD&E Hospital, Exeter
Phosphate level test	4	per test	2	6	Laboratory Manager, Department of Clinical Chemistry, RD&E Hospital, Exeter

[a] FCE, finished consultant episode; HRG, Healthcare Resource Group; NSRC, National Schedule of Reference Costs; PCT, primary care trust.

TABLE 53 *Weighted average cost per cardiovascular-related hospitalisation*

	As per NSRC 2004 (£)[a]					Weighted average		
	Mean	Low	High	HRG	%[b]	Mean	Low	High
Arrhythmias	987	810	1766	E29	22.01%	217	178	389
Cardiac tamponade, others	1155	684	1696	E37	2.52%	29	17	43
Heart failure	1519	1113	2394	E18	9.43%	143	105	226
Stroke	2330	1288	3636	A22	5.66%	132	73	206
Ischaemic heart disease	937	720	1642	E22	21.38%	200	154	351
Myocardial infarction	1458	1090	2199	E11	10.69%	156	117	235
Pulmonary oedema	1262	760	1759	D37	18.87%	238	143	332
Peripheral vascular disease	1964	1095	2827	Q17	5.66%	111	62	160
Valve disorders	1580	848	2106	E42	3.77%	60	32	79
Weighted average cost of a CV-related hospitalisation					100%	1287	881	2021

[a] Source: NHS NSRC 2004[79] for non-elective inpatient finished consultant episodes (Table TNELIP, in Combined tables for NHS trusts and PCTs).
[b] Source: Appendix 3 of Amgen submission to NICE for Mimpara.

TABLE 54 *Cost of fracture-related hospitalisations*

	As per NSRC 2004 (£)[a]					Weighted average (£)		
	Mean	Low	High	HRG	%[b]	Mean	Low	High
Hip fractures, intracapsular	4839	3546	6029	H84	25%[c]	1210	886	1507
Hip fractures, extracapsular	5265	3733	6405	H82	25%[c]	1316	933	1601
Lower extremity fractures	3500	1473	4213	H36	22%	778	327	936
Upper extremity fractures	2083	1179	2690	H39	28%	1463	1037	1779
Weighted average cost of a CV-related hospitalisation					100%	4767	3184	5824
Minor fractures/dislocations	1168	554	1241	H45	44%	917	519	1184

[a] Source: NHS NSRC 2004[79] for non-elective inpatient finished consultant episodes (Table TNELIP, in Combined tables for NHS trusts and PCTs).
[b] Source: Appendix 3 of Amgen submission to NICE for Mimpara.
[c] Approximately half of all hip fractures are intracapsular (Singer, 1998[98]).

calculating dialysis costs are shown in Appendix 11.

Cost of cardiovascular-related hospitalisations

Table 53 shows how the case-mix of hospitalisations for different cardiovascular events was used to calculate a weighted average cost per cardiovascular hospitalisation (including lower and upper estimates). The case-mix was derived from the combined data on cardiovascular events in both trial arms of the four trials pooled by Cunningham and colleagues,[71] but reported in full detail in the Amgen submission to NICE.

Cost of fractures

Fractures in the model were classed as 'major' fractures (all of which are assumed to result in hospitalisation) and 'minor' fractures (*Table 54*). The mix of fracture locations and severity was taken from the four trials of the Cunningham paper[71] (which were also fully reported in Appendix 3 of the Amgen industry submission to

TABLE 55 *Application of costs by health state*

General description	Health states
Cost of cinacalcet (titration phase)	The titration state in the cinacalcet arm of the model
Cost of cinacalcet (maintenance)	All maintenance health states in the cinacalcet arm of the model except those following parathyroidectomy
Cost of vitamin D and phosphate binders	All health states in all arms of the model
Cost of regular PTH, calcium and phosphate tests	All health states in both arms of the model
Cost of CV event	All CV event (with hospitalisation) health states
Cost of (major) fracture event	All fracture event (with hospitalisation) health states
Cost of occasional minor fractures	Effectively all health states in both arms of model (applied as a proportion of the major fracture rate for each level of PTH control)

NICE for Mimpara). According to data from the four Amgen trials reported by Cunningham (but only reported in the Amgen industry submission for Mimpara, Appendix 3), 44% of minor fractures attract the cost of hospital inpatient treatment.

Health state costs per cycle and state transitions

The ways in which costs described above are applied in the decision model are shown in *Table 55*. No costs are attached to death. Costs of parathyroidectomy are attached to all transitions from any of the very uncontrolled PTH (and eligible for surgery) health states to either of the postsurgery health states.

Discounting

In accordance with Treasury advice, costs and benefits were discounted at 3.5%.[99]

Dealing with uncertainty

One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied independently of the other model inputs, have the greatest impact on the incremental cost-effectiveness of cinacalcet. These analyses examined the impact of:

- transition probabilities (including percentage of patients with controlled, uncontrolled and very uncontrolled PTH levels, the number of people ineligible for surgery and suffering adverse effects of surgery, the annual rate at which fractures occur, the annual rate at which cardiovascular events occur, the percentage of fractures classified as major, the percentage of people with controlled PTH levels whose levels become uncontrolled each year, and the percentage of people with uncontrolled PTH levels whose levels become very uncontrolled each year)
- relative risks (including the risk of fracture, cardiovascular event and mortality for people with different degrees of lack of control of PTH levels)
- utility values (including QoL for people with ESRD, the scaled reductions associated with fracture, cardiovascular events and increasing lack of control of PTH levels, and the QoL for patients having adverse effects after parathyroidectomy)
- costs (including the cost of cinacalcet and impact of dose changes, the cost of parathyroidectomy and the cost of treating fractures and cardiovascular events).

Probabilistic simulation

PSA was also undertaken using a Monte Carlo simulation. PSA takes account of the uncertainty in all the model parameters simultaneously and gives the probability, given this uncertainty, that the intervention under examination is cost-effective at a given level of WTP for an additional QALY. In this stochastic approach, the Markov model is run 1000 times for the hypothetical cohort using input values randomly drawn from probability density functions in each model run. In these simulations, ranges and distributions used were sampled from the transitions, utility values and costs shown in *Table 56*.

Cost-effectiveness of cinacalcet

Base-case results of cost-effectiveness

Base-case results for the economic model are shown in *Table 57* on a per-patient basis. For the modelled cohort, when dialysis costs are not included cinacalcet marginally improves QALYs

TABLE 56 *Ranges and distributions used in the PSA*

Parameter	Available range data	Source	Type of data	Distribution
General modifiers				
Proportion of fractures classified as major	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Proportion of patients unsuitable for surgery	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Modifier for multiple fractures	(1.4 to 3.3)	Stevenson, 2005[89]	Lowest and highest RR for multiple fractures by different sites	Normal
Modifier for multiple CV events	(1.781 to 2.776)	Derived from data in Trespalacios, 2003[85]	95% CI derived using standard formulae for a 2 × 2 matrix	Normal
Yearly probability of surgery	(5 to 20)	Maximum and minimum values estimated by EAG	Clinical opinion and assumption	Beta
RR of death either during or shortly after surgery	(1.52 to 2.22)	Kestenbaum, 2004[92]	95% CI	Log-normal
Proportion of deaths that are CV related	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Proportions of operations that are unsuccessful	(5 to 20)	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Proportion receiving standard treatment having controlled PTH	(4 to 20)	Systematic review, Table 16	Minimum and maximum levels from individual trials	Beta
Proportion receiving standard treatment having very uncontrolled PTH	(13 to 52)	Renal Registry shows that 34% (range 13–52%) of HD population does not meet target levels for PTH (Figure 9.18, Chapter 9, p. 10)[16]	Minimum and maximum values from individual trusts	Beta
Proportion receiving cinacalcet having controlled PTH	(35 to 46)	Systematic review, Table 16	Minimum and maximum levels from individual trials	Beta
Proportion receiving cinacalcet having very uncontrolled PTH	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Differential dropout rate between two arms of the model	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Proportion of people with controlled PTH that become uncontrolled each cycle (both arms)	(0.05 to 0.5)	Input from EAG	Clinical opinion and author assumption	Log-normal
Proportion of people with uncontrolled PTH that become very uncontrolled each cycle (both arms)	(0.05 to 0.5)	Input from EAG	Clinical opinion and author assumption	Log-normal
Proportion of adverse effects after surgery (both arms)	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Risk of death in CVE compared to EVF	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Normal

continued

TABLE 56 *Ranges and distributions used in the PSA (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
Risk of death in CFE state compared to EVF	(1.76 to 2.07)	Mittalhenkle, 2004[84]	95% CI for used parameter	Normal
Risk of death in FRE state compared to EVF	(1.70 to 2.00)	Mittalhenkle, 2004[84]	95% CI for used parameter	Normal
Risk of death in CVH state compared to EVF	None	Renal Registry; author assumption that SE is 1/10th of the central estimate	Assumption	Normal
Risk of death in CFH state compared to EVF	(1.76 to 2.07)	Mittalhenkle, 2004[84]	95% CI for used parameter	Normal
Risk of death in FRH state compared to EVF	(1.7 to 2.00)	Mittalhenkle, 2004[84]	95% CI for used parameter	Normal
Fractures				
Yearly rate of an initial major fracture event	(1.7 to 6.1) hip fractures per 1000 patient-years	Ball, 2002[27]	Minimum and maximum for different subgroup analyses	Log-normal
Risk of fracture for those with uncontrolled PTH levels compared to those with controlled PTH	(0.73 to 1.72)	Kim, 2004[88]	95% CI	Log-normal
Risk of fracture for those with very uncontrolled PTH levels compared to those with controlled PTH	(1.36 to 2.76)	Kim, 2004[88]	95% CI	Log-normal
Death event				
Age-dependent probability of death	(–13.166 to –11.309) (2.314 to 2.762)	Derived using data in Renal Registry	95% CIs for log lambda and gamma parameters used in calculation of each probability	Bivariate normal
RR of death both arms	(0.9087 to 0.9715) (0.0002 to 0.0003)	Derived from Block, 2004[19]	95% CIs for slope and parameters used in calculation of category estimates	Bivariate normal
Reduction in death risk postsurgery	(0.80 to 0.94)	Kestenbaum, 2004[92]	95% CI	Normal
CV event				
Percentage of people starting the model assumed to have a history of CV event	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Yearly probability of having an initial CV event	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Risk of CV event with uncontrolled PTH	(1.06 to 1.29)	Block, 2004[19]	95% CI for PTH ≥600	Log-normal
Risk of CV event with very uncontrolled PTH	(1.12 to 1.42)	Block, 2004[19]	95% CI for PTH ≥900	Log-normal

continued

TABLE 56 *Ranges and distributions used in the PSA (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
Risk of CV event postsurgery	(1.12 to 1.42)	Block, 2004[19]	95% CI for PTH ≥900	Log-normal
Cinacalcet dose information				
Dose during titration phase	(46 to 117)	Cunningham, 2005[71] as cited in Appendix 2 of the Amgen industry submission	Central value ±1 SD	Normal
Dose in all presurgical strata	(48 to 140)	Cunningham, 2005,[71] as cited in Appendix 2 of the Amgen industry submission	Central value ±1 SD	Normal
General costs in both arms of the model				
Cost of parathyroidectomy	(1470 to 2428)	Average unit costs for HRG H45 from NHS NSRC 2004[79]	Upper and lower quartiles	Log-normal
Cost of PTH test	(10 to 30)	Amgen industry submission	Upper and lower quartiles	Log-normal
Cost of CV-related hospitalisation	(881 to 2021)	Weighted average unit cost for relevant HRGs[79]	Upper and lower quartiles	Log-normal
Cost of major fracture-related hospitalisation	(3184 to 5824)	Weighted average unit cost for relevant HRGs[79]	Upper and lower quartiles	Log-normal
Cost of minor fracture	(519 to 1184)	44% average unit cost for HFG H45[79]	Upper and lower quartiles	Log-normal
Background care cost for people on dialysis ESRD (where included)	(1956 to 5864)	Costs of hospital-based dialysis inflated to 2005/06 costs based on 2003 HTA monograph by Mowatt[100]	Upper and lower quartiles	Log-normal
Utility values				
Value associated with a patient on HD	(0.58 to 0.74)	*Table 46*	SD = 0.29	Beta
Value associated with a patient on PD	(0.64 to 0.78)	*Table 46*	SD = 0.29	Beta
CV event	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
History of CV event	(0.67 to 1.00)	Weighted mean value for angina and dyspnoea, Martin, 1999[95]	IQR	Beta
Fracture state	(0.651 to 1.00)	Value for first year after fracture from Brazier, 2002[97]	95% CI	Beta
History of fracture state	(0.8255 to 1.00)	Long-term impact of hip fracture assumed to have half the impact of first year by Brazier, 2002[97]		Beta
Disutility associated with a minor fracture	(0.978 to 0.986)	Brazier, 2002[97]	95% CI	Beta
Scaled reduction applied to baseline utility for those with uncontrolled PTH levels	(0.8 to 1)	Assumption	Assumption	Uniform
Scaled reduction applied to baseline utility for those with very uncontrolled PTH levels	(0.8 to uncontrolled decrement)	Assumption	Assumption	Constrained uniform
Scaled reduction applied to baseline utility in postsurgical with adverse effects	(0.8 to 0.99)	Assumption		Uniform

IQR, interquartile range.

TABLE 57 *Discounted base-case cost-effectiveness results per patient for cinacalcet (dialysis costs excluded)*

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Standard care only	6,533	3.04	–	–	–
Cinacalcet plus standard care	27,700	3.39	21,167	0.34	61,890

TABLE 58 *Discounted base-case cost-effectiveness results per patient for cinacalcet (dialysis costs included)*

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Standard care only	81,523	3.04	–	–	–
Cinacalcet plus standard care	106,946	3.39	25,423	0.34	74,334

TABLE 59 *Patient-relevant outcomes in the economic model for 1000 people*

	Standard treatment alone *n* (%)	Standard treatment plus cinacalcet *n* (%)	Difference *n* (%)	Discounted cost per event avoided (£)
At least one major fracture	25 (2.5)	21 (2.1)	4 (0.4)	5,291,750
More than one major fracture	1 (0.1)	1 (0.1)	0	–
At least one CV event	438 (43.8)	434 (43.4)	4 (0.4)	All CV events
More than one CV event	726 (72.6)	687 (68.7)	39 (3.9)	492,256
Parathyroidectomy	211 (21.1)	64 (6.8)	147 (14.7)	143,993
Surgical mortality	9 (4.3% of surgeries)	3 (4.7% of surgeries)	0.4%	–

(0.34 QALYs per patient), but costs an additional £21,167 per patient.

The impact of including dialysis costs was also assessed. The ICER increases in this analysis as small survival improvements carry the additional cost of dialysis treatment. Results are shown in *Table 58*.

Event counts

Few differences in patient relevant outcomes are predicted by the model (*Table 59*). The exception is parathyroidectomy; a significant number of operations is avoided by the use of cinacalcet ($p < 0.001$).

In both arms of the model, the number of multiple cardiovascular events is high. This is due to a relatively large number of people having at least one cardiovascular event and some people having multiple events. Based on Renal Registry data, it was assumed that 15.7% of those entering the model have existing CVD and so enter the model in the 'history of cardiovascular' health state rather than the 'event-free' health state. They are subject to the increased risk of a further cardiovascular event and are counted as having had multiple cardiovascular events.

Approximately 2% of both arms experience a major fracture (hip/femur). This means that about 20% will have a minor fracture.

The costs of treating 1000 people in order to avoid one cardiovascular event, major fracture or parathyroidectomy are shown in *Table 59*.

The few differences between comparators are largely explained by the relatively high background death rate for this population. Any differences in mortality risk between the arms depend on differences in the number of people who have uncontrolled and very uncontrolled PTH levels compared with those who have controlled levels. The relative risks of adverse effects such as fracture, cardiovascular event and death are slight between these levels of PTH control (RR = 1.12 for fracture, 1.17 for cardiovascular event and 1.0505 for death). People with very uncontrolled PTH have a higher relative risk of all major events than those with more controlled PTH levels. However, because a

TABLE 60 *Comparison of event risk between PenTAG model outputs and Cunningham and colleagues*[71]

	PenTAG model: events per 100 patient-years			Cunningham data: events per 100 patient-years		
	Standard treatment	**Cinacalcet**	**RR (95% CI)**	**Standard treatment**	**Cinacalcet**	**RR (95% CI)**
CV event	20.7	17.9	0.87 (0.80 to 0.94)	19.7	15.0	0.61 (0.43 to 0.86)
Fractures (major and minor)	4.5	3.4	0.75 (0.63 to 0.90)	6.9	3.2	0.46 (0.22 to 0.95)
Parathyroidectomy	3.7	1.0	0.28 (0.21 to 0.36)	4.1	0.3	0.07 (0.01 to 0.55)

TABLE 61 *Survival predicted by the model base case*

	Survival 25th centile (years)	Median survival (years)	Survival 75th centile (years)
Standard treatment plus cinacalcet	2.25	5.00	8.75
Standard treatment alone	2.00	4.50	8.00

parathyroidectomy is likely for these people, the risk of a fracture quickly returns to the same level as those with controlled PTH levels postsurgery, and the risk of death is reduced to a level close to that experienced by the controlled group. In order to assess the impact of parathyroidectomy on cost–utility, the impact was assessed of removing it as an option in the model. If parathyroidectomy ceases to be a treatment option for anyone, the ICER drops by 12%; however, it remains well above usual levels of WTP at £54,119 per QALY.

It is possible to make a tentative comparison between the number of events predicted by the PenTAG model and those reported by Cunningham and colleagues.[71] This analysis assumes that the risk of an event is constant over time, and an approximate risk ratio is calculated based on the number of events reported and the aggregated state occupancy in each arm of the model. In all cases, confidence intervals in the two analyses of relative risk overlap (*Table 60*).

Although there are few differences in the number of cardiovascular outcomes between the PenTAG model arms, the timing is affected by cinacalcet. Median survival for the cinacalcet cohort is 5 years and median survival for the standard treatment cohort is 4.5 years. People taking cinacalcet have a small survival advantage that increases slightly over time (*Table 61*). Over 80% of the cohort is dead in both arms by 10 years of follow-up.

To examine the impact of stopping rules on the cost-effectiveness of cinacalcet, the analysis (dialysis costs excluded) was repeated so that those whose PTH levels remained very uncontrolled after the titration phase stopped receiving cinacalcet. The ICER in this scenario was £53,400 per QALY. Similarly, the analysis was repeated with only those reaching target levels after the titration phase continuing to receive cinacalcet. In this scenario, the ICER dropped to £44,000 per QALY.

Sensitivity analysis

The two primary outputs from a cost-effectiveness model are discounted costs and QALYs for the two arms being compared. The differences between these are the incremental cost and incremental QALYs of cinacalcet in comparison with standard treatment. The ICER and net benefit are two common ways of combining these two outputs of incremental cost and incremental benefit into one summary measure.

The ICER is the ratio of incremental cost of treatment to incremental benefits of treatment (i.e. cost difference/benefit difference). While this is useful in many situations, the fact that the ICER is a ratio measure can make the metric unstable as benefit differences approach zero. In addition, the ICER is often difficult to interpret in one-way sensitivity analysis where effects are non-linear.

Net benefit is calculated by first assigning a cost value to a benefit unit. The incremental benefit of the treatment arm of the model can then be rescaled in cost units using this valuation. If a QALY is valued at £30,000, for example, then a

marginal benefit of 100 QALYs between arms can be expressed in cost units as £3,000,000. The net benefit of the treatment is then calculated by simply offsetting the incremental cost against the incremental benefit of treatment as defined in cost units (i.e. the benefit difference between arms expressed in pounds minus the cost difference expressed in pounds).

The advantage of reporting net benefit is that it behaves in a more linear way than the ICER and incorporates a WTP threshold that makes it easier to interpret. The disadvantage of using net benefit is that it relies on a specific level of valuation for each unit of benefit. The present analysis used the commonly assumed maximum willingness to pay of £30,000 per QALY.

One-way sensitivity analyses

One way sensitivity analyses for a range of transition probability, utility and cost values were used to examine the impact of the uncertainty associated with individual inputs. These have been expressed graphically showing the net benefit of new values based on a QALY value of £30,000. Because of the number of parameters used in the model, the results are presented on separate graphs for transitions (*Figure 5*), costs (*Figure 6*) and utilities (*Figure 7*). Bars that appear to the right of the axis represent a higher net benefit with cinacalcet, while those to the left of the axis show lower net benefit. An improvement of 100% is necessary for cinacalcet to be considered cost-effective at £30,000 per QALY. In this (deterministic) analysis, the model appears particularly sensitive to transitions, utilities and costs:

- Transitions
  - the difference between model arms in the proportion of people who have very uncontrolled levels of PTH (>85 pmol/l)
  - the differential rate of disease progression between the cinacalcet and standard care arms
  - the percentage of patients who withdraw from cinacalcet treatment
  - the relative risk of death for people with uncontrolled levels of PTH
  - the relative risk of death for people with very uncontrolled levels of PTH
- Utilities
  - the difference in QoL for people with very uncontrolled PTH levels compared with people with controlled PTH levels
- Costs
  - the price of cinacalcet
  - the differential cost of cinacalcet depending on the degree of PTH control
  - whether or not the cost of dialysis is included in the analysis.

The relative risk of a cardiovascular event for people whose PTH levels are not controlled did not have a large effect in this analysis. This was investigated further by using a scaled increase in relative risk of cardiovascular event across all degrees of uncontrolled PTH levels in the cinacalcet arm. Through this method it was found that cinacalcet would become cost-effective only if the number of initial cardiovascular events was reduced by 57% and the number of multiple cardiovascular events was reduced by 83% compared with the standard treatment arm.

Fracture risk also appeared to have little impact. Investigating this, it was found that if there were no fractures in the cinacalcet arm, the ICER fell to £60,746 per QALY.

Threshold analyses

The one-way sensitivity analysis reveals those inputs to which the model is most sensitive. The authors explored whether independent alterations in these key inputs could affect the ICER to such an extent that cinacalcet might be considered cost-effective.

These graphs are also expressed as net benefit at an assumed WTP threshold of £30,000 per QALY. Cost-effectiveness is shown as positive net benefit values.

Threshold analysis for the cost of cinacalcet

Threshold analysis for the cost of cinacalcet shows that it would be considered cost-effective (at a WTP threshold of £30,000 per QALY) if the cost were reduced to 8p or less per milligram, from the current cost of 14.5p/mg (*Figure 8*).

Threshold analysis for the QoL for people with 'very uncontrolled' PTH

In the base case, people with very uncontrolled levels of PTH are assumed to experience a 15% reduction in their QoL compared with those with controlled levels of PTH. Given that the potential benefit of cinacalcet lies in its ability to control PTH levels for more people, a difference in QoL between having controlled PTH and very uncontrolled PTH influences cost-effectiveness.

Figure 9 shows that if the utility value for people with very uncontrolled PTH was half that for people with controlled PTH (base case 0.6735),

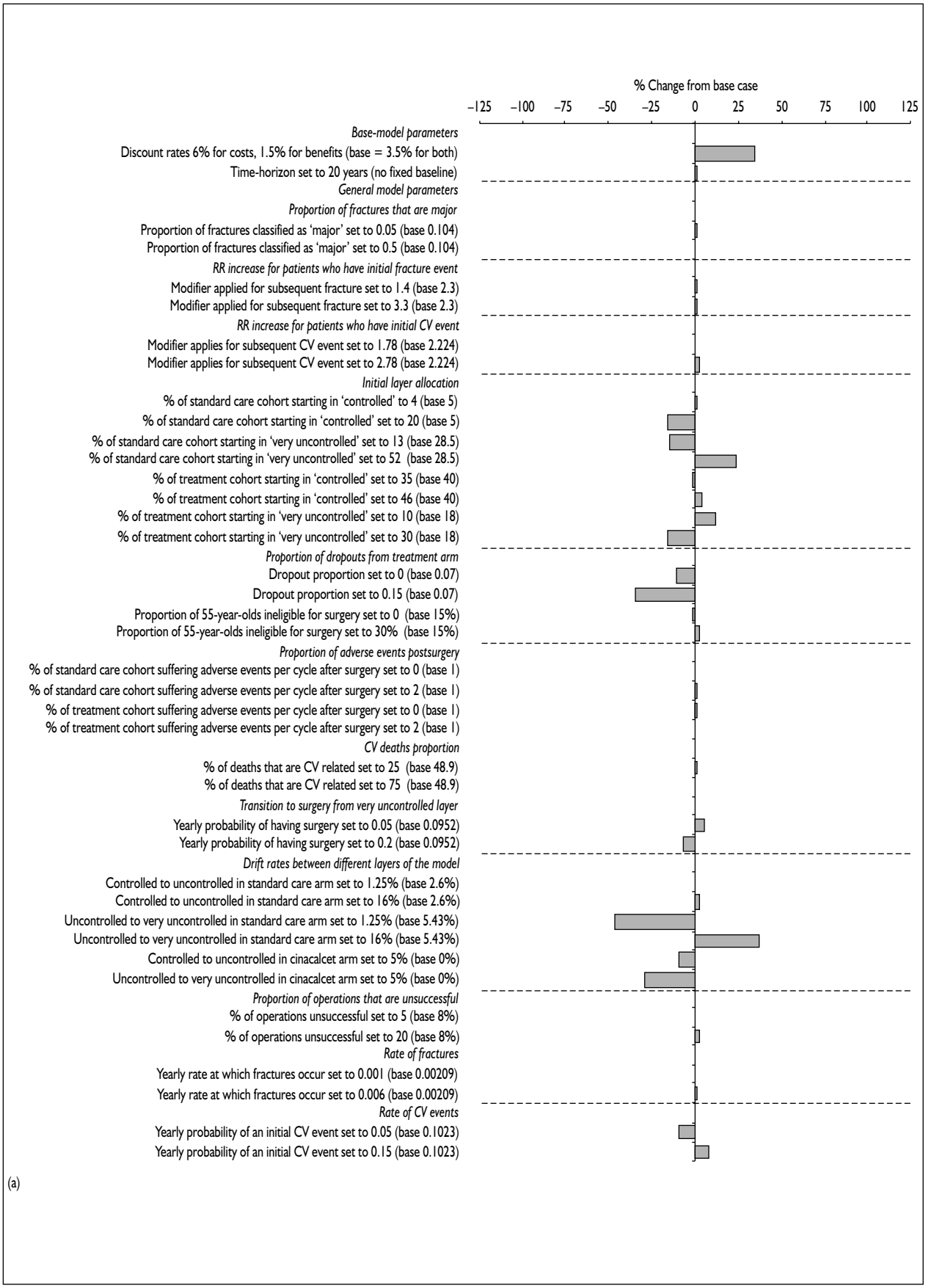

FIGURE 5 *One-way sensitivity analysis for transition inputs in the economic model: percentage change in net benefit at WTP of £30,000 per QALY. (a) General model parameters; (b) transition parameters.*

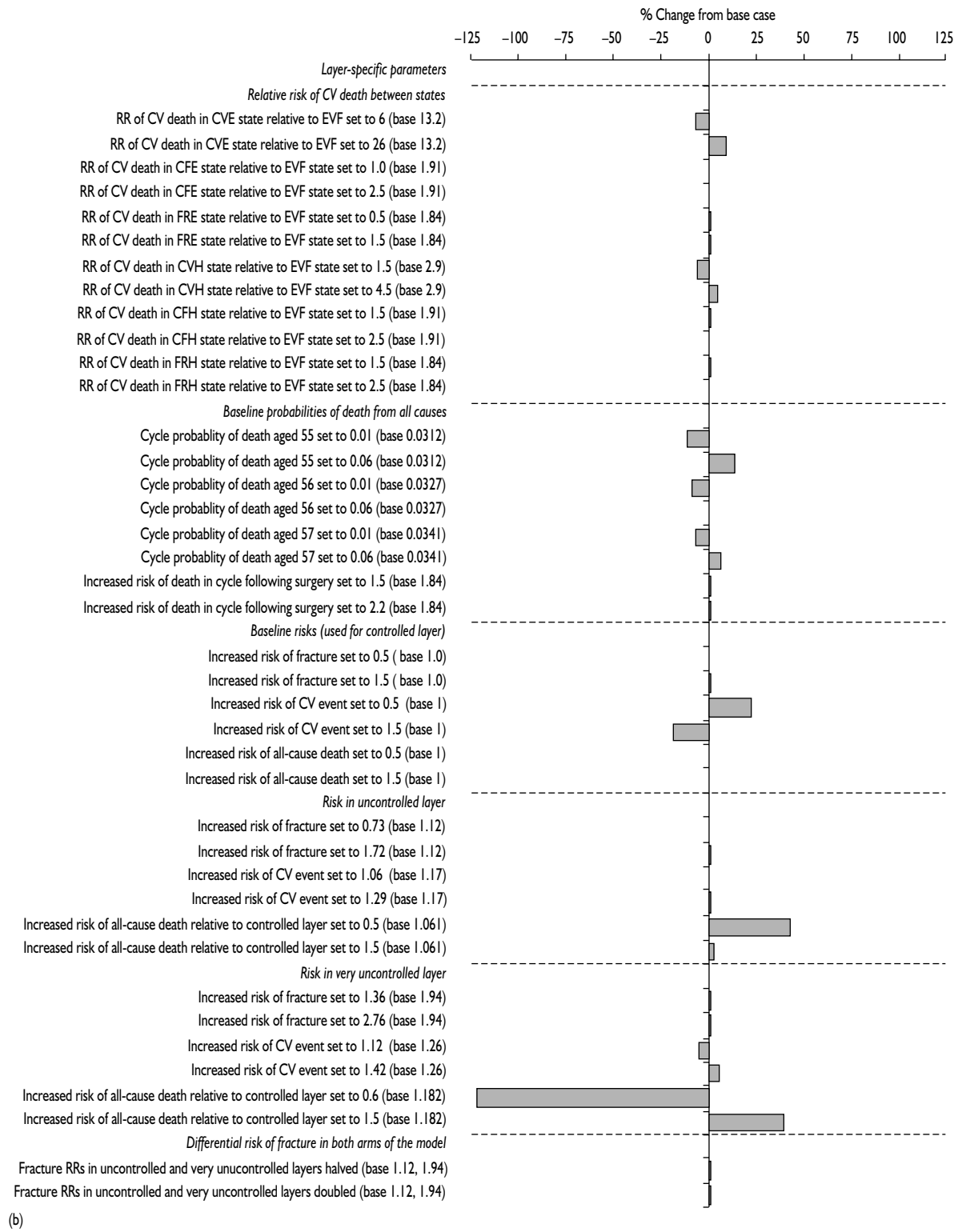

FIGURE 5 *(cont'd) One-way sensitivity analysis for transition inputs in the economic model: percentage change in net benefit at WTP of £30,000 per QALY. (a) General model parameters; (b) transition parameters.*

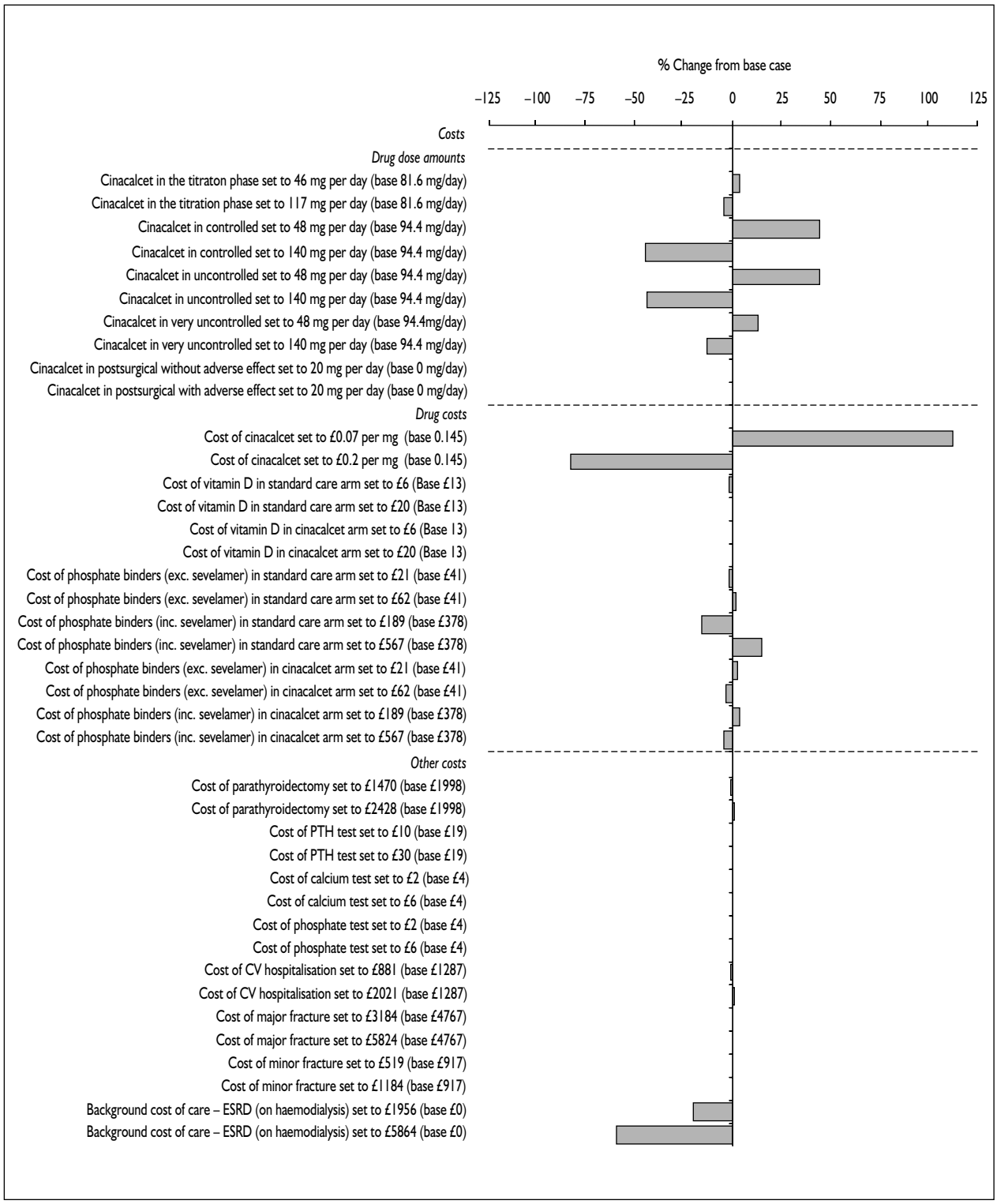

FIGURE 6 *One-way sensitivity analysis for cost inputs in the economic model: percentage change in net benefit at WTP of £30,000 per QALY*

then cinacalcet may be considered cost-effective. This assumes that the symptoms of very uncontrolled PTH levels reduce the utility value for those in the event-free state to 0.3368 (from the base-case value of 0.5725). As all other utility values following cardiovascular events or fractures are applied as a scaled reduction to the event-free health state in the model, all these utility values for people with very uncontrolled PTH levels will also be reduced.

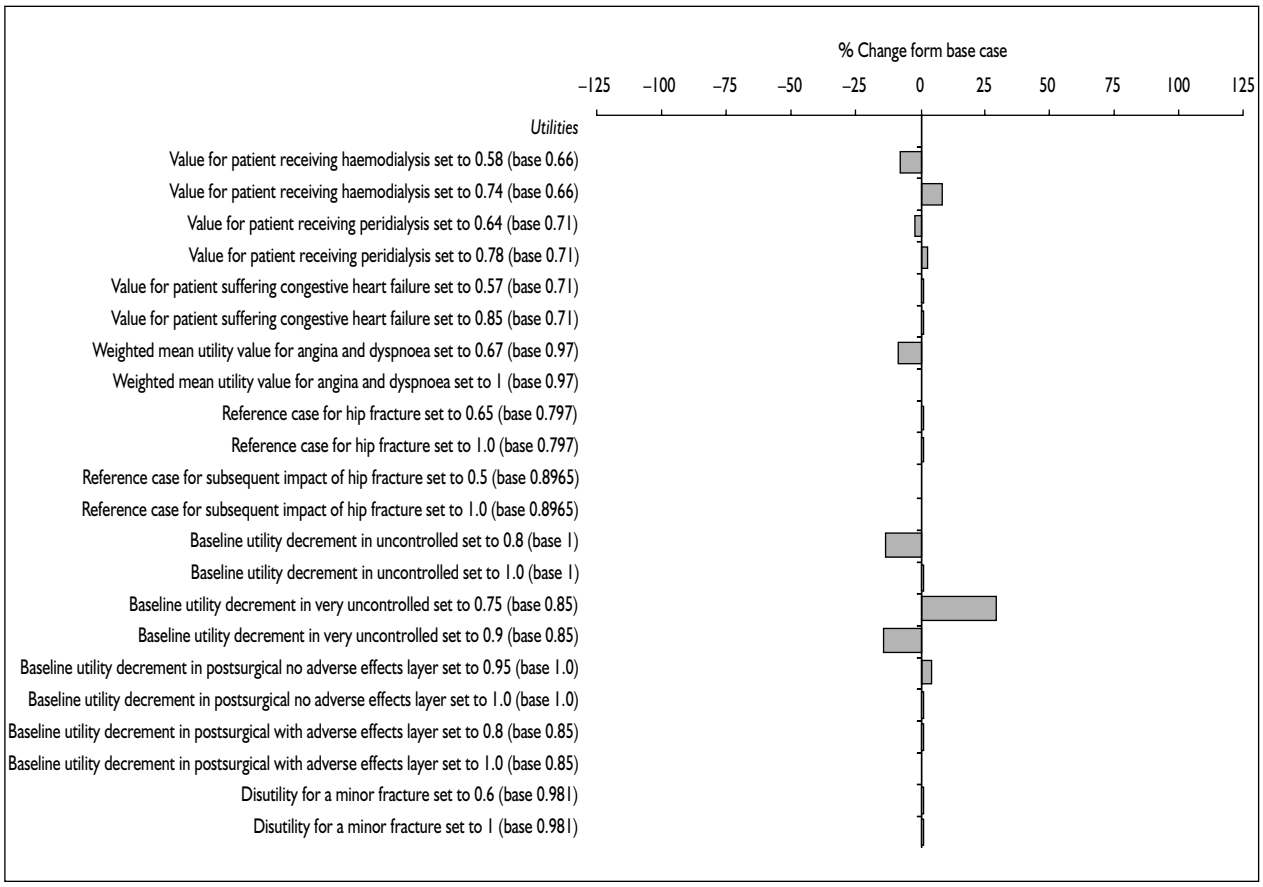

FIGURE 7 *One-way sensitivity analysis for utility values in the economic model: percentage change in net benefit at WTP of £30,000 per QALY*

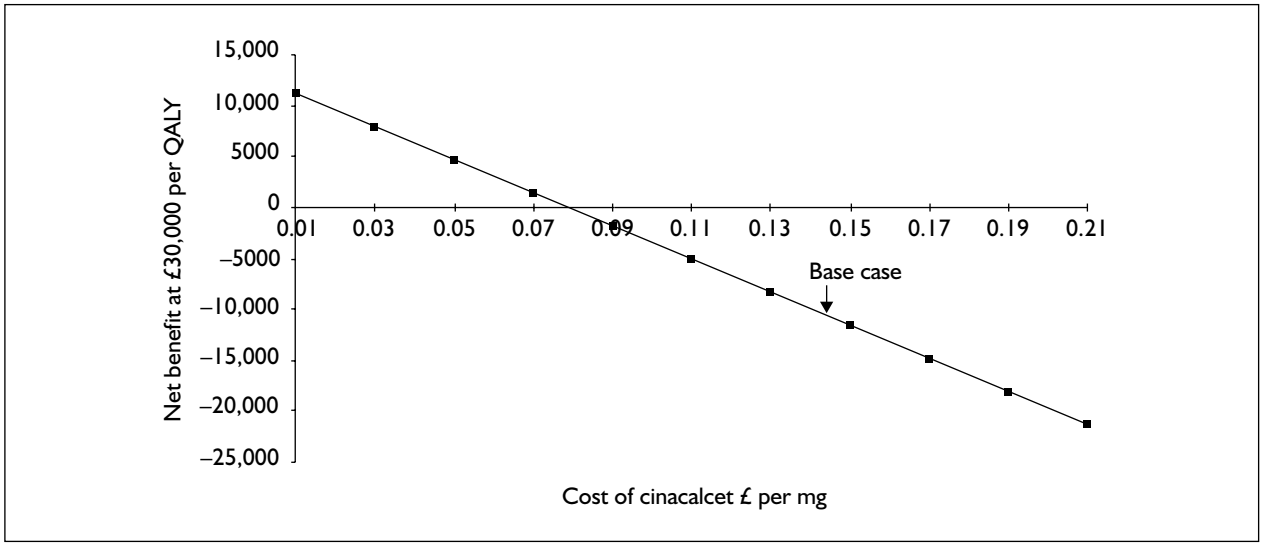

FIGURE 8 *Threshold analysis for the cost of cinacalcet*

Threshold analysis for the QoL for people after parathyroidectomy

In the base case, people who have had a successful parathyroidectomy are assumed to have the same QoL as those with controlled levels of PTH. Given that a potential benefit of cinacalcet is reducing the need for parathyroidectomy, lower QoL for people after parathyroidectomy compared with those who have controlled levels of PTH will have a favourable effect on cost-effectiveness.

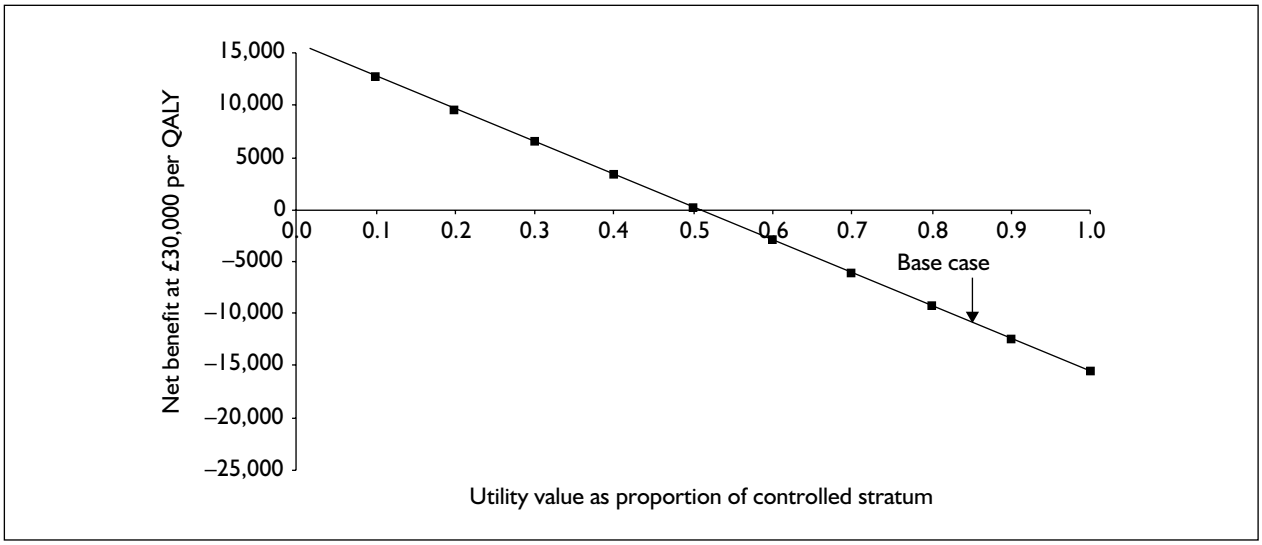

FIGURE 9 *Threshold analysis showing utility value for people with very uncontrolled PTH as a proportion of that for people with controlled PTH levels*

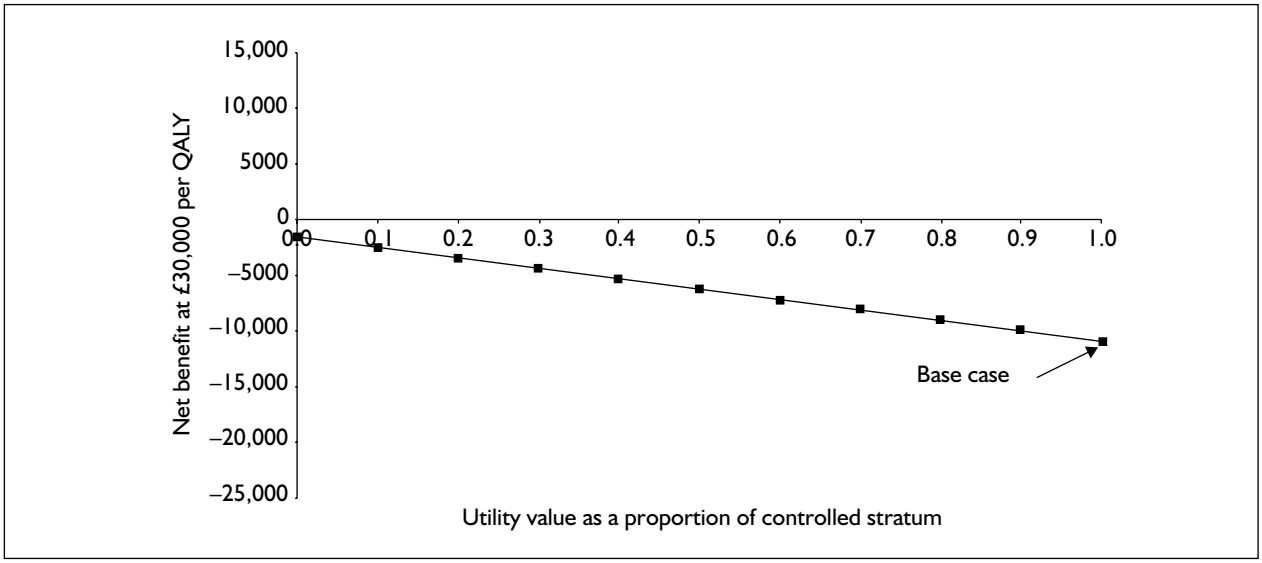

FIGURE 10 *Threshold analysis showing utility value postparathyroidectomy as a proportion of that for people with controlled PTH levels*

Figure 10 shows that as the utility value for people who have had a parathyroidectomy decreases, the benefit of cinacalcet treatment increases. However, even if the impact of parathyroidectomy were so bad that the utility value afterwards were zero (as bad as being dead), cinacalcet would still not be cost-effective at a WTP threshold of £30,000 per QALY.

Threshold analysis for the relative risk of death for 'uncontrolled' PTH levels

In the base case, people who have very uncontrolled levels of PTH are at slightly greater risk of death than those with controlled levels of PTH (RR 1.1824). As a potential benefit of cinacalcet is reducing the number of people who have uncontrolled levels of PTH, a larger relative risk of adverse effects of very uncontrolled PTH levels will increase the benefit of cinacalcet.

Figure 11 shows that if the risk of death for people with very uncontrolled PTH levels were increased to more than double (RR 2.2) that of those in controlled levels of PTH, cinacalcet could be considered cost-effective at a WTP threshold of £30,000 per QALY.

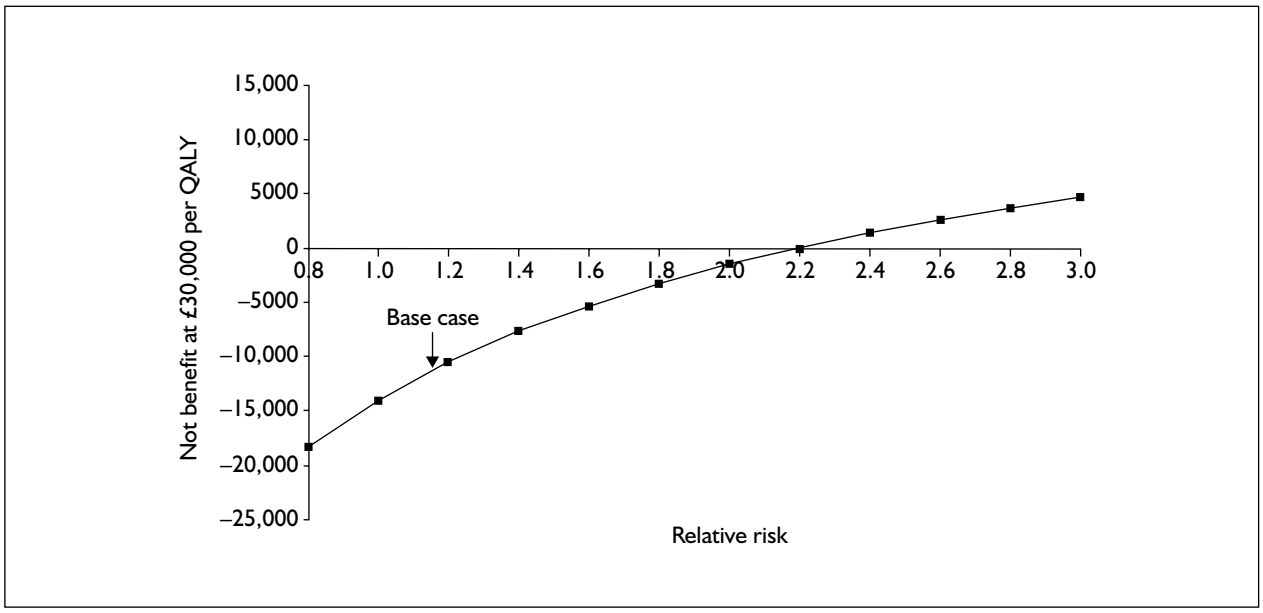

FIGURE 11 *Threshold analysis of the relative risk of death for people with very uncontrolled PTH levels compared with controlled PTH*

As the relative risk of death is also increased for those with uncontrolled PTH levels, this parameter was further explored as a two-way sensitivity analysis. It was found that the ICER could be reduced to below £30,000 per QALY if the relative risks of mortality for those with uncontrolled and very uncontrolled PTH levels compared with those with controlled levels were both increased by a scale factor of 0.6994. Such an increase in relative risk increases the median survival for those treated with cinacalcet from 5.00 years to 6.00 years, avoiding 99 deaths in the first 5 years compared with those treated with standard treatment alone.

Threshold analysis for the percentage of people treated with cinacalcet who have 'very uncontrolled' levels of PTH

In the base case, 18% of people with SHPT who receive cinacalcet still have very uncontrolled levels of PTH after the titration phase, compared with 28.5% of those treated with standard treatment. Data from the Renal Registry were used to assign the proportion of people who did not reach target levels of PTH to having uncontrolled or very uncontrolled levels of PTH. The impact of altering this percentage was assessed through threshold analysis.

Figure 12 shows that even if treatment with cinacalcet resulted in no people retaining very uncontrolled levels of PTH, cinacalcet would not be considered cost-effective at a WTP threshold of £30,000.

Parathyroidectomy is a relatively positive treatment in the model, with advantages after surgery in terms of risk and utility. It is only available to those with very uncontrolled levels of PTH. Therefore, this may confound the impact of PTH control, with those having very uncontrolled levels of PTH actually benefiting because of the impact of surgery. Therefore, the impact of different proportions of people having very controlled levels of PTH with cinacalcet was explored, but without surgery as a treatment option. The results are shown in *Figure 13*. This shows that, in the absence of parathyroidectomy, even if no patients have a very uncontrolled level of PTH, cinacalcet is still not cost-effective at a WTP threshold of £30,000 per QALY.

Two-way sensitivity analysis for disease progression

There are currently no data about how well SHPT is controlled over time with cinacalcet. The base case assumes that once PTH levels are controlled, people treated with cinacalcet will remain controlled for the rest of their lifetime. By contrast, those receiving standard treatment progress from controlled to uncontrolled PTH levels at a rate of 10% a year and from uncontrolled to very uncontrolled at 20% a year. The impact of introducing a rate of disease progression with cinacalcet was investigated. A two-way analysis was undertaken, with progression from controlled to uncontrolled PTH levels and from uncontrolled to very uncontrolled levels examined simultaneously.

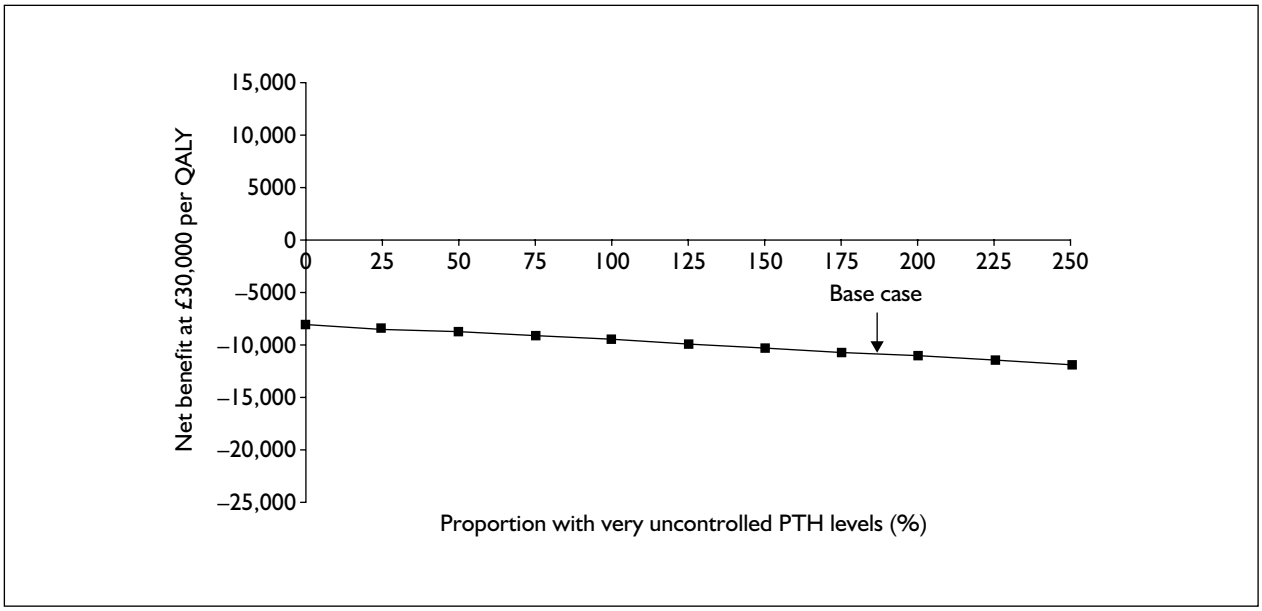

FIGURE 12 *Threshold analysis of the proportion of people who have very uncontrolled levels of PTH despite treatment with cinacalcet*

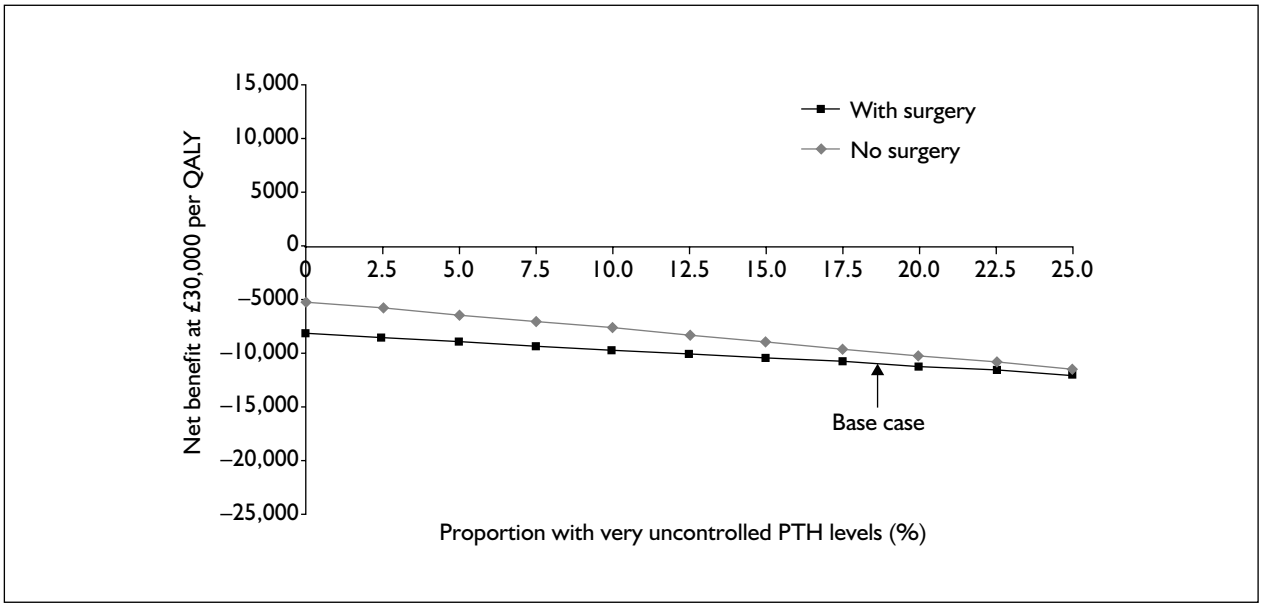

FIGURE 13 *Threshold analysis of the proportion of people who have very uncontrolled levels of PTH despite treatment with cinacalcet where parathyroidectomy is not a treatment option*

The results are shown in *Table 62*. The ICER increases if disease progression occurs despite treatment with cinacalcet. If the rates are equal to, or greater than those with standard care, then cinacalcet is dominated. This means that people gain fewer QALYs for greater cost, suggesting that the intervention does more harm than good.

Probabilistic simulation

Outputs for the Monte Carlo simulation are shown in *Figures 14* and *15*. For the modelled cohort, these illustrate the ICER values for 1000 simulated trials. A cost-effectiveness acceptability curve (CEAC) has also been calculated showing, at different levels of WTP for an additional QALY, the probability that cinacalcet is cost-effective.

The simulation output (*Figure 14*) shows that cinacalcet is cost-effective in just 0.5% of simulations undertaken; although slightly more QALYs are always accrued, the additional costs of treatment means that the ICER is almost always greater than £30,000 per QALY. The CEAC shows that cinacalcet is unlikely to be the most cost-

TABLE 62 *Impact of disease progression with cinacalcet on the ICER*

Annual rate of progression from uncontrolled to very uncontrolled PTH levels	Annual rate of progression from controlled to uncontrolled PTH levels with cinacalcet					
	0%	10%	20%	30%	40%	50%
0%	61,890	74,175	77,281	78,648	79,413	79,901
10%	113,744	1,111,669.95	Dominated	Dominated	Dominated	Dominated
20%	137,573	Dominated	Dominated	Dominated	Dominated	Dominated
30%	150,774	Dominated	Dominated	Dominated	Dominated	Dominated
40%	159,115	Dominated	Dominated	Dominated	Dominated	Dominated
50%	164,856	Dominated	Dominated	Dominated	Dominated	Dominated

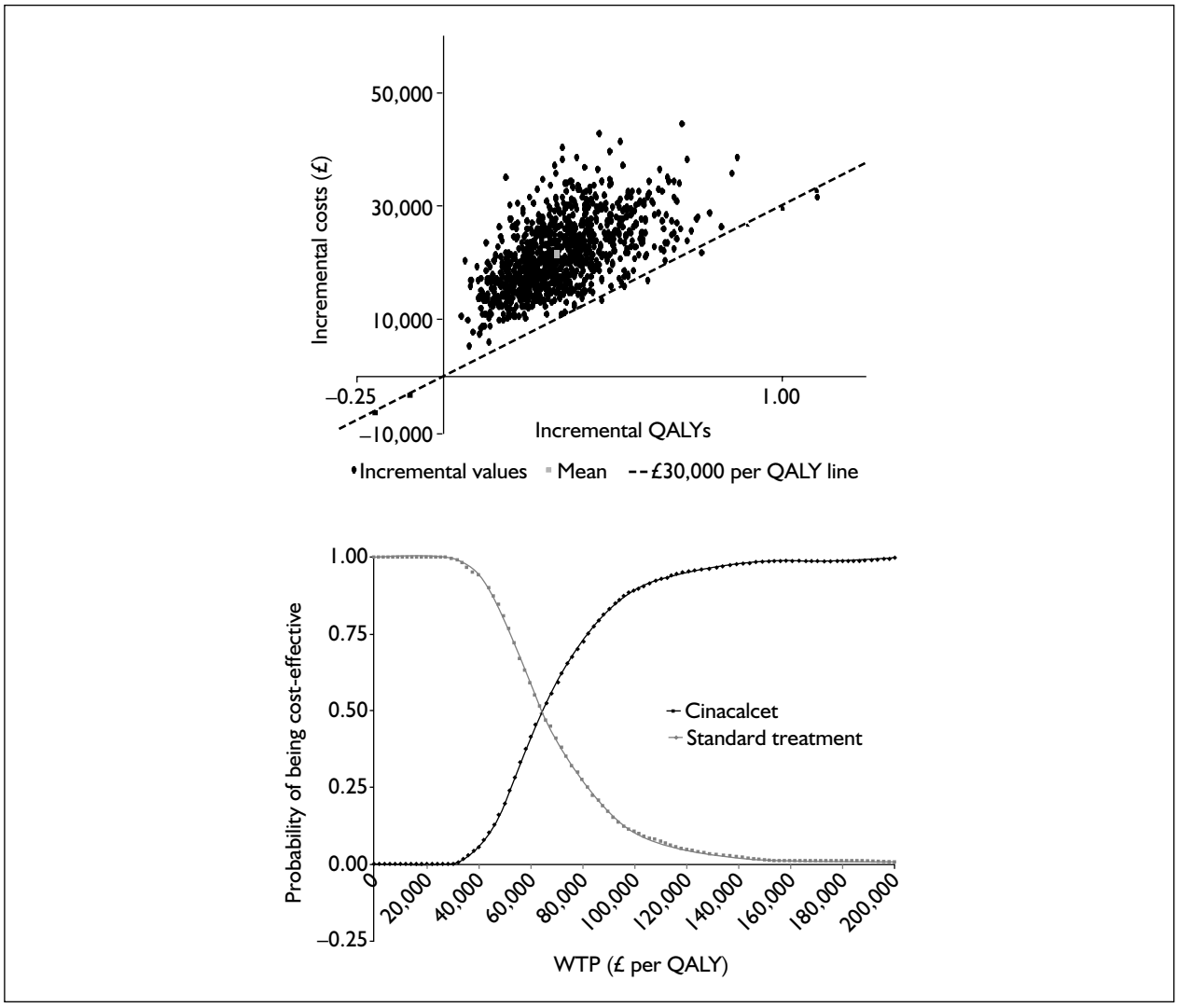

FIGURE 14 *Simulation output (1000 trials) for the base case and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis cost excluded)*

effective option below a WTP threshold of about £62,000.

Probabilistic analysis was also run for the base case including the cost of dialysis, with similar results (*Figure 15*).

Cost-effectiveness for people with different degrees of SHPT

From the systematic review, cinacalcet appears to have more impact on people who have uncontrolled PTH (>32 to <85 pmol/l) than those with very uncontrolled PTH (>85 pmol/l). The

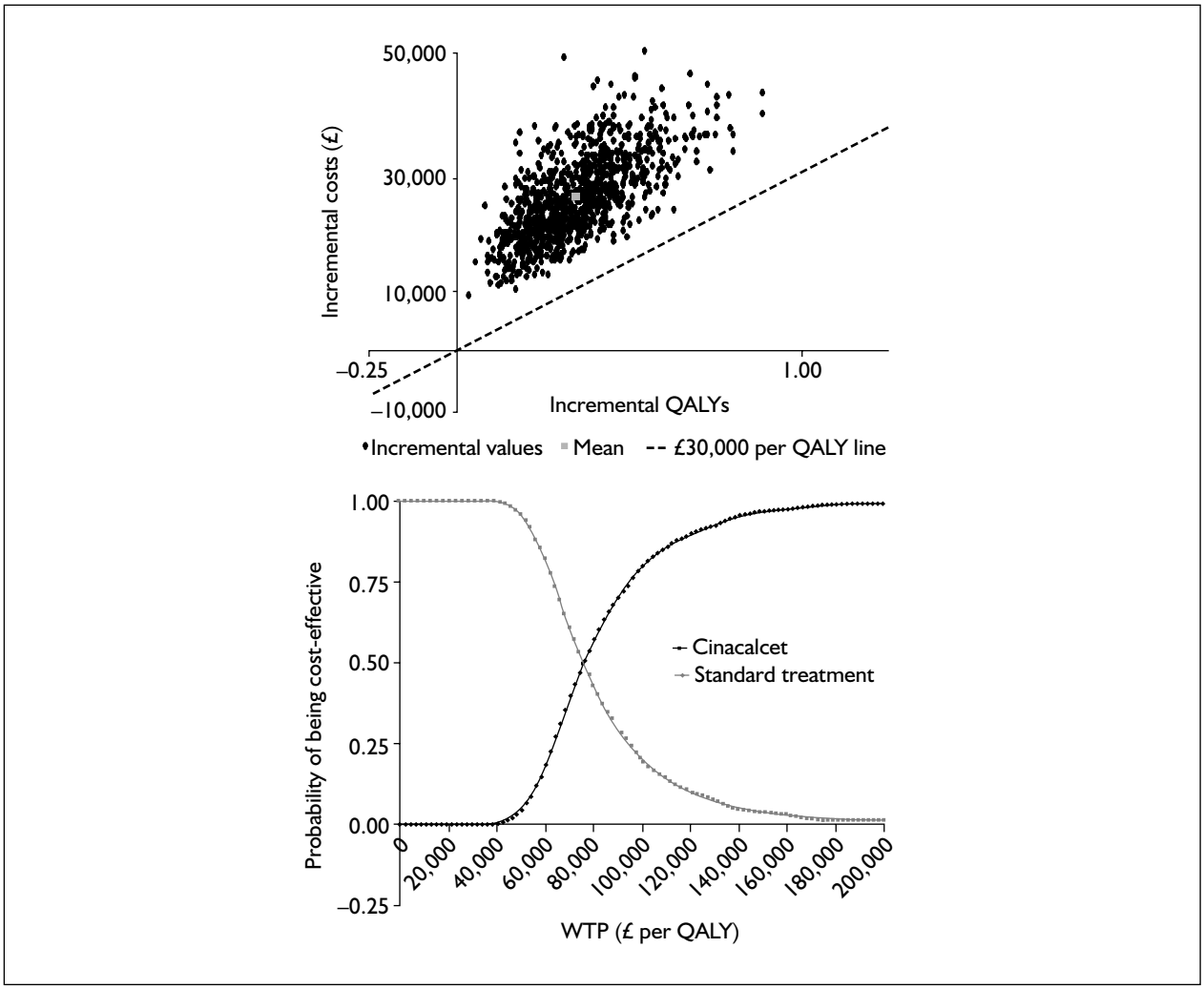

FIGURE 15 *Simulation output (1000 trials) for the base case and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis costs included)*

TABLE 63 *Cost-effectiveness of cinacalcet in people with uncontrolled levels of PTH (dialysis costs excluded)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY)
Standard treatment only	6,466	3.06	–	–	–
Standard treatment plus cinacalcet	27,905	3.43	21,438	0.37	57,442

cost–utility was investigated for these two groups separately and the results are shown in *Tables 63* and *64*. Although the ICER is lower in people with uncontrolled PTH than in those with very uncontrolled PTH levels, in neither case is cinacalcet likely to be considered cost-effective.

Scenario analyses

Methods for scenario analysis 1 based on Cunningham and colleagues[71]

The base-case model uses the relative risk of fracture, cardiovascular events and mortality according to the level of PTH control achieved with cinacalcet compared with standard treatment. However, the reviewers also wanted to examine the impact of using the data reported by Cunningham and colleagues.[71] This would both provide validation and allow more direct comparison of the present model's results with those submitted to NICE by Amgen, which were directly based on the Cunningham study.

The analysis by Cunningham and colleagues[71] does not rely on intermediate markers (serum

TABLE 64 *Cost-effectiveness of cinacalcet in people with very uncontrolled levels of PTH (dialysis costs included)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY)
Standard treatment only	6,667	3.02	–	–	–
Standard treatment plus cinacalcet	27,155	3.27	20,488	0.25	81,479

levels of PTH, calcium and phosphate), but directly relates treatment with cinacalcet to the risk of fracture and cardiovascular events and overall mortality in the short term. To emulate this, the model structure was simplified so that all patients treated with cinacalcet have the same average risk of adverse events and all those treated with standard treatment have the same average risk of adverse effects. That is, the strata representing different levels of PTH control in the base-case model are effectively collapsed into one.

Differences between the arms of the model thus come from the reported within-trial difference in average risk of fracture, cardiovascular events and death based on treatment choice of cinacalcet or standard care. These are taken from the analysis by Cunningham and colleagues,[71] which is based on retrospective data for 6 months of follow-up of 1136 people, and 12 months follow-up of 48 people with SHPT. Additional data come from a 6-month extension period in one of the 6-month studies (n = 266).

Incorporating fracture data from Cunningham and colleagues[71]

The analysis used fracture rates on standard treatment reported by Cunningham and colleagues.[71] This is reported as event rates per 100 patient-years, so the equivalent rate per year was calculated and applied as a constant annual probability in the model.

No distinction was made in the report by Cunningham and colleagues[71] between major and minor fractures, but rather between upper and lower extremity fractures. To incorporate these data into the PenTAG model, the rate for all fractures in the standard treatment arm of 0.069 events per year was used, as reported by Cunningham and colleagues.[71] As in the PenTAG model base case, it was assumed that 10.36% of these are major fractures. Neither the report by Cunningham and colleagues[71] nor the model supplied by Amgen makes allowance for increased risk of a subsequent fracture after the initial fracture, so it was also assumed that the risk for subsequent fractures was the same as for initial fractures.

Rates of fracture for patients treated by cinacalcet are derived from the hazard ratio reported by Cunningham and colleagues.[71]

Incorporating cardiovascular event data from Cunningham and colleagues[71]

In the PenTAG base-case model, cardiovascular events are derived from a baseline probability of an event occurring for patients with controlled PTH levels, and applying a suitable relative risk value for people with more uncontrolled levels of PTH based on the literature. Cardiovascular events are reported in the same way as fracture data by Cunningham and colleagues[71] and are incorporated into the PenTAG model in the same way. To compare the values used in the base-case model and in the version of the model using Cunningham data, a weighted average of the values for people with all severities of PTH level was compared with the value derived in the base-case model. Annual risks shown in the two versions of the model are shown in *Table 65*.

Rates are lower in the base case than reported in the Cunningham data. Reasons for this are not clear. It could be that the small, selected sample with extrapolation from brief follow-up in the paper by Cunningham and colleagues[71] led to overestimation of both the incidence of cardiovascular events and the difference between standard treatment and cinacalcet in the longer term.

As was the case with fractures, no modification is made for increased risk of cardiovascular event after an initial cardiovascular event. The model submitted to NICE by Amgen incorporates the increased risk for subsequent events by modifying the base probability, but the method used is not stated, so the analysis could not be replicated.

Incorporating parathyroidectomy data from Cunningham and colleagues[71]

Rates of parathyroidectomy reported by Cunningham and colleagues[71] were used in the PenTAG model in the same way as fracture and cardiovascular event data. The model assumes that only one parathyroidectomy is possible.

TABLE 65 *Comparison of the relative risk values used in the modelled scenarios*

Description of parameter	PenTAG model using Cunningham, 2005[71]	PenTAG base-case model
Annual probability of CV event in people receiving standard treatment only	0.1788	0.12103
Annual probability of CV event in people receiving standard treatment plus cinacalcet	0.13929	0.10704

TABLE 66 *Data used in scenario analysis 1 using data from Cunningham and colleagues*[71]

	Events per 100 patient-years with standard treatment	HR applied for cinacalcet	Source
Parathyroidectomy	4.1	0.07	Cunningham, 2005[71]
Fracture	6.9	0.46	Cunningham, 2005[71]
CV hospitalisation	19.7	0.61	Cunningham, 2005[71]
Mortality	16.25	0.81	Age-specific death rate from the Renal Registry assumed to represent death rate with standard treatment. HR for additional cinacalcet taken from Cunningham, 2005[71]

Mortality data

The mortality rate reported by Cunningham and colleagues[71] is artificially low compared with known mortality rates in large cohort studies such as the Renal Registry. Therefore, the age-specific average 10-year probabilities of death were used, as reported in the Renal Registry for all-cause death (*Table 66*). The economic submission to NICE by Amgen also rejected the mortality rate reported in the Cunningham paper as too low.

Data used to populate the PenTAG model based on data from Cunningham and colleagues[71] are shown in *Table 66*.

All of the utilities, drug doses and costs used to populate the original PenTAG model have been retained, as has the rate of withdrawal from cinacalcet treatment.

Sensitivity analysis for scenario analysis 1 based on data from Cunningham and colleagues[71]

PSA was undertaken for this scenario. Most of the range data, for utilities, costs and some general assumptions, were as for the base case. Where different parameters were used, these are shown in *Table 67*.

Results for the cost-effectiveness of cinacalcet in scenario analysis 1 based on data from Cunningham and colleagues[71]

The cost-effectiveness of cinacalcet using data from the Cunningham report in the PenTAG model is shown in *Table 68*. Compared with the base case in the PenTAG model, incremental costs and QALYs with cinacalcet are higher, and the ICER is lower. However, cinacalcet is still not likely to be considered cost-effective at usually acceptable levels of WTP. The PenTAG results using the Cunningham data are only slightly higher than the figure of £35,600 per QALY reported in the Amgen submission to NICE.

Using the Cunningham data, the model predicts greater incremental survival with cinacalcet than the PenTAG base case. This is illustrated in *Table 69*. The PenTAG base case shows a slight long-term survival advantage with cinacalcet. This is more pronounced using the Cunningham data as the proportion of the cohort surviving is both smaller in the standard care arm and larger in the cinacalcet arm of the model.

Results of PSA for scenario analysis 1

Outputs for the PSA excluding costs of dialysis are shown graphically in *Figure 16*. In 5.8% of simulations, cinacalcet is cost-effective at a WTP threshold of £30,000 per QALY. It is dominated (costs more but confers fewer QALYs) in 0.5% of simulations. The CEAC predicts a very small possibility of cinacalcet being cost effective at £30,000 per QALY, and only becoming cost-effective above a WTP threshold of about £44,000 per QALY.

Outputs for the PSA including costs of dialysis are shown in *Figure 17*. In this analysis no simulations

TABLE 67 *Parameter ranges used in scenario analysis 1 based on data from Cunningham and colleagues*[71]

Parameter	Available range data	Source	Type	Distribution
Yearly rate of a fracture event	(3.9 to 9.9) fractures per 100 patient-years	Industry submission	Assume 95% CI	Log-normal
Yearly probability of CV events	(16.4 to 27.4) events per 100 patient-years	Industry submission	Assume 95% CI	Beta
Yearly probability of surgery	(0.0208 to 0.0685)	Industry submission	Assume 95% CI	Beta
Age-dependent yearly probability of death for category 55–64 years old	(0.136 to 0.164)	Industry submission	Assume 95% CI	Beta
Age-dependent yearly probability of death for category 65–74 years old	(0.19 to 0.228)	Industry submission	Assume 95% CI	Beta
Age-dependent yearly probability of death for category 75–84 years old	(0.256 to 0.296)	Industry submission	Assume 95% CI	Beta
Age-dependent yearly probability of death for category ≥85 years old	(0.288 to 0.391)	Industry submission	Assume 95% CI	Beta
HR associated with reduction in CV events between arms of model	(0.5 to 0.72)	Industry submission	95% CI	Log-normal
HR associated with reduction in fracture events between arms of model	(0.32 to 0.64)	Industry submission	95% CI	Log-normal
HR associated with reduction in mortality events between arms of model	(0.57 to 1.05)	Industry submission	95% CI	Log-normal
HR associated with reduction in surgery events between arms of model	(0.02 to 0.19)	Industry submission	95% CI	Log-normal

TABLE 68 *Cost-effectiveness of cinacalcet using data from Cunningham and colleagues*[71] *(dialysis costs excluded)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY)
Standard treatment only	9,021	3.10	–	–	–
Standard treatment plus cinacalcet	38,060	3.77	29,039	0.68	42,999

TABLE 69 *Survival analysis of standard treatment and cinacalcet arms of the model using data from Cunningham and colleagues*[71]

	Survival 25th quartile	Median survival	Survival 75th quartile
Standard treatment alone	1.75	4.25	8.25
Standard treatment plus cinacalcet	2.25	5.50	10.50

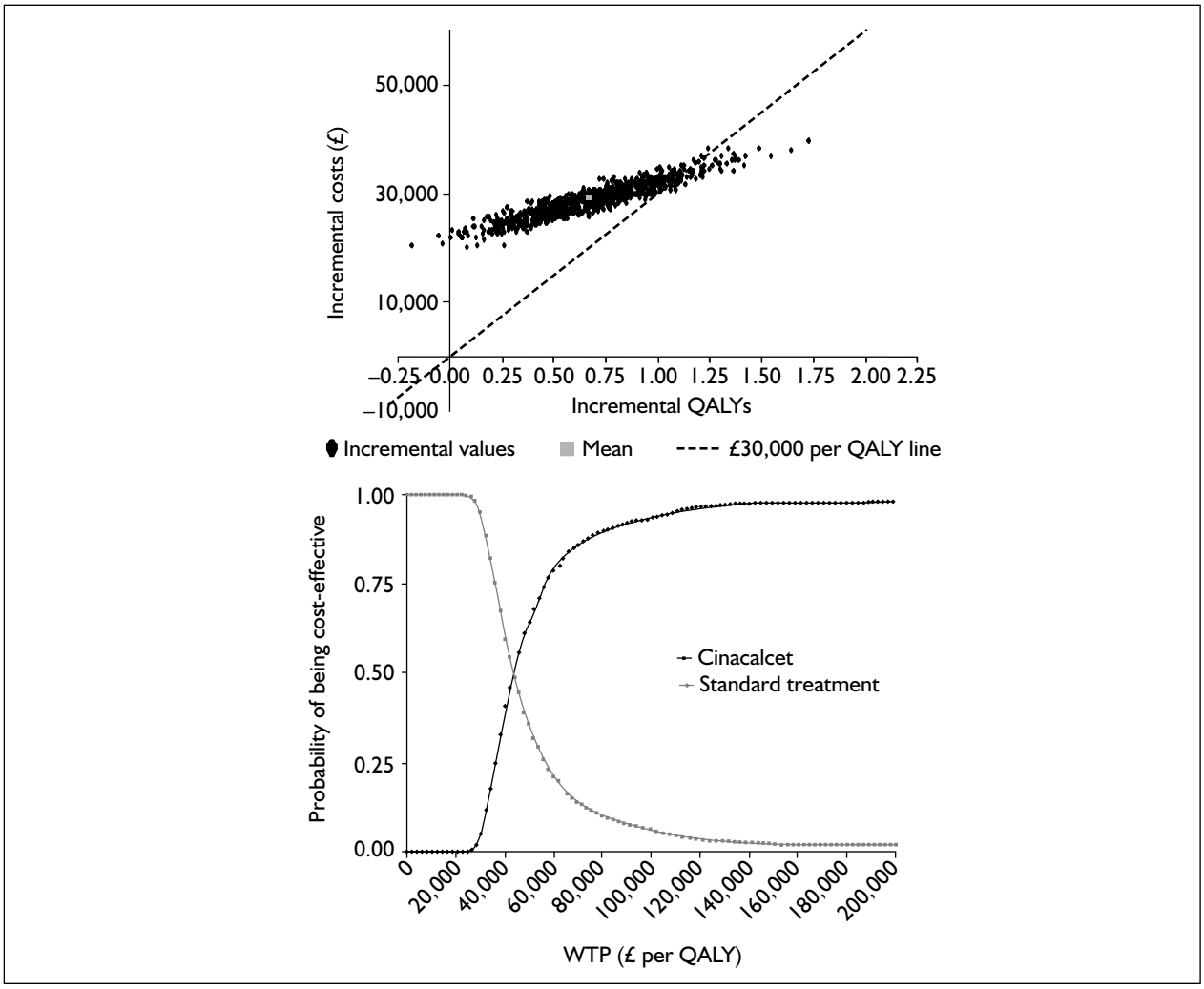

FIGURE 16 *Simulation output (1000 trials) for scenario analysis 1 based on Cunningham and colleagues[71] and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis costs excluded)*

show cinacalcet having an ICER of less than £30,000 per QALY and it is dominated in 0.5% of simulations. The CEAC shows that cinacalcet is likely to be more cost-effective than standard care above a WTP threshold of about £66,000 per QALY.

Scenario analysis 2: Exploration of the impact of cinacalcet through estimated impacts on Ca × P control

Owing to data limitations, the PenTAG model was based on a single biomarker for risk of adverse events. This is a limitation for two reasons: first, it is known that the levels of PTH, calcium and phosphate are interconnected and, secondly, PTH levels may not be the strongest marker of risk for cardiovascular events or mortality. However, the systematic review shows that there is very limited information about the impact of cinacalcet on other biochemical markers, especially in relation to its impact on PTH. The only available information is that 91% of those treated with cinacalcet who achieve a PTH level of 26.5 pmol/l or below also have a reduction in Ca × P levels from their baseline level.

The potential impact of this was explored in the model, although the analysis should be regarded as purely exploratory.

Methods for scenario analysis 2 on the impact of cinacalcet on Ca × P

Percentage of people meeting both PTH and Ca × P targets

It was assumed that all of those who are reported as having a reduction in Ca × P in the systematic review have a reduction to the KDOQI guideline target of 4.4 $mmol^2/l^2$ or lower (there is currently no Renal Association target for this marker). All those not achieving a reduction are assumed to

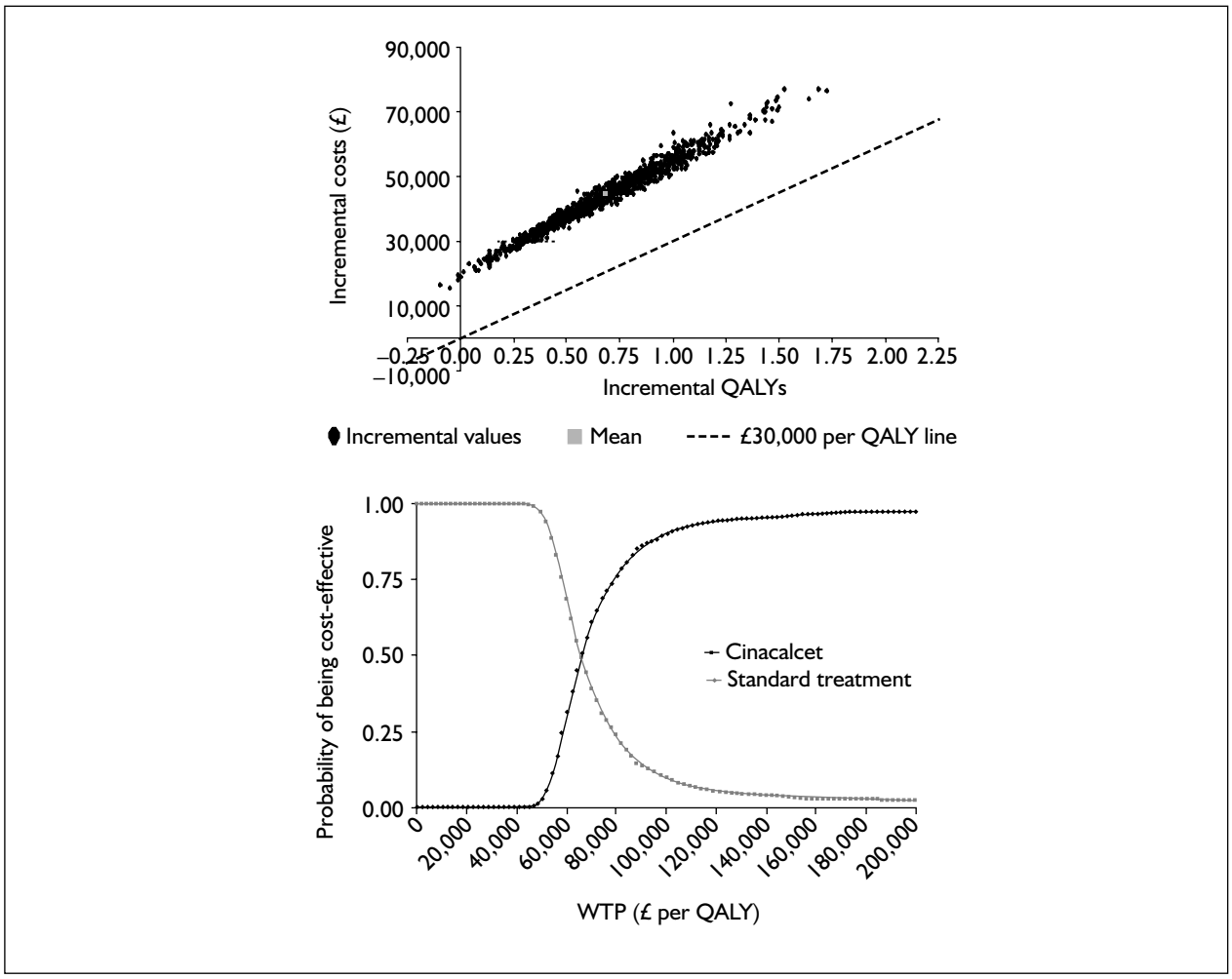

FIGURE 17 *Simulation output (1000 trials) for scenario analysis 1 based on Cunningham and colleagues[71] and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis costs included)*

have elevated Ca × P product levels, despite having controlled PTH levels. It was also assumed that none of those who have uncontrolled or very uncontrolled PTH has a Ca × P that reaches KDOQI target levels. These assumptions are likely to bias in favour of cinacalcet. In effect, this is a best case scenario for cinacalcet because it assumes that nearly all of those with controlled PTH levels achieve target levels for Ca × P, while none of those with uncontrolled PTH does so.

Relative risk of cardiovascular event and mortality

Relative risks of cardiovascular events and mortality are based on the risk at different levels of Ca × P, taken from the paper by Block and colleagues (n = 40,538).[19] This paper reports relative risks for Ca × P levels in 5 mg^2/dl^2 bands from below 30 mg^2/dl^2 to above 80 mg^2/dl^2. As the confidence intervals for all those below 44 mg^2/dl^2 contain 1, this was also used as the reference range. A plot of the relative risk of mortality against the midpoints of these value ranges was then taken, and a linear trend fitted. The relative risk of mortality was used for the midpoint of this fitted trend line, which equates to the risk at 72 mg^2/dl^2. Although this is somewhat arbitrary, it was not considered inappropriate in the context of an exploratory analysis. This gives a relative risk of mortality of 1.63 for people who do not have Ca × P control compared with those with Ca × P levels that meet the KDOQI targets.

A similar process was undertaken to establish the relative risk of cardiovascular event for people with Ca × P based on the findings of Block and colleagues.[19] This gives a relative risk of cardiovascular event of 1.38 for people who do not have Ca × P control compared with those with levels that meet the KDOQI targets.

The relative risk of mortality and cardiovascular event for people with controlled PTH is a weighted average of the risk for those with

TABLE 70 *Cohort proportion used in scenario analysis 2 based on Ca × P impact*

			Percentage of cohort in each group after initial treatment			
			Standard treatment		Cinacalcet treatment	
PTH levels	Ca × P target met (%)	Ca × P target not met (%)	Ca × P target met (%)	Ca × P target not met (%)	Ca × P target met (%)	Ca × P target not met (%)
Controlled	91	9	4.55	0.45	36.4	3.6
Uncontrolled	0	100	0	66.5	0	42.0
Very uncontrolled	0	100	0	28.5	0	18.0

elevated Ca × P and those whose Ca × P levels meet the target level (*Table 70*).

Relative risk of fracture

As PTH levels are thought to be the best marker of bone disease, the relative risk for fracture based on PTH levels was used, as in the base case.

Data used to populate the model for both arms after the initial treatment (titration phase) are shown in *Table 70*. These are based on the average populations with controlled PTH and Ca × P levels [see *Table 27* (p. 35)].

Sensitivity analysis for scenario analysis 2 based on Ca × P levels

PSA was used to explore the impact of underlying parameter uncertainty on cost-effectiveness. Most of the data used were the same as in the base-case economic model. Different ranges and sources used for the proportion of patients entering different levels of Ca × P control are shown in *Table 71*.

Results for scenario analysis 2 using data on Ca × P levels

The results for this speculative analysis are shown in *Table 72*. The ICER is considerably reduced from the model that bases the risk of adverse effect solely on PTH levels. However, it is still higher than is usually accepted as representing a cost-effectiveness option.

More conservative assessment of the impact of cinacalcet on Ca × P levels

This analysis is likely to be biased in favour of cinacalcet since it assumes that all those with reduced levels of Ca × P also have a reduced level of PTH. Any of the patients who have uncontrolled PTH levels are therefore considered to also have uncontrolled Ca × P levels. For a more conservative assessment, the analysis used data from the Renal Registry, which show that 67% of people on RRT have controlled Ca × P levels that meet the KDOQI guidelines.[16] This more conservative estimate was used to run a second version of this exploratory model. Data used to populate this model are shown in *Table 73* and the results are shown in *Table 74*. The ICER in this estimate is higher, owing to more people with uncontrolled PTH now being assumed to have control of Ca × P levels and so having a lower relative risk of mortality and cardiovascular events.

Results of PSA for scenario analysis 2 based on Ca × P levels

Outputs for the Monte Carlo simulation are shown in *Figure 18*. For the modelled cohort in the scenario analysis based on Ca × P levels, this illustrates the ICER values of 1000 simulated trials. The CEAC shows the probability that cinacalcet is cost-effective, in scenario 2, at various levels of WTP for an additional QALY. *Figure 18* shows the PSA results when dialysis costs are excluded. Cinacalcet is cost-effective at a WTP threshold of £30,000 per QALY in 5.8% of simulations. Cinacalcet only becomes likely to be cost-effective above a WTP threshold of around £40,000 per QALY.

Figure 19 shows the PSA results when dialysis costs are included. None of the simulations shows cinacalcet to be cost-effective at a WTP threshold of £30,000 per QALY. Cinacalcet only becomes likely to be cost-effective above a WTP threshold of £60,000 per QALY.

Sources of uncertainty in the model are summarised in *Table 75*.

Potential model limitations

There is convincing evidence of the impact of cinacalcet on serum biomarkers such as PTH and Ca × P. However, the long-term clinical implications of this are unclear. Crucially, the evidence for an impact on clinical events such as mortality, cardiovascular event, fracture and parathyroidectomy is based on one, short-term,

TABLE 71 *Range and distribution data used in scenario analysis 2 based on Ca × P levels*

Parameter	Available range data	Source	Type of data	Distribution
Proportion receiving standard treatment having controlled Ca × P	(1 to 5)	Author assumption	Values represent ±50% of central estimate	Beta
Proportion receiving standard treatment having very uncontrolled Ca × P	(14.25 to 42.75)	Author assumption	Values represent ±50% of central estimate	Beta
Proportion receiving cinacalcet having controlled PTH	(18.2 to 54.6)	Author assumption	Values represent ±50% of central estimate	Beta
Proportion receiving cinacalcet having uncontrolled PTH	(9 to 27)	Author assumption	Values represent ±50% of central estimate	Beta
Differential dropout rate between two arms of the model	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Proportion of those with controlled PTH that become uncontrolled each cycle (both arms)	(0.05 to 0.5)	Input from EAG	Clinical opinion and author assumption	Log-normal
Proportion of those with uncontrolled PTH that become very uncontrolled each cycle (both arms)	(0.05 to 0.5)	Input from EAG	Clinical opinion and author assumption	Log-normal
Proportions that suffer adverse effects after surgery (both arms)	None	Author assumption that SE is 1/10th of the central estimate	Assumption	Beta
Fracture				
Yearly rate of an initial major fracture event	(1.7 to 6.1) hip fractures per 1000 patient-years	Ball, 2002[27]	Minimum and maximum for different subgroup analyses	Log-normal
Risk of fracture for those with uncontrolled PTH levels compared with those with controlled levels	(0.73 to 1.72)	Kim, 2004[88]	95% CI	Log-normal
Risk of fracture for those with very uncontrolled PTH levels compared with those with controlled levels	(1.36 to 2.76)	Kim, 2004[88]	95% CI	Log-normal
Death event				
Age-dependent probability of death	(–13.166 to –11.309) (2.314 to 2.762)	Derived using data in Renal Registry	95% CIs for log lambda and gamma parameters used in calculation of each probability	Bivariate normal
Risk of death in any of the strata in either arm of the model	(–1.9817 to 0.12329) (0.0205 to 0.02551)	Derived from Block, 2004[19]	95% CIs for slope and intercept parameters used in calculation of category estimates	Bivariate normal
Reduction in death risk postsurgery	(0.80 to 0.94)	Kestenbaum, 2004[92]	95% CI	Normal

continued

TABLE 71 *Range and distribution data used in scenario analysis 2 based on Ca × P levels (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
CV event				
Yearly probability of having an initial CV event	None	Author assumption that SE is 1/15th of the central estimate	Assumption	Beta
Risk of CV event in any of the model strata	(0.2586 to 0.8353) (0.0066 to 0.0167)	Derived from Block, 2004[19]	95% CIs for slope and intercept parameters used in calculation of category estimates	Bivariate normal

TABLE 72 *Scenario analysis 2 for the cost-effectiveness of cinacalcet based on the impact on Ca × P levels (dialysis costs excluded)*

	Costs (£)	Utilities (QALYs)	Incremental costs	Incremental QALYs	ICER (£ per QALY)
Standard treatment only	5,089	2.38	–	–	–
Standard treatment plus cinacalcet	23,512	2.85	18,422	0.47	38,855

TABLE 73 *Cohort proportions used in the conservative exploratory model of Ca × P impact*

			Percentage of cohort in each group after initial treatment			
			Standard treatment		Cinacalcet treatment	
PTH levels	Ca × P target met (%)	Ca × P target not met (%)	Ca × P target met (%)	Ca × P target not met (%)	Ca × P target met (%)	Ca × P target not met (%)
Controlled	0.91	0.09	4.55	0.45	36.4	3.6
Uncontrolled	0.67	0.33	44.33	22.17	28.0	14.0
Very uncontrolled	0.67	0.33	19.0	9.5	12.0	6.0

TABLE 74 *Speculative analysis for the cost-effectiveness of cinacalcet based on the impact on Ca × P levels: conservative estimate (dialysis costs excluded)*

	Costs (£)	Utilities (QALYs)	Incremental costs	Incremental QALYs	ICER (£ per QALY)
Standard treatment only	4,742	3.2	–	–	–
Standard treatment plus cinacalcet	27,885	3.46	23,142	0.25	91,894

post hoc analysis. Therefore, data were used from large cohort studies about the risk of clinical events in relation to levels of biomarkers, particularly PTH.

Serum levels of biomarkers such as PTH, calcium and phosphate are interrelated and complex. Furthermore, the relationship between combinations of biomarkers and long-term clinical outcomes is complex and has not been characterised. The covariance between markers is unknown. Therefore PTH was modelled independently, which may overestimate or underestimate the risk of clinical events. However, the assumptions used here in modelling Ca × P with PTH levels probably provide an optimistic view for the impact of cinacalcet on the risk of long-term consequences.

The calculation of cost-effectiveness is based on reaching particular target levels of PTH. There may be benefits for those whose PTH levels are

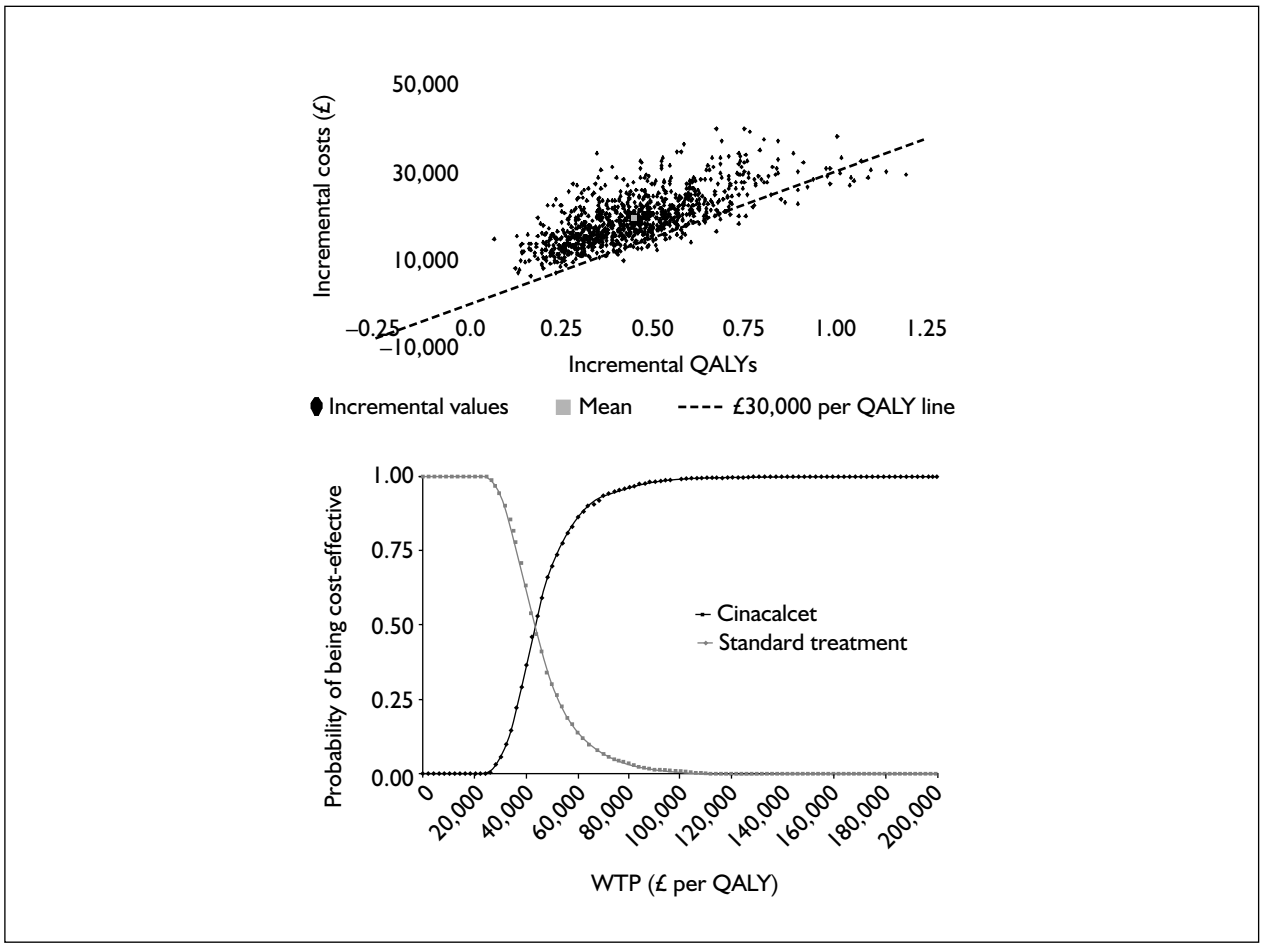

FIGURE 18 *Simulation output (1000 trials) for scenario analysis 2 based on Ca × P control and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis costs excluded)*

reduced, but remain above the threshold. This constraint was placed on the analysis by the data as there is no current evidence that would allow a more finely graded model to be developed. Cost-effectiveness among those with uncontrolled PTH might be underestimated.

It is not known whether control of PTH with cinacalcet will be sustained. It is possible that underlying disease progression will still occur, or that effectiveness may not be sustained over the long term. Compliance is also a known problem, with up to 86% of dialysis patients non-compliant with at least one aspect of their treatment.[30] Cinacalcet is an additional medication for people who may already be taking large amounts of medication. Further, cinacalcet is associated with increased nausea and vomiting. The base case assumes that there is no loss of control with cinacalcet, but that disease progression affects those treated with standard care. This is likely to bias in favour of cinacalcet.

Parameters within the model are differentiated both between the degree of PTH control (the model strata) and between health states within each of these model strata. However, the model does not accommodate interactions between these two sources of variance. Any potential covariance between the degree of control of PTH and the relative risk of cardiovascular death between the health states within the strata is not modelled (for example, if a non-fatal cardiovascular event confers greater relative risk of mortality for those with very uncontrolled levels of PTH compared with those who have controlled levels of PTH). As there are insufficient data to model these possible interactions, equivalent relative risk was assumed at all degrees of PTH control. As it seems unlikely that there is a negative interaction between these two types of risk, this may bias against cinacalcet.

Several assumptions had to be made in relation to fracture in this population. The pattern of fractures experienced in people with ESRD due to

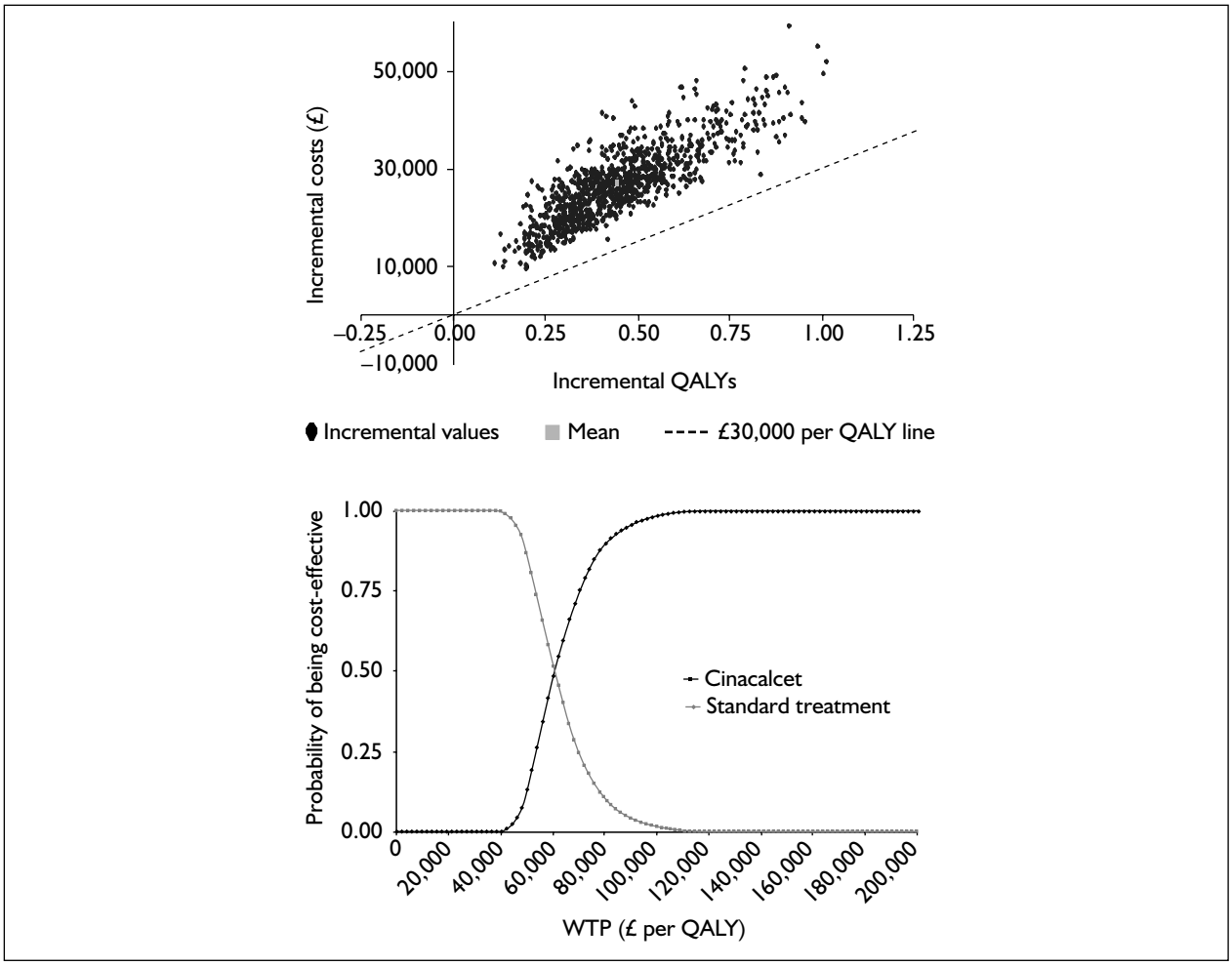

FIGURE 19 *Simulation output (1000 trials) for scenario analysis 2 based on Ca × P control and CEAC showing the probability that cinacalcet is cost-effective at various levels of WTP (dialysis costs included)*

SHPT is not clear, so general population data were used. The interaction between the risks of first fracture or cardiovascular events and subsequent events is also unclear. The risk of death from fractures in people with renal osteodystrophy from SHPT is not well understood and assumptions from a different condition were included. The paucity of evidence in relation to many of these factors led to the need to make a range of linked assumptions, about which much uncertainty must remain. The direction of any potential bias is not clear.

Oversuppression of PTH by cinacalcet is not included in the model. Assuming that downward dose adjustment would take place in such cases, the model will overestimate the treatment costs for cinacalcet.

The model is based on cinacalcet trial populations with an average age of 55 years; however, the average age of accepting RRT in the UK is 65 years. It is not known whether the effectiveness of cinacalcet is affected by age. Younger age is likely to bias the model in favour of cinacalcet as background death rates would be higher among older people.

QoL in SHPT is not well understood and so assumptions based on clinical opinion were made in the model on the amount of reduction in utility according to level of biochemical control.

QoL following cardiovascular events or fractures in this population is not known and may be different from values obtained in the general population or other disease groups. Assumptions based on different populations were included in the model and the impact of any bias this may introduce is not clear.

The cost of dialysis was excluded from the base-case analysis. However, it is usually accepted that costs relating to the treatment of the condition

TABLE 75 *Summary of model uncertainty*

	Source of variable	Level of uncertainty in the data	Impact of uncertainty on the model	Overall rating of importance
Transitions				
RR of death for people with very uncontrolled PTH levels	Cohort study	High	Very high	Very important
RR of death for people with uncontrolled PTH levels	Cohort study	High	High	Important
Disease progression	Clinician opinion	Very high	High	Important
Percentage of people who withdraw from treatment with cinacalcet	Experience in RCTs	Moderate	Moderate	Moderately Important
Differential proportion of people with very uncontrolled PTH levels	Systematic review	Low	Moderate	Not Important
Utilities				
Utility reduction with very uncontrolled PTH levels	Clinician opinion	Very high	High	Important
Utility reduction with uncontrolled PTH levels	Clinician opinion	Very high	Moderate	Moderately Important
Costs				
Inclusion of dialysis costs in the analysis	Author assumption based on input from NICE	High	High	Important
Dose of cinacalcet	Use in RCTs	Moderate	High	Moderately Important
Cost of cinacalcet	List price	Low	Very high	Not important

under examination should be included in cost-effectiveness analyses. It is certainly arguable that, as SHPT is so closely associated with ESRD, costs of ESRD should be included. The exclusion of dialysis costs favours cinacalcet in the analysis.

The model assumes some changes to standard medical treatment of SHPT with the addition of cinacalcet based on clinical opinion. The model therefore assumes that people with refractory SHPT are more likely to receive expensive non-calcium-based phosphate binders. In reality, clinical practice is likely to vary between centres. Assuming more use of these expensive drugs in people with very uncontrolled PTH may bias in favour of cinacalcet.

Comparison of Amgen and PenTAG economic evaluations

Differences in structure and inputs

Table 76 shows the main differences between the PenTAG and Amgen economic analyses. In general, similar types of resource use are captured in both analyses and most of the unit costs are also similar.

There are major differences between the analyses with regard to the assumptions that drive effectiveness. For example, whereas the Amgen analysis attributes a permanent utility decrement of 0.09 following either a cardiovascular or major fracture event (and 0.18 following both), the equivalent permanent utility reductions in the PenTAG model are 0.02 and 0.068, respectively, or 0.0865 having had both types of event.

Most importantly, the transition probabilities that govern the different rates of these events, and different mortality between cinacalcet and standard treatment, are based on different sources. The relative incidence of these events in the Amgen analysis is taken directly from the Cunningham study. In contrast, for the PenTAG analysis, the level of PTH control was modelled separately as the main driver of the risk of these events. This is one of the major factors accounting for differences between the results.

TABLE 76 *Comparison of Amgen and PenTAG base-case analyses of cinacalcet highlighting main differences in study design*

	Amgen analysis	**PenTAG analysis**
Type of model	Markov model	Markov model
Outputs	Costs QALYs	Costs QALYs
Start age and time-horizon	A 55-year-old mixed-gender cohort 15 years (30 cycles)	A 55-year-old mixed-gender cohort Followed until all are dead
Model structure and Markov states	Model reflects: pre- and postparathyroidectomy states; history of having had a CV event, having had a major fracture or having had both or neither ('event free') Attributes risk of CV and fracture events from pooled trial results directly to each arm of model (without explicit simulation of PTH levels)	Includes parathyroidectomy and postparathyroidectomy states Models the risk of CV and fracture events as a function of level of PTH control
Cycle length	6 months	3 months
Allowable transitions	Cannot experience more than one of CV event, major fracture or parathyroidectomy in any 6-month period	Can experience both types of major event in same 3-month period
Population modelled	Patients with PTH > 31.6 pmol/l (>300 pg/ml)	Patients with PTH > 31.6 pmol/l (>300 pg/ml)
Background utility before experiencing major fracture or CV events	0.681	0.6735 for those with controlled PTH, 0.6398 for uncontrolled PTH levels, 0.6062 for very uncontrolled PTH levels
CV event assumptions	Permanent utility decrement of 0.09 Cost of event: £1817	Initial 3-month utility of 0.478, then 0.6533 thereafter Cost of event: £1287
Major fracture event assumptions	Permanent utility decrement of 0.09 Cost of event: £3814	Initial 3-month utility of 0.5368, then 0.6051 thereafter Cost of event: £4767
Utility after both CV and major fracture event	0.5 (= 0.68 – 0.09 – 0.09)	Initial 3-month utility of 0.384, then 0.5870 thereafter
Postparathyroidectomy assumptions	No utility decrement Risk of complications the same as under cinacalcet	Assumed same utility levels as having controlled PTH, and same utility impacts of adverse events as preparathyroidectomy Higher mortality in immediate postparathyroidectomy period, same as those with controlled PTH levels
Costs included	Cinacalcet Hospital treatment of CV events Hospital treatment of major fractures Treatment of minor fractures Parathyroidectomy Regular blood tests for PTH	Cinacalcet Background cost of dialysis Hospital treatment of CV events Hospital treatment of major fractures Treatment of minor fractures Parathyroidectomy Regular blood tests for PTH, calcium and phosphate levels
Mortality a function of	Age plus a risk reduction for those on cinacalcet	Age-related non-surgical (all-cause) mortality, plus excess mortality associated with: having uncontrolled and very uncontrolled PTH levels, perioperative mortality (following parathyroidectomy), and postparathyroidectomy

TABLE 77 *Key differences in outputs for the Amgen and PenTAG models*

	Amgen analysis	PenTAG analysis
% surviving 5 years, cinacalcet	52.0%	50.1%
% surviving 5 years, standard care	44.0%	47.4%
% surviving 10 years, cinacalcet	23.8%	19.5%
% surviving 10 years, standard care	16.5%	16.8%
Mean survival, cinacalcet	6.37	6.25
Mean survival, standard care	5.67	5.62
Incremental survival (years):	0.70	0.63
Mean QALYs, cinacalcet	3.40	3.39
Mean QALYs, standard care	2.87	3.04
Incremental QALYs:	0.53	0.34
Mean cost, cinacalcet	£21,900	£27,670
Mean cost, standard care	£3,000	£6,533
Incremental cost:	£19,000	£21,167
Incremental cost per QALY (discounted)	£35,600	£61,890
Incremental cost per QALY (undiscounted)	£32,750	£ 55,633

Differences in outputs

The base-case ICERs of the two analyses differ by more than £26,000 (in the PenTAG analysis cinacalcet produces extra QALYs at a cost of £61,800 per QALY, compared with £35,600 in the Amgen analysis). The most probable reasons for this difference are presented below, but since there are so many different numerical assumptions (parameters) in each model, and also substantive differences in the structural assumptions in each model, an exhaustive analysis of why the base-case ICERs are so different is not possible here. *Table 77* summarises some key outputs from each analysis.

The difference in ICER arises from cinacalcet yielding 36% lower estimated QALY gains and generating 11% higher costs in the PenTAG analysis. However, in terms of their predictions of overall survival, the two models seem similar, for example resulting in a difference in mean incremental survival of less than 1 month (0.07 of a year). This suggests that differences in estimated QALY gains due to cinacalcet are explained by how much time people spend in health states of differing utility weight.

Figure 20 shows a comparison of the two models in terms of the amount of time spent in the main 'alive' Markov states. Note that while the health states along the *y* axis are the same as those in the Amgen model, for the PenTAG model these summarise a number of equivalent states (e.g. all cardiovascular events with cinacalcet across all the model strata representing different levels of PTH control).

Although the pattern of state occupancies generated by each model is broadly similar, there are a few notable differences, which may partly explain the differences in estimated QALYs and costs between the two analyses:

- Following treatment with either cinacalcet or standard care, people in the Amgen model experience significantly more major fractures and so spend over five times more time at postfracture levels of utility.
- People in the Amgen model are also much more likely to spend time in those health states that reflect past experience of both major fracture(s) and cardiovascular events (0.30 years with cinacalcet and 0.56 years with standard care, compared with equivalent mean state occupancies in the PenTAG analysis of 0.08 and 0.09 years, respectively). In the Amgen model, the utility associated with having experienced both types of event is 0.501, so this may contribute a significant amount of the estimated QALY gain due to cinacalcet.
- In the Amgen model the effectiveness of cinacalcet in avoiding or delaying parathyroidectomy is much greater than in the PenTAG model. The mean time spent in postparathyroidectomy states reduces from 0.86 years with standard care to 0.07 years with cinacalcet in the Amgen model, while the equivalent mean state occupancies in the PenTAG analysis are 0.96 and 0.31 years, respectively. However, in the Amgen model parathyroidectomy does not lead to any changes in QoL and is mainly a factor in driving costs.

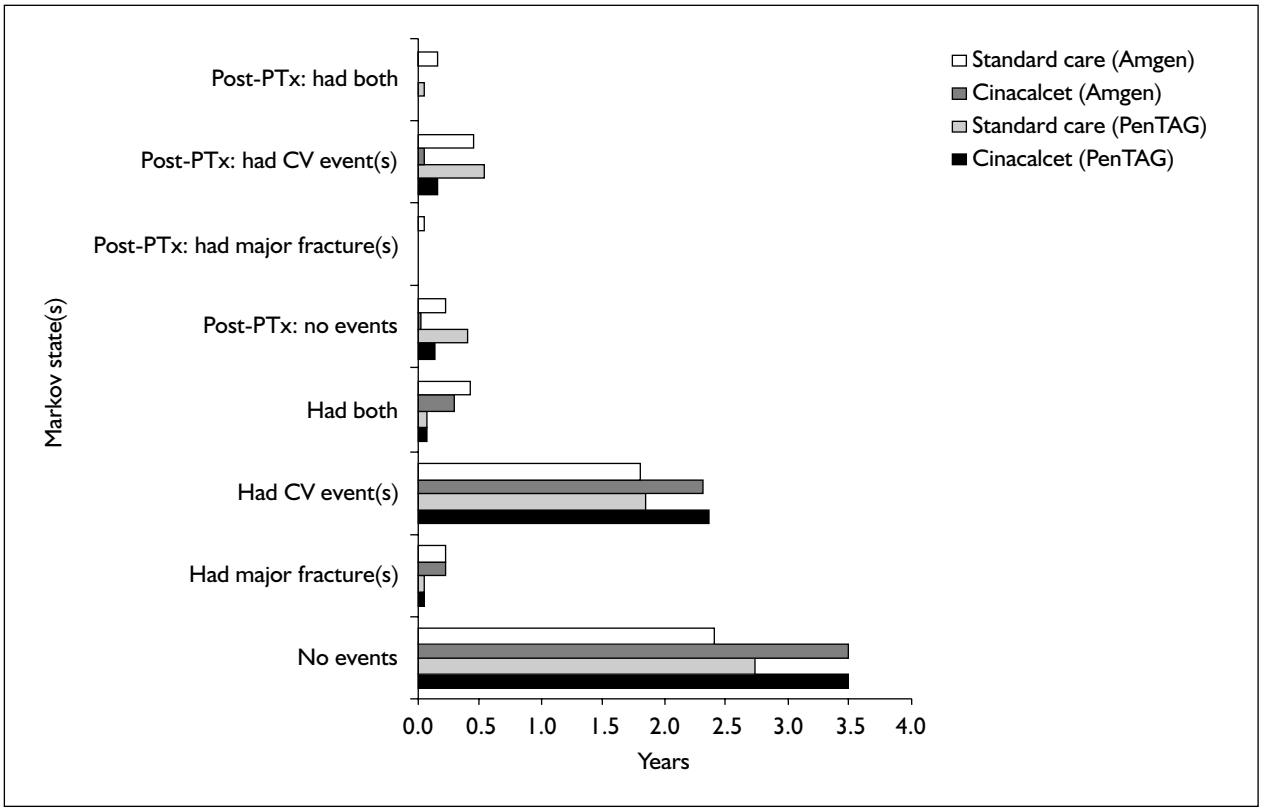

FIGURE 20 *Markov state occupancy in years for each model and comparator*

The way in which these state occupancies translate into QALY gains or losses in each model is shown in *Figures 21* and *22*. Because of the different model structures, and the more complicated system of utility values used in the PenTAG model, it is not possible to produce directly equivalent graphs. *Figure 21* shows that the QALY gains (undiscounted) of cinacalcet in the Amgen model are due mainly to fewer patients experiencing both fracture and cardiovascular events, and more remaining in the event-free states (whether before or after parathyroidectomy).

In contrast, in the PenTAG model, the QALY gains due to cinacalcet are not associated with changes in the proportion of people experiencing both types of adverse event (*Figure 22*). Instead, more than two-thirds of the QALY gains in the PenTAG model arise from a combination of people spending more time in event-free health states and avoiding very uncontrolled PTH. The remaining QALY gains are due almost entirely to fewer and delayed occurrence of cardiovascular events (again, combined with less of their survival time being with very uncontrolled PTH). Time spent in fracture-only-related Markov health states has almost no impact on the QALY gain due to cinacalcet in either analysis.

In addition, while overall survival estimates are similar between the two analyses, in the PenTAG analysis deaths associated with cardiovascular events or a history of a past cardiovascular event are modelled separately, and account for almost half of all deaths (either with cinacalcet or on standard care). By comparison, the Amgen analysis may overestimate the long-term QoL impacts of cardiovascular events because there is no simulated excess death rate associated with having such events.

An explanation of the differences in incremental cost between the two analyses would require full reporting of the mean lifetime occurrence of major and minor fractures, cardiovascular events and parathyroidectomies, for both cinacalcet and standard care. Such data were not reported in the Amgen submission, nor are they easy to generate from the model supplied. Therefore, no formal assessment was conducted of how the cost differences between the two analyses have arisen.

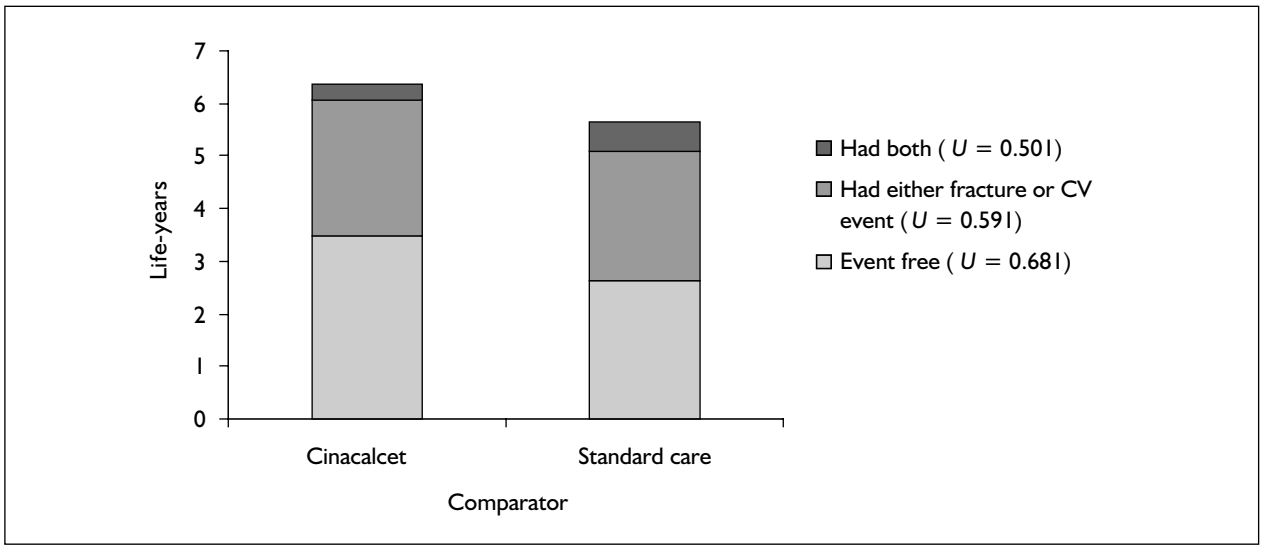

FIGURE 21 *State occupancy by utility weight in the Amgen model*

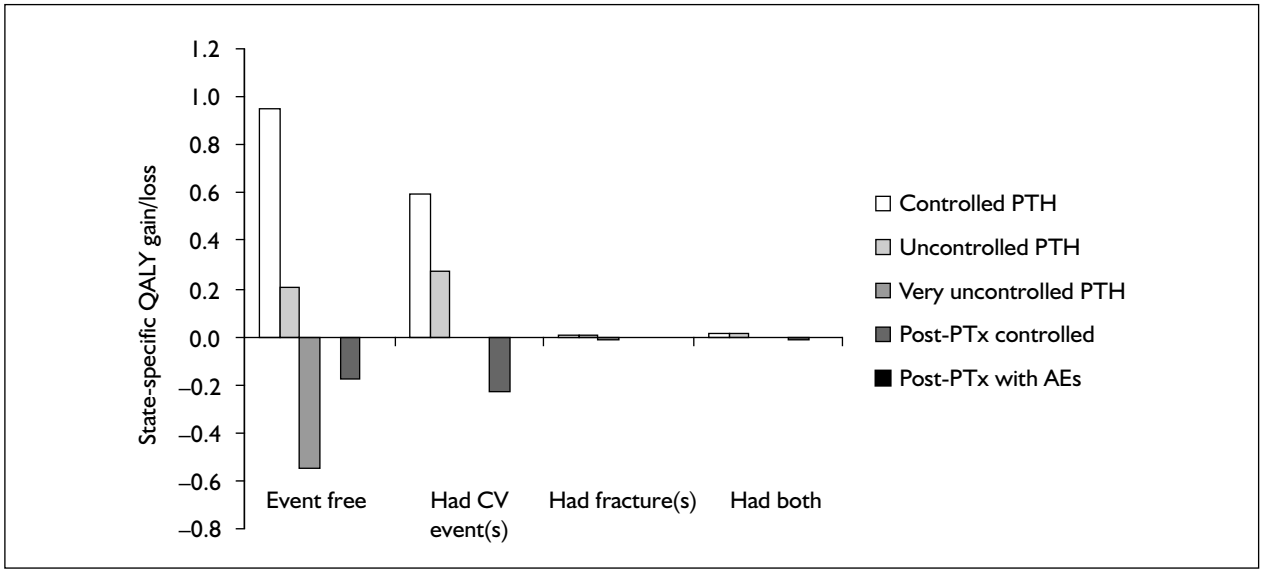

FIGURE 22 *Summary of the source of QALY gains and losses in the PenTAG model*

However, the state occupancy comparisons, presented above to explain the difference in estimated QALY gain, suggest that a key explanation of incremental cost differences between the analyses would be:

- the greater reductions in rates of cardiovascular events in the Amgen model (as derived from the Cunningham study data)
- slightly higher unit costs of hospital care for cardiovascular events in the Amgen analysis
- a greater reduction in the number (and delay in the timing of) parathyroidectomies with cinacalcet.

Current service cost and impact of new treatments

Existing costs for people with ESRD are high: haemodialysis costs about £18,000 annually, and peritoneal dialysis £9000. The cost of standard treatment for SHPT is modest; the model predicts it will cost £6500 for the lifetime of a 55-year-old (median survival 5 years).

Using costs obtained from the economic model presented here, it is possible to estimate the impact of adopting cinacalcet as additional treatment for those with uncontrolled SHPT.

TABLE 78 *Estimated number of people with ESRD and elevated PTH levels*

Parameter	Data	Source
Prevalence of RRT	636 pmp	Renal Registry
% of those on RRT on dialysis	54%	Renal Registry
Population England and Wales	53,045,600	Census 2001
No. of people on dialysis in England and Wales	18,218	Calculated
% of people with PTH levels >32 pmol/l	34%	Renal Registry
No. of people with elevated PTH levels	6194	Calculated

There are approximately 6000 people on dialysis with elevated PTH levels in England and Wales (*Table 78*). Assuming that the lifetime cost (median survival 5 years) in the model for a 55-year-old is the average cost for this population, the cost to treat all those in England and Wales would be about £131 million.

Using data in *Table 78* for an average hospital trust serving about 250,000 people, 29 people on dialysis would have SHPT. The additional cost of treating these people for a median of 5 years with cinacalcet would be £613,000.

BOX 3 *Summary of results of the cost-effectiveness analysis*

- No published cost–utility studies of cinacalcet were identified. Amgen submitted a Markov model to NICE which estimated an ICER of £35,600 per QALY. Subgroup analyses of those with moderate and severe hyperparathyroidism produced estimates £30,400 and £48,300 per QALY, respectively.
- PenTAG designed a Markov model to assess the cost–utility of cinacalcet in addition to standard care compared with standard care alone for people with SHPT with ESRD.
- A cohort of 1000 55-year-olds was modelled until all the cohort was dead.
- The base case showed that cinacalcet conferred a small number of additional QALYs (0.34) for an additional £21,167 per person, giving an ICER of £61,890 per QALY. This is not likely to be considered cost-effective.
- One-way sensitivity analyses showed that the model was sensitive to the cost of cinacalcet, the utility value for people with very uncontrolled levels of PTH and the relative risk of mortality for people with very uncontrolled levels of PTH compared with those with controlled PTH.
- PSA showed that cinacalcet was only likely to be cost-effective at levels of WTP over £62,000 per QALY.
- Subgroup analysis in people with moderately uncontrolled levels of PTH only reduced the ICER, but cinacalcet was still not likely to be considered cost-effective (£57,400 per QALY).

Chapter 5
Discussion

Summary of findings

Cinacalcet is more effective than standard treatment in bringing SHPT under control, as measured using PTH and other markers of biochemical disruption in SHPT in people with ESRD. However, there is very limited evidence about the impact of this on clinically important outcomes such as cardiovascular events and death. Evidence of the impact of cinacalcet on biochemical markers is also short term.

The economic evaluation suggests that, under almost all assumptions, the incremental cost-effectiveness of introducing cinacalcet would be greater than £30,000 per QALY from the perspective of the UK NHS.

The economics of introducing cinacalcet are subject to much uncertainty, but based on the modelling carried out in this assessment, cinacalcet is unlikely to be considered a cost-effective intervention by NHS commissioners. Only above a WTP threshold of £62,000 per QALY is there a good chance that cinacalcet is cost-effective.

Interpretation of findings

Despite evidence that cinacalcet brings biochemical markers of SHPT to target levels more effectively than standard treatment, a combination of factors leads to cinacalcet appearing to represent relatively poor value for money. The background death rate for people with ESRD is high, even among the relatively young cohort modelled. Conversely, the relative risk of mortality for people with slightly elevated PTH levels appears low, so the potential impact of cinacalcet may be limited. The impact of SHPT on cardiovascular event rates, and potential for control of this risk, is particularly important in the evaluation of cinacalcet. Cinacalcet is expensive and, even if dialysis costs are excluded and it is assumed that there will be some cost-savings owing to reduced phosphate binder treatment, cinacalcet is unlikely to be considered cost-effective.

The place of parathyroidectomy appears to vary between UK centres, based on the availability of surgeons and clinician preferences. Surgery appears to be an effective therapy, despite relatively frequent recurrence. Recent Australian management advice for SHPT suggests that parathyroidectomy should remain the preferred treatment option for those with PTH levels elevated above 85 pmol/l.[37] Without trial evidence comparing cinacalcet and parathyroidectomy, the optimal treatment approach remains unknown and the present analysis does not focus on this. In the treatment of very severe PTH, where parathyroidectomy is contraindicated, cinacalcet may be an appropriate alternative.

The published evidence for the direct impact of cinacalcet on outcomes such as cardiovascular event, fracture and mortality is limited to one retrospective analysis of the four main RCTs of its biochemical effects. The short follow-up, lack of detail about the people who entered the trial extension and unclear censoring procedures, as well as the inclusion of a fitter population than is found in clinical practice, make interpretation of these results difficult.

Strengths and weaknesses

Strengths of the evaluation

The systematic review of the effectiveness and cost-effectiveness of cinacalcet in SHPT is comprehensive and has been carried out by an independent research team.

PenTAG's economic evaluation allows exploration of the potential for cinacalcet to be used at different levels of PTH control and for the impact of different risk markers to be explored.

Potential limitations of the evaluation

Evidence for the direct impact of cinacalcet on cardiovascular events, fractures and mortality is very limited. The relationship between biomarkers and long-term outcomes is complex and not well characterised, and the covariance between different markers is unknown. Therefore, the impact of single biomarkers, such as PTH levels, was modelled, which may overestimate or underestimate the risk of clinical events. However, the assumptions used here in modelling Ca × P provide an optimistic view of the potential risk of long-term consequences with cinacalcet treatment.

The main source for relative risk data based on biochemical markers was the large, US cohort study by Block and colleagues.[19] This was used because it was recent, was the largest identified study and provided data about fracture, cardiovascular hospitalisation and mortality risk in the same cohort for the key biochemical markers. However, it was assumed that these data are accurate and applicable to the UK population.

It is not known for how long biochemical control will be maintained in people who achieve it with cinacalcet. The impact of disease progression and of compliance with medication regimens may be important, but is not currently characterised. The base-case assumption that progression to more severe degrees of hyperparathyroidism continues fairly rapidly with standard treatment but is arrested with cinacalcet is likely to bias the results in favour of cinacalcet.

The possibility of oversuppression of PTH by cinacalcet is not reflected in the model. Assuming that downward dose adjustment would take place in such cases, the model may overestimate the treatment costs for cinacalcet.

A number of assumptions was used to model fractures in ESRD, as the authors were unable to identify specific data in the relevant population. The pattern of fractures experienced in people with ESRD due to SHPT is not well documented, so general population data on fracture distribution were used in the model. It is not known whether and how such data are different from the pattern of fractures in people with ESRD. In addition, the interaction between the risks of first fracture and subsequent events is unclear in this population, and it was assumed that this is similar to the risks for people with osteoporosis. Further, the risk of death associated with fractures in people with renal osteodystrophy associated with SHPT is not well understood. Again, assumptions were based on data from those with osteoporosis. It is not clear whether these assumptions will overestimate or underestimate risk for renal osteodystrophy. The paucity of evidence in relation to many of these factors led to the need to make a range of linked assumptions, about which much uncertainty must remain.

The risk of a subsequent cardiovascular event after an initial cardiovascular event is not known in this population. Data were identified relating to the additional risk of subsequent heart failure after an initial event. It is not known whether this is an underestimation or overestimation of the risk of all cardiovascular events after any initial cardiovascular event.

The model assumes that a reduction in the use of expensive phosphate binders might be expected in people who respond to cinacalcet. Data for the exact mix and dosage of drugs used with and without cinacalcet are scarce.

The impact of drug regimen changes on patients is also unknown. It is possible that the quantity and type of drugs taken may influence QoL and compliance. If cinacalcet were to prove a more reliable method of controlling PTH in the long term, this may reduce anxiety over this aspect of ESRD. In addition, cost-benefits in terms of less clinical time and less specialist dietitian input are possible but as yet undocumented.

QoL in SHPT is not well understood, and assumptions were made based on clinical opinion as to the reduction in utility according to level of biochemical control. QoL (SF-36) data collected with the cinacalcet trials suggested that there was little difference in QoL for those treated with cinacalcet compared with those treated with standard care. The model may thus have overestimated the impact of PTH levels on QoL and so the impact of cinacalcet. Conversely, there were differences in two items of the SF-36: the physical component and bodily pain scores. If such elements were affected at lower degrees of SHPT than were modelled, the impact of cinacalcet may have been underestimated.

QoL changes following cardiovascular events or fractures in this population are not well characterised and may be different from values obtained in the general population or other disease groups. Assumptions based on non-ESRD populations have been included in the model and the size and direction of any bias introduced is not clear.

Diabetes is known to affect adversely survival for those with ESRD. The model has not explicitly considered the impact of diabetes in people treated with cinacalcet for SHPT. The impact on clinical outcomes of controlling PTH in diabetic and non-diabetic populations is not known. Those with diabetes already have an increased risk of cardiovascular events and the proportion of risk attributable to SHP may be relatively low, leading to a limited potential role for cinacalcet. The trial data used to populate the model included about 30% people with diabetes, which is similar to the 27% diabetes co-morbidity recorded by the UK

Renal Registry. However, mortality in the trials was low for the relevant age group reported in the Renal Registry. It is possible that those people with diabetes included in the trials were fitter or had better controlled diabetes than in usual clinical practice.

The model predicts median survival of 5 years with cinacalcet and 4.5 years with standard care. The Renal Registry estimates median survival for people at medium mortality risk of 7.4 years (for non-diabetics under 55 and diabetics aged 55–64) and for people at high risk of 3.5 years (for diabetics over 55 and non-diabetics aged over 65). It is not clear whether this is an overestimation or underestimation of the risk for people with SHPT.

The scope for this report has been the effectiveness of cinacalcet in people with existing SHPT. It is not known whether preventing the progression to HPT initially is possible with cinacalcet and whether this could be a more useful indication. Similarly, the impact of avoiding calcification in younger populations could reap greater benefits.

Interpretation in the context of other studies in the area

No published economic evaluations of cinacalcet in SHPT were identified. The PenTAG model is more comprehensive and flexible than the model submitted to NICE by the manufacturers of cinacalcet, although both models adopt a similar basic structure.

The PenTAG model replicates the findings of the Amgen model when appropriate adjustments to input parameters are made.

Need for further research

- Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long-term clinical outcomes are of paramount importance to improve future efforts to model the effectiveness of cinacalcet or other similar agents.
- Longer term studies of the maintenance of PTH control in SHPT and of the clinical impact with cinacalcet are needed. Such studies should explicitly examine the impact of cinacalcet in subgroups based on age and diabetes.
- A better understanding of the epidemiology of fractures in SHPT is needed, including the pattern of fractures experienced in SHPT and their consequences in terms of health service use, QoL and mortality.
- The impact on QoL of fracture, cardiovascular events and very uncontrolled PTH levels in people with SHPT in dialysis should be investigated.

Chapter 6
Conclusions

Cinacalcet is more effective in bringing SHPT under control than standard care, as measured using PTH (40% versus 5%) and other markers of biochemical disruption in SHPT. However, there is very limited direct evidence about the impact of this on clinically important outcomes such as cardiovascular events and death.

The economic evaluation suggests that, under almost all assumptions, the incremental cost-effectiveness of introducing cinacalcet would be considerably greater than £30,000 per QALY from the perspective of the UK NHS.

The economics of introducing cinacalcet are subject to much uncertainty, but based on the modelling carried out in this assessment, cinacalcet is unlikely to be considered a cost-effective intervention by NHS commissioners.

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Contribution of authors

Rob Anderson (Health Economist) obtained costs for the model, contributed to writing the report (economics chapter) and provided the critique of the economic evaluation provided by the manufacturer. Richard D'Souza (Consultant in Renal Medicine) contributed to the development of the protocol, contributed to editing the report and provided clinical input into the model design. Ruth Garside (Research Fellow) provided overall project management, assessed abstracts for inclusion and exclusion, contributed to writing and editing the report, contributed to the design of the model and identified model input data. Stuart Mealing (Research Assistant) developed and executed the economic model and assisted in its design, and contributed to writing the report (economics chapter). Martin Pitt (Research Fellow) designed and supervised the development and execution of the economic model, and contributed to writing the report (economics chapter). Chris Roome (Interface Development Pharmacist) extracted data and contributed to writing the report (systematic review chapter). Ailsa Snaith (Visiting Research Fellow) extracted data and contributed to writing the report (background and systematic review chapters). Ken Stein (Senior Lecturer in Public Health) wrote the protocol, assessed abstracts for inclusion and exclusion, contributed to the design of the model and edited the report. Karen Welch (Information Scientist) undertook literature searches for the project and commented on drafts of the protocol and the report.

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Appendix 1

Renal Registry reports of mortality risk according to serum phosphate, calcium and calcium–phosphate product[16]

TABLE 79 *Relative hazard of mortality by dialysis modality by phosphate levels*

Serum phosphate level (mmol/l)	Relative hazard of mortality	
	HD	PD
0.9	1.05	1.07
1.0	1.03	1.05
1.1	1.02	1.03
1.2	1.01	1.02
1.3	1.01	1.00
1.4	1.00	1.00
1.5	1.00	1.00
1.6	1.01	1.00
1.7	1.01	1.00
1.8	1.03	1.01
1.9	1.05	1.02
2.0	1.06	1.04
2.1	1.09	1.06
2.2	1.11	1.08
2.3	1.15	1.11
2.4	1.18	1.15
2.5	1.22	1.20
2.6	1.27	1.25

TABLE 80 *Relative hazard of mortality by dialysis modality by calcium levels*

Serum calcium level (mmol/l)	Relative hazard of mortality	
	HD	PD
2.0	1.08	1.08
2.5	1.04	1.04
3.0	1.00	1.00
3.5	1.00	1.00
4.0	1.00	1.00
4.5	1.03	1.00
5.0	1.05	1.03
5.5	1.09	1.07
6.0	1.14	1.12
6.5	1.23	1.20
7.0	2.12	2.12
7.5	2.13	2.05

TABLE 81 *Relative hazard of mortality by dialysis modality by Ca × P levels*

Serum Ca × P level (mmol/l)	Relative hazard of mortality	
	HD	PD
2.0	1.02	1.07
2.5	1.00	1.03
3.0	1.00	1.00
3.5	1.00	1.00
4.0	1.00	1.00
4.5	1.02	1.05
5.0	1.07	1.09
5.5	1.12	1.17
6.0	1.19	1.29
6.5	1.29	1.46
7.0	1.41	1.76
7.5	1.57	2.26

Appendix 2

Expert advisory group

Ms Caroline Ashley (Renal Pharmacist, Royal Free Hospital)
Dr Henry Brown (Consultant Nephrologist, Belfast City Hospital)
Professor Terry Feest (Professor of Nephrology, Richard Bright Renal Unit, University of Bristol)
Dr Jonathan Kwan (Clinical Director of Renal Services, SW Thames Renal and Transplantation Unit, St Helier Hospital)
Professor Alison MacLeod (Professor of Nephrology, Department of Medicine and Therapeutics, University of Aberdeen)
Dr Paul Roderick (Senior Lecturer in Public Health, Cochrane Renal Group, Centre for Kidney Research, University of Sydney)
Dr RJ Winney [Consultant Nephrologist (Retired), Royal Infirmary of Edinburgh]

Appendix 3

Protocol

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence.

Protocol
August 2005

Project title

The effectiveness and cost-effectiveness of cinacalcet for the treatment of hyperparathyroidism secondary to impaired renal function.

Project team

Ruth Garside[1] [Research Fellow (Lead)]
Dr Martin Pitt[1] (Research Fellow)
Stuart Mealing[1] (Research Assistant)
Dr Rob Anderson[1] (Senior Lecturer in Health Economics)
Karen Welch[2] (Information Officer)
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Plain English summary

This project will review the evidence for the use of cinacalcet, a new treatment for hyperparathyroidism, which is a common complication of renal failure. Hyperparathyroidism disrupts the body's biochemical balance and may result in a range of symptoms; fractures sustained without significant trauma; problems with blood vessels and the heart; and increased risk of death. The assessment report will draw together all relevant evidence on cinacalcet in a systematic review. It will also assess whether the introduction of cinacalcet is likely to represent good value for money to the NHS.

Decision problem

Purpose

The purpose of the report is to support the NICE Appraisal Committee in the development of Guidance for the NHS in England and Wales on the use of cinacalcet.

Cinacalcet

Cinacalcet (Mimpara®) is indicated for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. It is the first of a new class of calcimimetic drugs, which acts by increasing parathyroid sensitivity to serum calcium to reduce secretion of parathyroid hormone (PTH). This, in turn, reduces serum calcium. Cinacalcet received marketing approval in October 2004.[101]

Cinacalcet is a first-in-class agent and so has no direct comparator. Vitamin D and phosphate binders are used to ameliorate the effects of increased PTH secretion in chronic kidney disease (CKD). In some cases of advanced hyperparathyroidism, where parathyroidectomy may be considered, there is interest in whether cinacalcet may obviate or delay the need for surgery. Cinacalcet is an oral preparation, with dosage titrated according to PTH response up to 180 mg per day.

Hyperparathyroidism in CKD

Secondary hyperparathyroidism (SHPT) is common in CKD.[3] It may develop early in CKD, at glomerular filtration rates (GFR) of less than 60 ml per minute, as a response to reduced serum

calcium, and progresses as renal function deteriorates. The pathogenesis of hyperparathyroidism in CKD is complex and incompletely understood. A range of factors has been implicated:[102]

- reduced serum calcium
- increase in plasma phosphate levels
- decreased vitamin D activity through a range of possible effects (e.g. reductions in renal calcitriol synthesis and reserve capacity and reduced parathyroid responsiveness to calcitriol)
- parathyroid tissue hyperplasia in response to uraemia
- altered parathyroid sensitivity to plasma calcium.

Elevated PTH levels from SHPT are seen in around 40% of patients on dialysis.[5] Very high levels of PTH may develop in uncontrolled hyperparathyroidism (>800 pg/ml), with nodular hyperplasia of the parathyroid glands. In such cases, parathyroidectomy may be considered. Around 10% of people on dialysis have such increased levels of PTH.[5]

Parathyroid stimulation in CKD has a range of clinical consequences, mediated by increased PTH synthesis and PTH-secreting cell proliferation.[3] PTH increases osteoclast activity and bone resorption, leading to high-turnover bone disease, which may include the typical features of osteitis fibrosa. High-turnover bone disease may be present in up to 75% of people on dialysis and results in raised serum calcium, phosphate and calcium–phosphate product (Ca × P). Fracture risk may be increased.[5] Treatment with vitamin D and phosphate binding agents may result in oversuppression of PTH so that bone turnover is reduced, resulting in adynamic bone disease. This predisposes to hypercalcaemia and may also be associated with pathological fractures.

SHPT may also be complicated by calcification at a range of sites. Of particular interest is cardiovascular calcification, possibly related to elevated Ca × P. Direct effects on the heart, resulting in left ventricular hypertrophy and dysfunction, may also result from raised PTH levels. These effects account for a proportion of the increased overall and cardiovascular mortality noted in people with CKD.[103]

Symptoms of hyperparathyroidism include tiredness, malaise, muscle weakness, bone and joint pain, abdominal pain, weakness and pruritis.

The Renal Association Register has demonstrated considerable variation in serum phosphate, calcium and PTH control in the UK.[13] In particular, phosphate control is considered to be poor and wide variation in levels of PTH is noted in relation to the Renal Association recommendation that PTH concentration should be three to four times the upper limit of the assay used. The Renal Association Standard does not suggest that there is any clinical risk from oversuppression of PTH.[13]

Current management and place of cinacalcet

Prophylaxis is considered appropriate in asymptomatic patients with hyperparathyroidism as bone changes and parathyroid hyperplasia may be difficult or impossible to reverse.[3,102] National and international guidelines support the attainment of target levels for serum PTH, calcium and phosphate concentrations.[10,104,105] The main approaches to treatment are:

- reduction in serum phosphate by the use of phosphate binding agents and, to a lesser extent, dietary restriction
- reduction in PTH by supplementation of vitamin D.

The optimum choice of phosphate binding agent is unclear. Aluminium-containing agents (e.g. aluminium hydroxide or aluminium carbonate) may contribute to increased aluminium toxicity and are discouraged.[10] Calcium-containing binders (e.g. calcium carbonate or calcium acetate) were the mainstay of treatment until the development of concerns about the associated risk of vascular calcification in people on haemodialysis.[3] Sevelamer hydrochloride is a non-calcium-containing phosphate binder which also reduces serum lipid levels. It is licensed for use only in people on haemodialysis and is considerably more expensive than other phosphate binders. The Renal Association recommends that the choice of phosphate binding agent should be individualised to each patient.[10]

In cases of uncontrolled SHPT, typically with nodular parathyroid hypertrophy and very high levels of PTH, parathyroidectomy may be indicated.

Cinacalcet is an additional therapeutic option in hyperparathyroidism. The extent to which the need for other treatments may be reduced is unclear.

Report methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of cinacalcet. The review will be undertaken systematically following the general principles published by the NHS Centre for Reviews and Dissemination.[65] The research protocol will be updated as necessary as the research programme progresses. Any changes to the protocol will be reported to NCCHTA and NICE.

Population

- *Inclusion criteria*: people on peritoneal or haemodialysis for ESRD of any underlying cause with hyperparathyroidism.
- *exclusion criteria*: people with CKD not on dialysis.
- *interventions*: cinacalcet HCI in licensed doses.

Comparators

- Standard care, which may include:
  - phosphate binders
  - vitamin D
  - parathyroidectomy.

Outcomes

The following outcomes will be included in the systematic review if reported in available primary studies:

- mortality
- incidence of cardiovascular events
- incidence of fractures
- health-related quality of life
- symptoms related to hyperparathyroidism
- serum PTH, calcium, phosphate and Ca × P levels
- parathyroidectomy
- hospitalisation.

Search strategy and inclusion criteria

The search strategy will comprise the following main elements:

- searching of electronic databases
- contact with manufacturers of cinacalcet through NICE
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

Databases

Electronic databases, including MEDLINE (Ovid); PubMed (previous 6 months for latest publications); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE, NHS EED and HTA databases; BIOSIS (EDINA); NRR (National Research Register); Web of Science, Science Citation Index (SCI) and ISI Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website.

Inclusion

For the review of clinical effectiveness, only RCTs will be included. This criterion will be relaxed for consideration of adverse events, for which observational studies may be included.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion

- Non-randomised studies (except for adverse events)
- animal models
- preclinical and biological studies
- narrative reviews, editorials and opinions
- non-English-language papers
- reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

Data extraction strategy

Data will be extracted by one researcher and checked by another.

Quality assessment

Consideration of study quality will include the following factors:

- *trial characteristics:*
  - timing, duration and location of the study
  - method of randomisation
  - allocation concealment
  - blinding
  - numbers of participants randomised, excluded and lost to follow-up
  - whether ITT analysis is performed
  - methods for handling missing data
  - appropriateness of statistical analysis
- *study participants:*
  - baseline characteristics: age, gender, cause of ESRD, baseline laboratory values, use of phosphate binders and vitamin D
  - inclusion criteria
  - exclusion criteria.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be

used to estimate a summary measure of effect on relevant outcomes based on ITT analyses.

Meta-analysis will be carried out using fixed and random effects models, using STATA software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

Report methods for synthesis of evidence of cost-effectiveness

The sources detailed in the previous section will be used to identify studies of the cost-effectiveness of cinacalcet. Stand-alone cost-analyses based in the UK NHS will also be sought. The authors consider it very unlikely that cost-effectiveness analyses will have been published in the scientific literature at this early point in the diffusion of cinacalcet. Contact with the manufacturers of cinacalcet and other agencies (e.g. INAHTA) are more likely to identify relevant evaluations.

Available cost-effectiveness analyses will be critically appraised using the frameworks established by the Consensus on Health Economic Criteria[106] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[107]

In addition, a new economic evaluation will be carried out from the perspective of the UK NHS using a decision-analytic modelling approach. Model structure will be determined in consultation with clinical experts and will include the longer term consequences of hyperparathyroidism (fractures, cardiovascular events and mortality), if appropriate data are available. Further literature searches will be carried out to identify studies that relate serum PTH and biochemistry to these longer term outcomes. As the evidence base for long-term use of cinacalcet is extremely limited, a range of assumptions will be made regarding sustained effectiveness. If possible, impact on the need for parathyroidectomy will be included.

Resource use will be specified and valued from the perspective of the NHS in 2004. Cost data will be extracted from published work, NHS reference costs and sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be derived from individual NHS trusts or groups of trusts. Costs will be discounted at 3.5%.

Health-related quality of life will be incorporated by the application of preference weights (utility) to disease states. Utility values will be sought using the sources detailed in the previous section. Outcomes will be discounted at 3.5%.

The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of cinacalcet will be estimated in terms of:

- cost to achieve normalisation of PTH
- cost per event avoided (fracture, cardiovascular event)
- cost per life-year gained
- cost per QALY.

Analysis of uncertainty will focus on cost utility, assuming that cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Handling the company submission(s)

Information provided by sponsors will be included in the report if, in the judgement of the assessment group, it meets relevant inclusion criteria.

A critique of any economic evaluations, including models, submitted by industry will be carried out using the frameworks established by the Consensus on Health Economic Criteria[106] and ISPOR.[107]

Any data designated as commercial in confidence or academic in confidence in sponsor submissions and incorporated in the assessment report will be highlighted and the source identified.

Competing interests of authors

Dr Richard D'Souza received an honorarium from Amgen in 2004 for making a presentation to clinical nephrology staff in Devon on SHPT and its management.

Appendix 4

Search strategy

Clinical searches

MEDLINE (OVID) 1966–2006

1. cinacalcet.tw.
2. (mimpara or sensipar).tw.
3. (AMG adj '073').mp.
4. calcimimetic$1.tw.
5. 1 or 2 or 3 or 4
6. hyperparathyroidism secondary/
7. 'secondary hyperparathyroidism'.tw.
8. kidney failure chronic/
9. 'ESRD'.tw.
10. renal dialysis/
11. hemodialysis/
12. peritoneal dialysis/
13. peritoneal dialysis continuous ambulatory/
14. 'CAPD'.tw.
15. kidney diseases/
16. 'chronic kidney disease$1'.tw.
17. 'CKD'.tw.
18. renal osteodystrophy/
19. phosphorus/bl
20. calcium/bl
21. Hypocalcemia/
22. parathyroid hormone/
23. 'PTH'.tw.
24. parathyroid glands/
25. or/6-24
26. 5 and 25
27. vitamin d/tu, dt
28. lanthanum/
29. phosphates/
30. 'vitamin D analogue$1'.tw.
31. calcitriol.tw.
32. receptors calcitriol/
33. receptors calcium sensing/
34. doxercalciferol.tw.
35. paracalcitol.tw.
36. zemplar.tw.
37. alfacalcidol.tw.
38. falecalcitriol.tw.
39. alfacalcidol.tw.
40. hydroxycalciferol$1.tw.
41. ergocalciferols/
42. (sevelamer or RenaGel).tw.
43. or/27-42
44. 5 and 43
45. 26 or 44
46. parathyroidectomy/
47. 5 and 46
48. (surviv$3 or outcome or mortality or morbidity).tw.
49. quality of life/
50. HRQOL.tw.
51. mortality/
52. morbidity/
53. or/48-52
54. 5 and 53
55. 45 or 54
56. limit 55 to humans

EMBASE (OVID) 1980–2006

1. cinacalcet/
2. cinacalcet.tw.
3. (mimpara or senispar).tw.
4. (AMG adj1 '073').tw.
5. calcimimetic$1.tw.
6. calcimimetic agent/
7. or/1-6
8. secondary hyperparathyroidism/
9. chronic kidney failure/
10. 'ESRD'.tw.
11. dialysis/
12. hemodialysis/
13. peritoneal dialysis/
14. continuous ambulatory peritoneal dialysis/
15. 'CAPD'.tw.
16. kidney disease/
17. 'chronic kidney disease$1'.tw.
18. 'chronic renal disease$1'.tw.
19. 'CKD'.tw.
20. renal osteodystrophy/
21. hypocalcemia/
22. parathyroid hormone/
23. 'PTH'.tw.
24. parathyroid gland/
25. or/ 8-24
26. 7 and 25
27. vitamin d derivative/
28. lanthanum carbonate/
29. phosphate binding agent/
30. calcitriol/
31. calcitriol receptor/
32. calcitriol derivative/
33. receptors calcitriol/
34. doxercalciferol/
35. paricalcitol/
36. zemplar.tw.
37. alfacalcidol/
38. falecalcitriol/

39. oxacalcitriol/
40. '25 hydroxycalciferol'/
41. calcium carbonate/
42. calcium acetate/
43. calcium sensing receptor/
44. sevelamer hydrochloride/
45. (Sevelemar or RenaGel).tw.
46. or/27-45
47. 7 and 46
48. parathyroidectomy/
49. 7 and 48
50. (surviv$3 or outcome or mortality or morbidity).tw.
51. quality of life/
52. HRQOL.tw.
53. HRQOL.ti.
54. wellbeing/
55. 7 and (50 or 51 or 52 or 53 or 54)
56. 26 or 47 or 49 or 55
57. limit 56 to human
58. from 57 keep 1-233

Quality of life and economic searches

MEDLINE (OVID)

Utility values, parathyroidectomy, 1995–2006

1 parathyroidectomy/
2 parathyroidectomy.ti,ab.
3 1 or 2
4 utility value$1.ti,ab.
5 utility analys$.ti,ab.
6 cost utility.ti,ab.
7 (health adj5 utility).ti,ab.
8 utility assessment$.ti,ab.
9 utility difference$.ti,ab.
10 (time trade$ or time tradeoff or timetradeoff).ti,ab.
11 TTO.ti,ab.
12 trade off index score$.ti,ab.
13 standard gamble$.ti,ab.
14 (utility measure or utility scor$).ti,ab.
15 quality weight$.ti,ab.
16 cost of illness/
17 utility loss.ti,ab.
18 factor analysis statistical/
19 sickness impact profile/
20 everett rogers$.ti,ab.
21 DOI.ti,ab.
22 diffusion of innovation$.ti,ab.
23 willingness to pay.ti,ab.
24 *health status/ 13338
25 (health state adj5 value$).ti,ab.
26 (utility adj5 value$).ti,ab.
27 or/4-26
28 3 and 27

Utility values, MI, 1995–2006

1 utility value$1.ti,ab.
2 utility analys$.ti,ab.
3 cost utility.ti,ab.
4 (health adj5 utility).ti,ab.
5 utility assessment$.ti,ab.
6 utility difference$.ti,ab.
7 (time trade$ or time tradeoff or timetradeoff).ti,ab.
8 TTO.ti,ab.
9 trade off index score$.ti,ab.
10 standard gamble$.ti,ab.
11 (utility measure or utility scor$).ti,ab.
12 quality weight$.ti,ab.
13 cost of illness/
14 utility loss.ti,ab.
15 factor analysis statistical/
16 sickness impact profile/
17 everett rogers$.ti,ab.
18 DOI.ti,ab.
19 diffusion of innovation$.ti,ab.
20 willingness to pay.ti,ab.
21 *health status/
22 (health state adj5 value$).ti,ab.
23 (utility adj5 value$).ti,ab.
24 or/1-23
25 myocardial infarction/
26 24 and 25
27 *myocardial infarction/
28 24 and 27
29 limit 28 to (humans and english language)
31 limit 29 to yr='1995 - 2005'

Utility values, fractures, spontaneous, 1995–2006

1 utility value$1.ti,ab.
2 utility analys$.ti,ab.
3 cost utility.ti,ab.
4 (health adj5 utility).ti,ab.
5 utility assessment$.ti,ab.
6 utility difference$.ti,ab.
7 (time trade$ or time tradeoff or timetradeoff).ti,ab.
8 TTO.ti,ab.
9 trade off index score$.ti,ab.
10 standard gamble$.ti,ab.
11 (utility measure or utility scor$).ti,ab.
12 quality weight$.ti,ab.
13 cost of illness/
14 utility loss.ti,ab.
15 factor analysis statistical/
16 sickness impact profile/
17 everett rogers$.ti,ab.
18 DOI.ti,ab.
19 diffusion of innovation$.ti,ab.
20 willingness to pay.ti,ab.
21 *health status/
22 (health state adj5 value$).ti,ab.

23 (utility adj5 value$).ti,ab.
24 or/1-23
25 fractures spontaneous/
26 pathological fracture$.ti,ab.
27 25 or 26 5327
28 24 and 27 10
29 from 28 keep 1-10
30 (osteoporosis adj5 fracture$).ti,ab.
31 24 and 30 40
32 fractures/ 30477
33 dialysis/ 10281 34 hyperparathyroidism secondary/
35 kidney failure chronic/
36 ESRD.ti,ab.
37 end stage renal disease.ti,ab.
38 renal osteodystrophy/
39 renal dialysis/
40 hemodialysis/
41 peritoneal dialysis/
42 or/33-41
43 32 and 42
44 24 and 43
45 29 or 31
46 limit 45 to (humans and english language)
47 limit 46 to yr='1995 - 2005'

Cost-effectiveness, 1966–2006

1 exp economics/
2 exp economics hospital/
3 exp economics pharmaceutical/
4 exp economics nursing/
5 exp economics medical/
6 exp 'costs and cost analysis'/
7 value of life/
8 exp models economic/
9 exp fees/ and charges/
10 exp budgets/
11 (economic$ or price$ or pricing or pharmacoeconomic$ or pharmaeconomic$).tw.
12 (cost$ or costly or costin$ or costed).tw.
13 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw.
14 (expenditure$ not energy).tw.
15 (value adj2 (money or monetary)).tw.
16 budget$.tw. (9480)
17 (economic adj2 burden).tw.
18 'resource use'.ti,ab.
19 or/1-18
20 letter.pt.
21 editorial.pt.
22 comment.pt.
23 or/20-22
24 19 not 23
25 exp hyperparathyroidism/
26 'secondary hyperparathyroidism'.ti,ab.
27 hyperparathyroidism secondary/
28 or/25-27
29 ESRD.ti,ab.
30 'end stage renal disease$'.ti,ab.
31 dialysis/
32 dialysis.ti,ab.
33 hemodialysis/
34 peritoneal dialysis/
35 peritoneal dialysis continuous ambulatory/
36 CAPD.ti,ab.
37 'chronic kidney disease$'.ti,ab.
38 'chronic renal disease$'.ti,ab.
39 'chronic kidney failure'.ti,ab.
40 'chronic renal failure'.ti,ab.
41 or/29-40
42 24 and 28 and 41
43 limit 42 to (humans and english language)

EMBASE (OVID)

Utility values, parathyroidectomy, 1980–2006

1 parathyroidectomy/
2 parathyroidectomy.ti,ab.
3 1 or 2
4 utility value$1.ti,ab.
5 utility analys$.ti,ab.
6 cost utility.ti,ab.
7 (health adj5 utility).ti,ab.
8 utility assessment$.ti,ab.
9 utility difference$.ti,ab.
10 health care utilization/
11 health state utility values/
12 (time trade$ or time tradeoff or timetradeoff).ti,ab.
13 TTO.ti,ab.
14 wilcoxon signed ranks test/
15 trade off index score$.ti,ab.
16 standard gamble$.ti,ab.
17 or/4-16 17493
18 3 and 17
19 linear regression analysis/
20 3 and 19
21 18 or 20

Utility values, fractures, spontaneous, 1980–2006

1 spontaneous fracture$.ti,ab.
2 pathologic fracture/
3 pathologic$ fracture.ti,ab.
4 1 or 2 or 3
5 utility value$.ti,ab.
6 utility analys$.ti,ab.
7 cost utility.ti,ab.
8 (health adj5 utility).ti,ab.
9 utility assessment$.ti,ab.
10 utility difference$.ti,ab.
11 (time trade off or timetradeoff or timetrade off).ti,ab.
12 TTO.ti,ab.
13 trade off index scor$.ti,ab.
14 standard gamble$.ti,ab.
15 (utility measure or utility scor$).ti,ab.

16 quality weight$.ti,ab.
17 utility loss.ti,ab.
18 or/5-17
19 4 and 18

Utility values, MI, 1995–2006

1 utility value$.ti,ab.
2 utility analys$.ti,ab.
3 cost utility.ti,ab.
4 (health adj5 utility).ti,ab.
5 utility assessment$.ti,ab.
6 utility difference$.ti,ab.
7 (time trade off or timetradeoff or timetrade off).ti,ab.
8 TTO.ti,ab.
9 trade off index scor$.ti,ab.
10 standard gamble$.ti,ab.
11 (utility measure or utility scor$).ti,ab.
12 quality weight$.ti,ab.
13 utility loss.ti,ab.
14 or/1-13
15 myocardial infarction.ti.
16 heart infarction/
17 acute heart infarction/
18 myocardial infarction.ti,ab.
19 14 and (15 or 16 or 17 or 18)
20 limit 19 to (human and english language)
21 limit 20 to yr=’1995 - 2005’ 37 DISPLAY

Cost-effectiveness, 1980–2006

1 (cost$ adj2 effective$).ti,ab.
2 (cost$ adj2 benefit$).ti,ab.
3 cost effectiveness analysis/
4 cost benefit analysis/
5 budget$.ti,ab.
6 cost$.ti.
7 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
8 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti.
9 (price$ or pricing$).ti,ab.
10 (financial or finance or finances or financed).ti,ab.
11 (fee or fees).ti,ab.
12 cost/
13 cost minimization analysis/
14 cost of illness/
15 cost utility analysis/
16 drug cost/
17 health care cost/
18 health economics/
19 economic evaluation/
20 economics/
21 pharmacoeconomics/
22 budget/
23 ‘resource use’.ti,ab.
24 economic burden.ti,ab.
25 or/1-24
26 (editorial or letter).pt.
27 25 not 26
28 ESRD.ti.
29 ‘end stage renal failure’.ti.
30 dialysis/
31 dialysis.ti,ab.
32 hemodialysis/
33 peritoneal dialysis/
34 exp hyperparathyroidism/
35 secondary hyperparathyroidism/
36 continuous ambulatory peritoneal dialysis/
37 CAPD.ti,ab.
38 chronic kidney failure/
39 ‘chronic renal disease$’.ti,ab.
40 ‘chronic kidney disease$’.ti,ab.
41 28 or 29 or 30 or 31 or 32 or 33 or 36 or 37 or 38 or 39 or 40
42 34 or 35
43 27 and 41 and 42
44 27 and 41
45 27 and 42
46 parathyroidectomy/
47 parathyroidectomy.ti,ab.
48 27 and (46 or 47)
49 limit 43 to (human and english language)

Epidemiology searches

MEDLINE (OVID) 2000–2006

1 hyperparathyroidism secondary/ep
2 *hyperparathyroidism secondary/et
3 hyperparathyroidism secondary/
4 ‘secondary hyperparathyroidism’.tw.
5 exp incidence/
6 exp prevalence/
7 (incidence or prevalence).tw.
8 exp risk-factors/ 173611
9 (etiolog$ or epidemiolog$ or aetiolog$).ti,ab.
10 1 or 2
11 or/5-9
12 11 and (3 or 4)
13 10 or 12
14 limit 13 to (humans and english language)
15 limit 14 to yr=’2000 - 2005’

EMBASE (OVID) 2000–2006

1 secondary hyperparathyroidism/ep
2 *secondary hyperparathyroidism/et
3 secondary hyperparathyroidism/
4 ‘secondary hyperparathyroidism’.tw.
5 (incidence or prevalence).tw.
6 (etiolog$ or epidemiolog$ or aetiolog$).ti,ab.
7 1 or 2 173 DISPLAY
8 (pathogenesis and hyperparathyroidism and secondary).ti.

9 (develop$ adj1 secondary adj1 hyperparathyroidism).ti.
10 (develop$ adj secondary adj1 hyperparathyroidism).ab.
11 3 and (5 or 6 or 8 or 9 or 10)
12 1 or 2 or 11
13 *secondary hyperparathyroidism/
14 13 and (5 or 6 or 8 or 9 or 10)
15 1 or 2 or 14
16 limit 15 to (human and english language and yr='2000 - 2005')
17 limit 12 to (human and english language and yr='2000 - 2005')
18 (letter or editorial or comment).pt.
19 17 not 18

Risk factors modelling: EMBASE (Ovid) 1980–2006 and MEDLINE (Ovid) 1966–2006

Combined EMBASE and MEDLINE with deduplicated set

1 esrd.tw.
2 'end stage renal disease'.ti,ab.
3 *kidney failure chronic/
4 *chronic kidney failure/
5 or/1-4
6 dialysis/ or hemodialysis/
7 CAPD.tw.
8 peritoneal dialysis/ or peritoneal dialysis continuous ambulatory/
9 continuous ambulatory peritoneal dialysis/
10 or/6-9
11 5 and 10
12 renal osteodystrophy/
13 *fracture/
14 *fractures/
15 fracture.ti.
16 *cardiovascular disease/co, si
17 *cardiovascular diseases/et, me, co
18 (cardiovascular or cardiac or vascular).ti.
19 or/12-18
20 11 and 19
21 phosphate blood level/
22 calcium blood level/
23 hypercalcemia/si
24 calcium/ec
25 *mineral metabolism/
26 phosphate/ec
27 phosphorus/bl
28 calcium/bl
29 or/21-28
30 20 and 29
31 risk.tw.
32 risk factors/
33 time factors/
34 risk assessment/
35 risk factor/
36 high risk population/
37 disease severity/
38 disease association/
39 mortality/ or morbidity/
40 'cardiovascular mortality'.ti,ab.
41 'cardiovascular risk factor$1'.ti,ab.
42 death.ti,ab.
43 or/31-42
44 30 and 43
45 limit 44 to english language
46 limit 45 to humans
47 from 46 keep 1-67
48 remove duplicates from 47
49 from 48 keep 1-66
50 from 48 keep 1-46
51 from 50 keep 1-46
52 from 48 keep 47-66
53 from 52 keep 1-20
54 parathyroid hormone/
55 20 and 43 and 54
56 limit 55 to english language
57 limit 56 to humans
58 57 not 48
59 remove duplicates from 58

Quality of life searches

MEDLINE (OVID)

Search 1: QoL – ESRD, dialysis, 1995–2006

1 'end stage renal failure'.ti,ab
2 quality of life/
3 (hrqol or qol).ti,ab.
4 quality adjusted life year/
5 quality adjusted life.ti,ab.
6 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
7 disability adjusted life.ti,ab.
8 daly$.ti,ab. 353
9 (euroqol or euro qol or eq5d).ti,ab.
10 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
11 quality of well being.ti,ab.
12 quality of wellbeing.ti,ab.
13 qwb.ti,ab.
14 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
15 or/2-14 54094
16 esrd.ti,ab. 4437
17 dialysis.ti. 20099
18 end stage renal disease.ti,ab.
19 *renal dialysis/
20 1 or 16 or 17 or 18 or 19
21 15 and 20 1073 DISPLAY
22 limit 21 to (humans and english language)
23 child/

24 infant/
25 22 not 23
26 25 not 24
27 (letter or editorial or comment).pt.
28 26 not 27
29 limit 28 to (humans and english language and yr="1995 - 2005")
30 limit 29 to yr="2000 - 2005"

Search 2: QoL – primary or secondary hyperparathyroidism or parathyroidectomy, 1996–2005

1 quality of life/
2 (hrqol or qol).ti,ab.
3 quality adjusted life year/
4 quality adjusted life.ti,ab.
5 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
6 disability adjusted life.ti,ab.
7 daly$.ti,ab.
8 (euroqol or euro qol or eq5d).ti,ab.
9 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
10 quality of well being.ti,ab.
11 quality of wellbeing.ti,ab.
12 qwb.ti,ab.
13 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
14 or/1-13
15 child/
16 infant/
17 (letter or editorial or comment).pt.
18 hyperparathyroidism secondary/
19 'secondary hyperparathyroidism'.ti,ab.
20 14 and (18 or 19)
21 from 20 keep 1-9
22 hyperparathyroidism/
23 14 and 22
24 parathyroidectomy/
25 14 and 24
26 20 or 23 or 25
27 KDQOL.ti,ab.
28 'kidney disease quality of life'.ti,ab.
29 18 and (27 or 28)
30 19 and (27 or 28)
31 22 and (27 or 28)
32 24 and (27 or 28)
33 29 or 30 or 32 2
34 26 or 33 29
35 limit 34 to (humans and English language)

Appendix 5

Flowchart for included trials

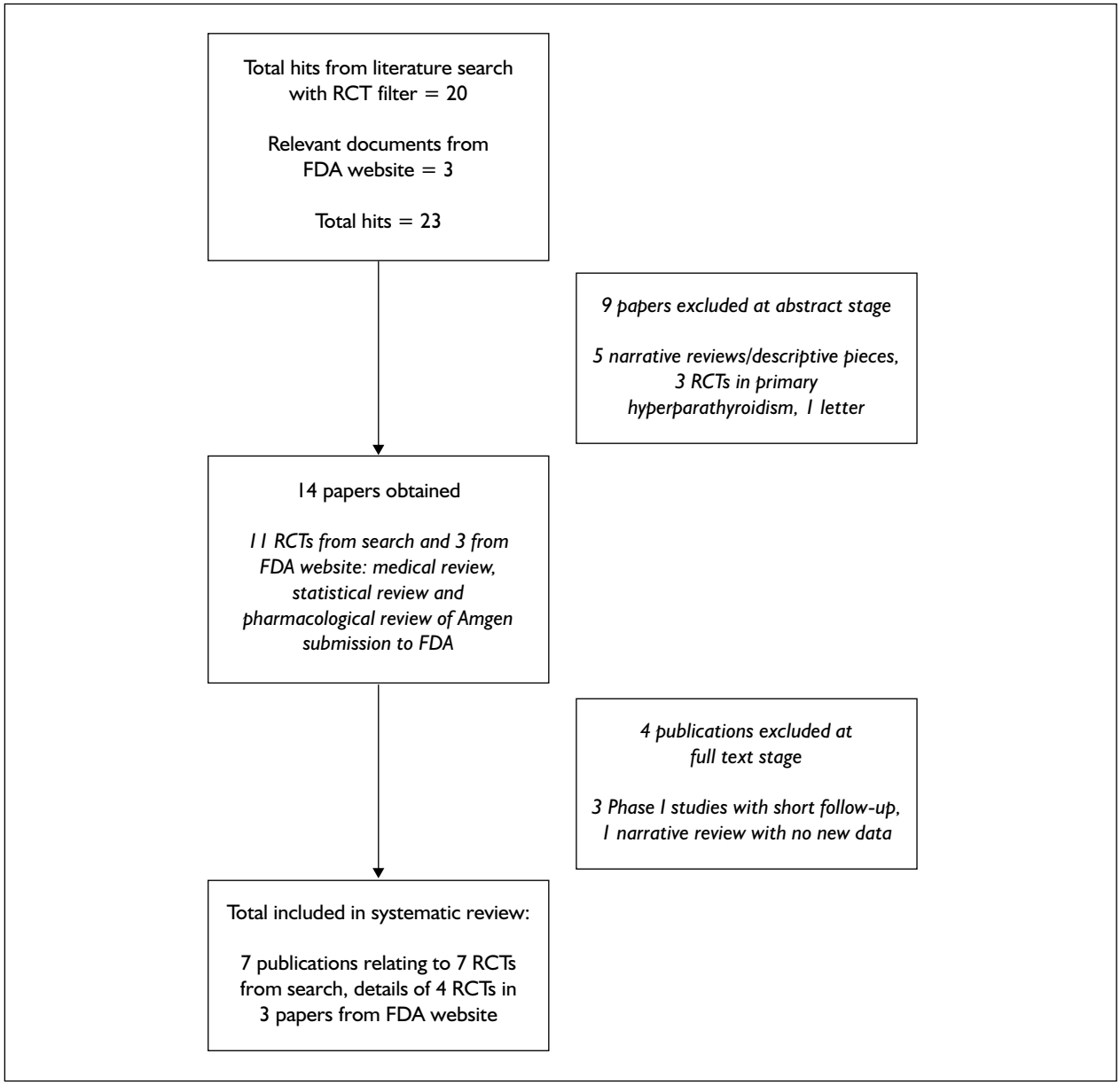

FIGURE 23 *Flowchart for trials included in the review*

Appendix 6

Excluded studies

Goodman WG, Frazao JM, Goodkin DA, Turner SA, Liu W, Coburn JW. A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. *Kidney Int* 2000;**58**:436–45.
Abstract: *Background*: The calcimimetic agent R-568 lowers plasma parathyroid hormone (PTH) levels in hemodialysis patients with mild secondary hyperparathyroidism, but its efficacy in those with more severe secondary hyperparathyroidism has not been studied. *Methods*: Twenty-one patients undergoing hemodialysis three times per week with plasma PTH levels between 300 and 1200 pg/mL were randomly assigned to 15 days of treatment with either 100 mg of R-568 ($N = 16$) or placebo ($N = 5$). Plasma PTH and blood ionized calcium levels were measured at intervals of up to 24 hours after oral doses on days 1, 2, 3, 5, 8, 11, 12, and 15. *Results*: Pretreatment PTH levels were 599 ± 105 (mean ± SE) and 600 ± 90 pg/mL in subjects given R-568 or placebo, respectively, and values on the first day of treatment did not change in those given placebo. In contrast, PTH levels fell by 66 ± 5%, 78 ± 3%, and 70 ± 3% at one, two, and four hours, respectively, after initial doses of R-568, remaining below pretreatment values for 24 hours. Blood ionized calcium levels also decreased after the first dose of R-568 but did not change in patients given placebo. Despite lower ionized calcium concentrations on both the second and third days of treatment, predose PTH levels were 422 ± 70 and 443 ± 105 pg/mL, respectively, in patients given R-568, and values fell each day by more than 50% two hours after drug administration. Predose PTH levels declined progressively over the first nine days of treatment with R-568 and remained below pretreatment levels for the duration of study. Serum total and blood ionized calcium concentrations decreased from pretreatment levels in patients given R-568, whereas values were unchanged in those given placebo. Blood ionized calcium levels fell below 1.0 mmol/L in 7 of 16 patients receiving R-568; five patients withdrew from study after developing symptoms of hypocalcemia, whereas three completed treatment after the dose of R-568 was reduced. *Conclusions*. The calcimimetic R-568 rapidly and markedly lowers plasma PTH levels in patients with secondary hyperparathyroidism caused by end-stage renal disease.

Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W, *et al*. The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 2002;**13**:1017–24.
Abstract: Treatment with vitamin D sterols can lower plasma parathyroid hormone (PTH) in many patients with secondary hyperparathyroidism due to end-stage renal disease, but hypercalcemia, hyperphosphatemia, or both often develop during treatment. As such, alternative therapeutic approaches to managing excess PTH secretion are needed. Calcimimetic agents directly inhibit PTH secretion by activating the calcium-sensing receptor in the parathyroid glands, but clinical experience with them is limited. Fifty-two hemodialysis patients with secondary hyperparathyroidism were given single orally administered doses of the calcimimetic agent AMG 073 ranging from 5 to 100 mg, or placebo. Plasma PTH levels decreased 2 h after 25-, 50-, 75-, or 100-mg doses, falling by a maximum of 43 ± 29%, 40 ± 36%, 54 ± 28%, or 55 ± 39%, respectively. Plasma PTH levels decreased in all patients given doses of ≥25 mg but did not change in those who received placebo. In patients treated with daily doses of 25 or 50 mg of AMG 073 for 8 d, plasma PTH levels declined for the first 3 to 4 d and remained below baseline values after 8 d of treatment. Serum calcium concentrations also decreased by 5 to 10% from pretreatment levels in patients given 50 mg of AMG 073 for 8 d, but values were unchanged in those who received lower doses. Serum phosphorus levels and values for the calcium–phosphorus ion product both decreased after treatment with AMG 073. Thus, 8 d of treatment with AMG 073 effectively lowers plasma PTH levels and improves several disturbances in mineral metabolism that have been associated with soft tissue and vascular calcification and with adverse cardiovascular outcomes in patients with end-stage renal disease.

Ohashi N, Uematsu T, Nagashima S, Kanamaru M, Togawa A, Hishida A, *et al*. The calcimimetic agent KRN 1493 lowers plasma parathyroid hormone and ionized calcium concentrations in patients with chronic renal failure on haemodialysis

both on the day of haemodialysis and on the day without haemodialysis. *Br J Clin Pharmacol* 2004; **57**:726–34.
Abstract: *Aims*: Treatment with vitamin D sterols can lower plasma parathyroid hormone (PTH) in patients with secondary hyperparathyroidism; however, hypercalcaemia, hyperphosphataemia, or both, often develop. Calcimimetic agents, employed in alternative therapeutic approaches, directly inhibit PTH secretion by activating the calcium-sensing receptor in the parathyroid glands. *Methods*: In this study, patients were given orally 25, 50, and 100 mg doses of the calcimimetic agent KRN 1493 each on two occasions, on the day of haemodialysis and on the day without haemodialysis. *Results*: In the pharmacokinetic results, because the clearance of KRN 1493 by haemodialysis was much smaller than the systemic clearance, the influence of haemodialysis was not remarkable. In the pharmacodynamic study, on both the days with or without haemodialysis, plasma PTH concentrations decreased in a dose-dependent manner. Serum calcium concentrations decreased in association with the decrease in plasma PTH concentrations. Mild dose-dependent adverse effects (mainly nausea) were seen after the administration of KRN 1493 on both the day of haemodialysis and the day without haemodialysis. *Conclusions*: We conclude that the pharmacokinetics of KRN 1493 after a single administration were similar on the day of haemodialysis and the day without haemodialysis. KRN 1493 is safe and effective in suppressing PTH secretion and serum calcium concentrations on the day of haemodialysis and on the day without haemodialysis in patients with secondary hyperparathyroidism.

Szczech LA. The impact of calcimimetic agents on the use of different classes of phosphate binders: results of recent clinical trials. *Kidney Int Suppl* 2004;(90):S46–8.
Abstract: Calcimimetic agents bind to and activate the calcium-sensing receptor in the parathyroid glands, lowering the threshold for its activation by extracellular calcium and diminishing parathyroid hormone release from parathyroid cells. In three large randomized, controlled trials, cinacalcet given at doses of 30 to 180 mg orally each day was associated with effective reduction in parathyroid hormone levels over 26 weeks compared with placebo, and was consistently associated with a decrement in serum calcium, phosphorus levels, as well as a decrement in calcium–phosphorus product. In one study, there was a 5% incidence of hypocalcemia (serum calcium levels < 7.5 mg/dL on at least two consecutive measurements) among patients receiving cinacalcet, and less than 1% of patients receiving standard therapy ($p < 0.0001$). While there were no demonstrated differences between groups with regard to use of phosphate binders and vitamin D sterols in these randomized controlled trials, arguably, the combination of the effects on serum calcium, phosphorus, and calcium–phosphorus product may bring increased focus on the increased mortality risk associated with hypocalcemia.

Appendix 7

Data extraction tables

Block and colleagues (2004)[70]

TABLE 82 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Block *et al.*, 2004 *Country:* International: North America, Europe and Australia *Setting:* Multiple centres (125 sites) *Recruitment dates*: December 2001 to January 2003 *Study design:* Combined analysis of two identical Phase III randomised, double-blind, placebo-controlled trials	*Total number:* 741 Cinacalcet $n = 371$; placebo $n = 370$ *Inclusion criteria:* • Mean plasma iPTH level of ≥31.8 pmol/l established by three measurements obtained within a 30-day screening period • ≥18 years of age and in medically stable condition • Treated with HD three times per week for at least 3 months *Exclusion criteria:* • Evidence of cancer, active infection, diseases known to cause hypercalcaemia or serum Ca^{2+} level ≤2.1 mmol/l, corrected for albumin • Subjects receiving drugs such as flecainide, thioridazine and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolised by P-450 2D6		After screening period, subjects were randomised to cinacalcet or placebo *Intervention:* Cinacalcet *Intervention regimen:* 12-week dose-titration phase • Subjects initially received 30 mg cinacalcet (or placebo) orally, once daily • Doses were increased sequentially every 3 weeks during the dose-titration phase to 60, 90, 120 and 180 mg once daily – Increases in dose were permitted if: ◦ iPTH > 21.2 pmol/l and ◦ serum Ca^{2+} >1.95 mmol/l – Dose was not increased if: ◦ symptoms of hypocalcaemia or ◦ serum Ca^{2+} <1.95 mmol/l or ◦ adverse event that precluded an increase in the dose – Dose was reduced if: ◦ iPTH < 10.6 pmol/l on three consecutive study visits or ◦ adverse event required a reduction in the dose	*Primary outcome measure:* • Proportion of subjects achieving mean PTH level of ≤26.5 pmol/l during efficacy assessment phase. *Secondary measures:* • Proportion of subjects with reduction from baseline of ≥30% in mean PTH • Percentage change in values for – PTH – Ca^{2+} – phosphorus – Ca × P *Method of assessing outcomes:* • Plasma PTH levels, serum Ca^{2+} and phosphorus levels were measured at each study visit before haemodialysis – plasma PTH levels were measured using Nichols Allegro IRMA – full-length PTH was measured using Nichols BioIntact PTH assay • Serum levels of bone-specific alkaline phosphatase were measured at baseline and 26 weeks – bone-specific alkaline phosphatase was measured using Tandem-R Ostase two-site IRMA • Biochemical measurements were made at three regional reference laboratories (Europe, North America, Australia) *Length of follow-up:* Study duration 26 weeks

	Placebo	Cinacalcet
n	370	371
Age (years)	55 (15)	54 (14)
Gender		
Male	62	61
Female	38	39
Race		
White	61	56
Black	32	35
Other	7	9
Duration of dialysis (months), mean (SD)	72 (68)	72 (63)
Concomitant diabetes (%)	29	30
Use of vitamin D sterols (%)	67	66
Use of phosphate binders (%)	93	92

continued

TABLE 82 *Study details (cont'd)*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
			14-week efficacy assessment phase • Dose adjustments were permitted at 4-week intervals as above *Comparator regimen:* Placebo *Concurrent treatment:* • Concurrent phosphate binder permitted without restriction • Vitamin D sterols permitted – Dose increase permitted if: ◦ iPTH increased by >50% from baseline or ◦ serum Ca^{2+} <2.1 mmol/l or ◦ symptomatic hypocalcaemia – Dose reduction permitted if: ◦ serum Ca^{2+} >2.75 mmol/l or ◦ serum phosphorus > 2.1 mmol/l or ◦ Ca × P ≥5.65 $mmol^2/l^2$ or ◦ iPTH < 10.6 pmol/l on three consecutive study visits and the subject was on the lowest dose of cinacalcet *Note:* Proportion of subjects with PTH >84.8 pmol/l was limited to 20% of the total	

TABLE 83 *Results*

Primary outcomes

	Placebo (n = 370)	Cinacalcet (n = 371)	p
Mean PTH ≤250 pg/ml	19 (5%)	160 (43%)	<0.001

Secondary outcomes

	Placebo (n = 370)	Cinacalcet (n = 371)	p
≥30% reduction in PTH level	42 (11%)	239 (64%)	<0.001
≥30% reduction in PTH level (%) stratified according to baseline PTH level:			
300–500 pg/ml	10%	61%	<0.001
501–800 pg/ml	15%	69%	<0.001
>800 pg/ml	7%	63%	<0.001

Biochemistry results

	Placebo	From graph		Mean ± SE		Cinacalcet	From graph		Mean ± SE		
	Baseline	Week 12	Week 26	Week 13–26	% Change	Baseline	Week 12	Week 26	Week 13–26	% Change	p
Plasma PTH (pg/ml)	642 ± 19	680	660	693 ± 23	9 ± 2	643 ± 18	380	340	374 ± 19	–43 ± 2	<0.001 between groups
Plasma full-length PTH (pg/ml) (North American subjects only n = 410)	337 ± 16	375	375	396 ± 18	23 ± 4	326 ± 14	200	200	200 ± 15	–38 ± 3	<0.001 between groups
Serum Ca^{2+} (mg/dl)	9.9 ± 0.0			9.9 ± 0.0	0.4 ± 0.3	9.9 ± 0.0			9.2 ± 0.0	–6.8 ± 0.4	<0.001 between groups
Serum phosphorus (mg/dl)	6.2 ± 0.1			6.0 ± 0.1	0.2 ± 1.3	6.2 ± 0.1			5.6 ± 0.1	–8.4 ± 1.3	<0.001 between groups
Ca × P (mg^2/dl^2)	61 ± 0.8	59	60	60 ± 0.8	0.5 ± 1.3	62 ± 0.8	48	53	51 ± 0.8	–14.6 ± 1.3	<0.001 between groups
Bone-specific alkaline phosphate (ng/ml) Median (IQR)	24.2 (16.5 to 36.8)		22.6 (14.3 to 36.4)		–4 (–32.1 to 29.6)	23.3 (16.5 to 35.3)		15.6 (9.8 to 23.6)		–35.1 (–58.6 to –1.7)	
PTH level <250 pg/ml (% of subjects)		7%	8%				46%	58%			

continued

TABLE 83 *Results (cont'd)*

Biochemistry results (*continued*)

	Placebo	From graph		Mean ± SE		Cinacalcet	From graph		Mean ± SE		
	Baseline	**Week 12**	**Week 26**	**Week 13–26**	**% Change**	**Baseline**	**Week 12**	**Week 26**	**Week 13–26**	**% Change**	***p***
% Change in PTH level (relative to baseline)	0	9%	9%		9 ± 2	0	–46%	–48%		–43 ± 2	<0.001 between groups

Adverse events

	Placebo	Cinacalcet	*p*
Mortality	2%	2%	
Withdrawal due to adverse events	7%	15%	
Withdrawal due to nausea or vomiting	<1%	<5%	
≥1 adverse event reported	346/369 (94%)	333/365 (91%)	=0.21
Nausea	19%	32%	<0.001
Vomiting	16%	30%	<0.001
Upper respiratory tract infection	13%	7%	=0.007
Hypotension	12%	6%	=0.014
Serum Ca^{2+} <7.5 mg/dl on ≥2 consecutive measurements	<1%	5%	<0.001

TABLE 84 *Comments*

Methodological comments	
Selection/randomisation	Randomisation methods not detailed
	Stratification according to disease severity and baseline values for Ca × P
	No more than 20% of population could have PTH > 84.8 pmol/l
Groups similar at baseline?	Yes. No significant differences, but 5% more white race in placebo group and 4% more were using calcium-containing only phosphate binders
Eligibility criteria stated?	Yes
Blinding	Stated as double blind
	Method not detailed
Outcome measures	Objective
ITT	Yes
Protocol violations specified	No

continued

TABLE 84 *Comments (cont'd)*

Follow-up/attrition	All subjects accounted for? No, 32% of cinacalcet subjects did not complete 26 weeks of treatment. Reasons for 25% subjects' withdrawal provided 22% of placebo subjects did not complete 26 weeks of treatment. Reasons for 16% subjects' withdrawal provided Withdrawal specified?

	Placebo	**Cinacalcet**
Completed titration	325	306
Completed full 26 weeks	78%	68%
Discontinued due to AE	7%	15%
Withdrew consent	3%	4%
Kidney transplant	4%	4%
Died	2%	2%

Data analysis	Statistical tests used: • Combined analysis of two Phase III randomised, double-blind controlled trials • Cochran–Mantel–Haenszel test, stratified according to baseline PTH levels and Ca × P values, was used to examine differences between treatment groups during the efficacy assessment phase • Generalised Cochran–Mantel–Haenszel test was used for continuous variables • Cochran–Mantel–Haenszel tests were used to estimate relative risk of primary end-point in cinacalcet group, compared with placebo, according to age, gender, race, duration of dialysis, baseline biochemical variable, presence or absence of diabetes, and use of vitamin D sterols • Logistic regression was used to identify factors that predicted a reduction in PTH value of ≥30% • *t*-Tests used to compare efficacy period with baseline for continuous variables
Power calculation at design?	Not stated
Generalisability	Few exclusion criteria stated in publication High proportion of non-Caucasians No more than 20% of population could have PTH >84.8 pmol/l
Conflicts of interest	Studies supported by Amgen. Trial and lead authors substantially funded by Amgen and other pharmaceutical companies

General comments
Combined analysis of 2000172 and 2000183

Cunningham and colleagues (2005)[71]

TABLE 85 *Study details*

Study	Subjects	Subject characteristics		Intervention	Outcome measures
Cunningham *et al.*, 2005 *Country:* Pooled analysis of four trials International: Europe, North America and Australia Study 1: USA and Europe Study 2: North America Study 3: Europe and Australia Study 4: North America and Australia *Setting:* Multiple centres (202 sites) *Recruitment dates:* Not stated *Study design:* Pooled analysis of a 12-month Phase III trial and three 6-month Phase III trials All trials were randomised, double-blind and placebo controlled	*Total number:* 1184 Cinacalcet $n = 697$; placebo $n = 487$ *Inclusion criteria:* • ≥18 years old • PTH level ≥300 pg/ml • Albumin-corrected serum Ca^{2+} ≥8.4 mg/dl • Subjects had received HD three times per week for a minimum of 1–3 months or PD for ≥1 month *Exclusion criteria:* • Parathyroidectomy or MI within 3–6 months of the start of treatment • Change in vitamin D therapy within 30 days of the start of treatment • Use of flecainide, lithium, thoridazine, haloperidol or tricyclic antidepressant (except for amitriptyline) therapy within 21 days of the start of the trial • Gastrointestinal disturbances that could impair the absorption of the study drug • The existence of an unstable medical condition • Pregnancy or nursing			Study 1 (Phase II trial): 24-week titration phase and 28-week assessment phase Studies 2 and 3 (Phase III trials): 12-week dose-titration phase followed by 14-week evaluation phase Study 4 (Phase III study): 16-week dose-titration phase followed by 10-week evaluation phase *Intervention:* Cinacalcet *Intervention regimen:* • Subjects initially received 30 mg cinacalcet orally, once daily • Dose increased, in 20-mg (study 1) or 30-mg (studies 2–4) increments from 30 to 180 mg per day at 3- or 4-weekly intervals *Comparator regimen:* Placebo *Concurrent treatment:* • Phosphate binders were permitted, with dose changes allowed at the discretion of the investigator • Vitamin D sterols permitted – Dose reduction permitted if: ◦ serum Ca^{2+} ≥11 mg/dl or ◦ serum phosphorus ≥6.5 mg/dl or ◦ Ca × P ≥70 mg^2/dl^2	*Primary outcome measure:* • Parathyroidectomy • Fracture • Cardiovascular hospitalisation • All-cause and non-cardiovascular hospitalisation • Health-related QoL (SF-36) (not study 1) • Cognitive functioning scale from the KDQoL instrument (KDQoL-CF) (not study 1) *Method of assessing outcomes:* • Outcomes were identified prospectively based on reasons for discontinuation and adverse event data collected in all trials • Hospitalisations captured from adverse event form with reason for hospitalisation provided for each event • Reported events were confirmed using source document verification, and the medical records of all subjects were monitored during the study to facilitate complete event capture • Touch-screen technology for translated and culturally adapted versions of the subject-reported outcome instruments *Length of follow-up:* Studies 2–4 (Phase III trials): 26-week duration Study 1 (Phase II trial): 52-week duration

	Placebo	Cinacalcet
n	487	697
Age (years)		
Age at randomisation (years), mean ± SD	54.7 ± 14.6	53 ± 14.2
<65 years*	348 (71%)	538 (77%)
≥65 years	139 (29%)	159 (23%)
Gender		
Male	306 (63%)	425 (61%)
Female	181 (37%)	272 (39%)
Race		
White*	270 (55%)	332 (48%)
Black	166 (34%)	265 (38%)
Other	51 (10%)	100 (14%)
Duration of dialysis	70.1 ± 67.1	65.8 ± 59.9
Dialysis modality		
HD*	475 (98%)	663 (95%)
PD	12 (2%)	34 (5%)
Concomitant diabetes	154 (32%)	217 (31%)
Use of vitamin D sterols	327 (67%)	453 (65%)
Use of phosphate binders	451 (93%)	648 (93%)
Plasma PTH (pg/ml), mean (SD)	682 (399)	731 (531)
Serum Ca × P (mg^2/dl^2), mean (SD)	61.1 (15.1)	60.9 (16.0)

continued

TABLE 85 *Study details (cont'd)*

Study	Subjects	Subject characteristics		Intervention	Outcome measures
A 6-month extension trial of participants in two of the Phase III studies was also included				– Dose increase permitted if: ◦ serum Ca^{2+} <8.4 mg/dl *Notes:* Some of the trials limited the proportion of subjects with PTH >800 pg/ml to 20% of the total (studies 2 and 3)	
			Placebo	**Cinacalcet**	
		Serum calcium (mg/dl), mean (SD)	9.9 (0.8)	9.9 (0.8)	
		Serum phosphorus (mg/dl), mean (SD)	6.2 (1.5)	6.2 (1.7)	
		*Significantly different at baseline.			

CF, cognitive functioning.

TABLE 86 *Results*

Primary outcomes				
	Events per 100 patient-years		**RR for cinacalcet (95% CI)**	***p***
	Placebo	**Cinacalcet**		
Mortality	7.4	5.2	0.81 (0.45 to 1.45)	0.47
CV hospitalisation	19.7	15.9	0.61 (0.43 to 0.86)	0.005
All-cause hospitalisation	71.0	67.0	1.03 (0.87 to 1.22)	0.74
Fracture	6.9	3.2	0.46 (0.22 to 0.95)	0.04
Parathyroidectomy	4.1	0.3	0.07 (0.01 to 0.55)	0.009
Associated statistics				
	Placebo (*n* = 487)	**Cinacalcet (*n* = 697)**		
CV hospitalisation (*n*)	77	72		
Ischaemic heart disease	29	22		
Heart failure	19	26		
Arrythmia	18	17		
Peripheral vascular disease	7	2		
Stroke	4	5		
No. of fractures of lower extremities	7	11		
No. of other fractures	13	1		
No. of parathyroidectomies	12	1		
Changes in HRQoL scores (baseline to end of study) (+ scores indicate improvement)	**Placebo**	**Cinacalcet**	**Difference in score change (placebo-cinacalcet)**	***p***
SF-36 PCS	–0.8	+0.5	1.3	0.01
SF-36 MCS			0.3 (graph)	ns
SF-36 physical functioning			1.0 (graph)	ns
SF-36 role limitation – physical			1.2 (graph)	ns
SF-36 social functioning			0.5 (graph)	ns
SF-36 vitality			0.5 (graph)	ns
SF-36 role limitation – emotional			0.5 (graph)	ns
SF-36 mental health			0.7 (graph)	ns
Bodily pain scale	–1.0	+0.6	1.6	0.03
General health perception scale	–1.0	+0.2	1.2	0.02
Decline in self-reported physical function (PCS decrease >5 points) (% subjects)	23%	21%		0.52
Improvement in self-reported physical function (PCS increase >5 points) (% subjects)	20%	26%		0.03
Mean change in KDQoL-CF score	–0.8	+0.2	1.0	0.12

MCS, mental component score; PCS, physical component score.

TABLE 87 *Comments*

Methodological comments	
Selection/randomisation	All four trials randomised by computer-generated system Stratification in two Phase III trials (studies 2 and 3) according to baseline PTH and Ca × P Remaining Phase III study (study 4) randomised 3:1 (cinacalcet: placebo) and stratified according to dialysis modality and baseline PTH No stratification in Phase II study (study 1)
Groups similar at baseline?	Yes Characteristics with differences $p < 0.05$ were: • age <65 years (cinacalcet 77% vs control 71%), >65 years (cinacalcet 23% vs control 29%) $p = 0.025$ • age at randomisation (cinacalcet 53 ± 14.2 vs control 54.7 ± 14.6) $p = 0.037$ • ethnicity $p = 0.018$ • dialysis modality $p = 0.034$
Eligibility criteria stated?	Yes
Blinding	Not detailed: "blinds were maintained through numbered drug bottles" Subjects, provider and assessors
Outcome measures	Objective measures for primary outcomes; however, these were obtained from safety data and were not adjudicated Subjective QoL measures were also assessed
ITT	Yes, but subjective data excluded those with missing baseline ($n = 22$) and efficacy phase data ($n = 238$)
Protocol violations specified	No
Follow-up/attrition	All subjects accounted for? Not detailed Withdrawal specified? Not detailed Withdrawal reasons given? Not detailed
Data analysis	Statistical tests used: • Cox proportional hazards models, stratified by study, used for parathyroidectomy, fracture and death • Andersen–Gill model for hospitalisations • Kaplan–Meier time to event method for survival • *t*-Tests using least squares method (LSM) for the SF-36 and KDQoL-CF scores
Power calculation at design?	Not stated
Generalisability	Effect of limiting proportion of subjects with PTH >800 pg/ml High proportion of non-Caucasians
Conflicts of interest	Two authors are employees of Amgen. One author is a former employee of Amgen. Two authors served as scientific advisors to Amgen and have received financial support from Amgen
General comments	
Combined analysis of 2000172, 2000183, 2000188 and 2010141	

Lien and colleagues (2005)[75]

TABLE 88 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Lien *et al.*, 2005 *Country:* USA *Setting:* Single centre *Recruitment dates:* Not stated *Study design:* Part of randomised, double-blind, placebo-controlled, multicentre trials to evaluate the safety and efficacy of cinacalcet for treating SHPT	*Total number:* 14 Cinacalcet $n = 8$; placebo $n = 6$ (ten receiving haemodialysis and four who had stage 4 CKD (predialysis subjects) *Inclusion criteria:* • Mean plasma iPTH level of ≥31.8 pmol/l established by three measurements obtained within a 30-day screening period • ≥18 years of age and in medically stable condition • Treated with HD three times per week for at least 3 months *Exclusion criteria:* • Evidence of cancer, active infection, diseases known to cause hypercalcaemia or serum Ca^{2+} level ≤2.1 mmol/l, corrected for albumin • Subjects receiving drugs such as flecainide, thioridazine and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolised by P-450 2D6 NB. Inclusion/exclusion criteria taken from Block *et al.*, 2004,[70] as referenced in this paper	**Placebo** / **Cinacalcet** *n*: 6 / 8 Age (years), mean (SD): 47 (17) / 55 (16) Gender* Male: 5 / 4 Female: 1 / 4 Race Caucasian: 2 / 4 African–American: 1 / 1 Hispanic: 3 / 3 Dialysis status HD: 4 / 6 Predialysis: 2 / 2 *Significant difference in gender composition of the groups ($p < 0.05$) Concomitant vitamin D used by all but one of the HD patients (group not stated), not used in any predialysis patients	NB. Study design section taken from Block *et al.*, 2004,[70] which was referenced in this paper *Intervention:* Cinacalcet *Intervention regimen:* 12-week dose-titration phase • Subjects initially received 30 mg cinacalcet (or placebo) orally, once daily • Doses were increased sequentially every 3 weeks during the dose-titration phase to 60, 90, 120 and 180 mg once daily – Increases in dose were permitted if: ◦ iPTH ≥21.2 pmol/l and ◦ serum Ca^{2+} ≥1.95 mmol/l – Dose was not increased if: ◦ symptoms of hypocalcaemia or ◦ serum Ca^{2+} <1.95 mmol/l or ◦ adverse event that precluded an increase in the dose – Dose was reduced if: ◦ iPTH <10.6 pmol/l on three consecutive study visits ◦ adverse event required a reduction in the dose	*Primary outcome measure:* Not stated; however, study rationale was to compare BMD measurements between groups as this centre routinely recorded this as part of routine care • Lumbar spine (L2–4) BMD • Total proximal femur BMD including femoral neck, greater trochanter and proximal femur shaft *Secondary measures:* Serum levels of iPTH, calcium, phosphorus and alkaline phosphatase *Method of assessing outcomes:* • Lumbar spine (L2–4) and total proximal femur BMD measured by GE Medical Systems Lunar in-office DEXA scanner at baseline and study end • Plasma iPTH and serum calcium and phosphorus levels were measured at each study visit before the dose of study medication • Serum levels of alkaline phosphatase were measured at baseline and at the end of the study *Length of follow-up:* 26 weeks for HD subjects, 18 weeks for predialysis subjects

continued

TABLE 88 *Study details (cont'd)*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
			14-week maintenance phase • Dose adjustments were permitted at 4-week intervals as above Predialysis subjects • As above, but efficacy assessment phase shortened to 6 weeks *Comparator regimen:* Placebo *Concurrent treatment:* • Concurrent phosphate binder permitted without restriction • Vitamin D sterols permitted – Dose increase permitted if: ◦ iPTH increased by >50% from baseline or ◦ serum Ca^{2+} <2.1 mmol/l or ◦ symptomatic hypocalcaemia – Dose reduction permitted if: ◦ serum Ca^{2+} ≥2.75 mmol/l or ◦ serum phosphorus ≥2.1 mmol/l or ◦ Ca × P ≥5.65 $mmol^2/l^2$ or ◦ iPTH <10.6 pmol/l on three consecutive study visits and the subject was on the lowest dose of cinacalcet	

DEXA, dual-energy X-ray absorptiometry.

TABLE 89 *Results*

Primary outcomes

	Placebo (n = 6)		Cinacalcet (n = 8)	
	Baseline (mean ± SD)	**End of study (mean ± SD)**	**Baseline (mean ± SD)**	**End of study (mean ± SD)**
BMD and T-scores				
Femur BMD (g/cm^2)	0.921 ± 0.250	0.904 ± 0.244*	0.945 ± 0.169	0.961 ± 0.174*
Femur T-score	–1.03 ± 1.56	–1.30 ± 1.70	–0.76 ± 1.10	–0.65 ± 1.16*
Lumbar spine BMD (g/cm^2)	1.156 ± 0.276	1.149 ± 0.288	1.283 ± 0.219	1.269 ± 0.221
Lumbar spine T-score	–0.72 ± 2.31	–0.63 ± 2.23	–0.52 ± 1.69	–0.39 ± 1.69

Secondary outcomes

	Placebo (n = 6)		Cinacalcet (n = 8)	
	Baseline (mean ± SD)	**End of study (mean ± SD)**	**Baseline (mean ± SD)**	**End of study (mean ± SD)**
Chronic HD	n = 4		n = 6	
iPTH (pg/ml)	1009 ± 584	1295 ± 642	912 ± 296	515 ± 359*
Ca^{2+} (mg/ml)	10.8 ± 1.0	10.4 ± 1.0	9.7 ±1.0	9.2 ± 0.9
Phosphorus (mg/dl)	5.9 ± 1.3	6.5 ± 2.6	7.1 ± 2.5	6.4 ± 1.6
Alkaline phosphatase (U/l)	279 ± 371	223 ± 176	152 ± 72	128 ± 48
Predialysis	n = 2		n = 2	
GFR	21 ± 6	22 ± 2	25 ± 3	27 ± 11
iPTH (pg/ml)	207 ± 43	179 ± 33	210 ± 46	57 ± 51*
Ca^{2+} (mg/ml)	9.6 ± 0.2	9.4 ± 0.4	9.3 ± 0.6	8.8 ± 0.7
Phosphorus (mg/dl)	4.0 ± 0.6	3.5 ± 0.3	3.8 ± 0.6	3.9 ± 0.6
Alkaline phosphatase (U/l)	73 ± 6	68 ± 18	90 ± 8	97 ± 37

*$p < 0.05$ vs before treatment.

TABLE 90 *Comments*

Methodological comments	
Selection/randomisation	Completers at one centre participating in two separate RCTs
Groups similar at baseline?	No, placebo group had more male subjects ($p < 0.05$; however, part of larger multicentre trial so not designed to be similar)
Eligibility criteria stated?	No details. Reference Block *et al.*, 2004[70]
Blinding	Stated as double blind. No details
Outcome measures	Objective
ITT	No
Protocol violations specified	One HD subject admitted non-compliance
Follow-up/attrition	Analysis was on 'completers' from two other trials
Data analysis	Statistical tests used: • Statistical comparisons between pre- and post-treatment values were performed by paired, one-tailed Student's *t*-tests • For comparisons of data between the cinacalcet and placebo groups, non-paired, two-tailed Student's *t*-tests were used
Power calculation at design?	No. Part of larger study
Generalisability	Small sample of subjects at one centre Groups not well matched for age, race or dialysis status Substantial differences in baseline PTH between HD and predialysis subjects High proportion of non-Caucasian subjects
Conflict of interest	Supported by Amgen (study 20000188 and study 20000239)

General comments

"Study supported by Amgen Inc (study 2000188 and study 20000239)"; however, dose titration and efficacy assessment phase length do not match up with these trials
Were all completers at centre included?
Lumbar spine BMD decreased in both groups but T-score improved.

Lindberg and colleagues (2003)[72]

TABLE 91 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Lindberg *et al.*, 2003 *Country:* USA and Canada *Setting:* Multiple centres (25) *Recruitment dates:* Not stated *Study design:* Randomised, double-blind, placebo-controlled trial	*Total number:* 78 Cinacalcet $n = 39$; placebo $n = 39$ *Inclusion criteria:* • Treated for at least 3 months with HD • iPTH levels ≥300 pg/ml despite receiving standard care (phosphate binders and/or vitamin D sterols) • Age ≥18 years • Serum Ca^{2+} ≥8.8 mg/dl and <11.0 mg/dl (corrected for serum albumin) • Serum phosphorus ≥2.5 mg/dl • Ca × P <70 mg^2/dl^2 *Exclusion criteria:* • Vitamin D sterol dose changes during 21 days before enrolment • Dialysis calcium concentration, the dose of any supplements or the dose of oral phosphate binders changed during the 7 days before enrolment • Evidence of active infectious or malignant process or diseases known to cause hypercalcaemia • Haemoglobin concentration <9 g/dl or haematocrit <27% • Liver transaminases and bilirubin concentrations more than twice the upper limit of normal	See table below	After screening period, subjects randomised 1:1 to receive cinacalcet or placebo *Intervention:* Cinacalcet *Intervention regimen:* 12-week dose-titration phase • Subjects initially received 20 mg cinacalcet orally, once daily – Dose increased, through 30, 40 or 50 mg daily every 3 weeks if PTH ≥250 pg/ml or had not reduced by ≥30% from baseline, unless serum Ca^{2+} <7.8 mg/dl or symptomatic hypocalcaemia – Dose reduced if PTH <100 pg/ml on two consecutive weekly visits 6-week-maintenance phase *Comparator regimen:* Placebo *Concurrent treatment:* • Concurrent phosphate binders permitted without restriction • Vitamin D sterols permitted – Dose increase permitted if: ◦ iPTH increased by >50% from baseline or ◦ iPTH was ≥600 pg/ml – Dose reduction permitted if: ◦ serum Ca^{2+} ≥11.0 mg/dl or ◦ serum phosphorus ≥6.5 mg/dl or ◦ Ca × P ≥70 mg^2/dl^2 or ◦ iPTH was ≤100 pg/ml on the lowest dose of cinacalcet	*Primary outcome measure:* • Proportion of subjects with reduction in iPTH ≥30% between treatment groups during the maintenance phase *Secondary measures:* • Mean percentage change from baseline for iPTH, serum calcium, serum phosphorus and Ca × P between treatment groups during the maintenance phase Safety was assessed by monitoring adverse events, laboratory variables (haematology and biochemistry) and vital signs *Method of assessing outcomes:* • Laboratory assessments were made at weekly visits throughout the study • Assessments were made immediately before administering daily oral dose of study medication (24 hours after previous dose) • All laboratory determinations were determined at a central laboratory. iPTH levels were determined using double-antibody IRMA assay for the intact hormone *Length of follow-up:* 18 weeks

	Placebo	Cinacalcet
n	39	39
Age (years), mean (SD)	48.8 (15.6)	52.7 (16.4)
Gender		
Male	22 (56%)	24 (62%)
Female	17 (44%)	15 (38%)
Race		
Black	29 (74%)	26 (67%)
White	6 (15%)	10 (26%)
Asian	2 (5%)	2 (5%)
Hispanic	2 (5%)	1 (3%)
Duration of dialysis (months), mean (SD)	69.7 (53.9)	60.3 (58.3)
Use of vitamin D sterols	24 (62%)	26 (67%)
Use of phosphate binders	34 (87%)	34 (87%)

TABLE 92 *Results*

Primary outcomes

	Placebo (n = 39)	Cinacalcet (n = 38)
Proportion of subjects achieving mean reduction in PTH ≥30% during the maintenance phase	8%	38%

p = 0.001

Secondary outcomes (from graphical data)

	Week						p
	13	14	15	16	17	18	
Mean % change in PTH from baseline							
Placebo	17	22	22	27	24	28	
Cinacalcet	–22	–29	–20	–29	–33	–26	<0.001
Mean % change in serum calcium from baseline							
Placebo	–0.3	–0.3	0.3	–0.3	–1.2	1.5	
Cinacalcet	–5.6	–6.2	–3.8	–5.3	–4.0	–2.8	<0.001
Mean % change in phosphorus from baseline							
Placebo	10.0	12.8	13.9	8.9	9.4	10.0	
Cinacalcet	–8.3	–3.3	–2.8	–6.1	–12.8	–14.4	<0.001
Mean % change in Ca × P from baseline							
Placebo	10.7	14.6	15.3	9.3	9.8	12.0	
Cinacalcet	–12.9	–8.7	–8.0	–10.7	–16.0	–16.7	<0.001

Adverse effects

	Placebo	Cinacalcet
Nausea	31%	21%
Dyspnoea	13%	18%
Hypocalcaemia (asymptomatic)	NS	8%

Biochemistry results

	Placebo			Cinacalcet			
	Baseline	Week 13–18	% Change	Baseline	Week 13–18	% Change	p
Intact plasma PTH (pg/ml)	637 (456)	701 (70)	22%	632 (280)	460 (47)	–26%	<0.001
Serum Ca^{2+} (mg/dl)	9.7 (0.64)	NS	0%	9.7 (0.67)	NS	–4.7%	<0.001
Serum phosphorus (mg/dl)	5.6 (1.38)	NS	10.9%	6.3 (1.42)	NS	–7.5%	=0.003
CA × P (mg/dl^2)	53.8 (13.63)	NS	10.9%	60.7 (13.2)	NS	–11.9%	<0.001

Data are shown as mean (SD).
NS, not stated.

TABLE 93 *Comments*

Methodological comments

Selection/randomisation	Subjects randomised 1:1 to receive cinacalcet or placebo. Details not specified
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Blinding	Double-blind; not detailed
Outcome measures	Objective
ITT	Yes
Protocol violations specified	None specified
Follow-up/attrition	All subjects accounted for?

	Placebo	Cinacalcet
Randomised	39	39
Withdrew (no reasons stated)	5	7
No. completing 18 weeks	34	32

Data analysis	Statistical tests used: • Proportion of subjects with reductions in iPTH ≥30% between treatment groups was compared using the two-group χ^2 test • Mean percentage change from baseline for iPTH, serum Ca^{2+}, phosphorus and Ca × P between groups was compared using ANOVA model • The effect of the baseline demographic factors, gender, age, race, duration of dialysis, and vitamin D use on iPTH reductions was assessed by stepwise logistic regression analysis • Stepwise logistic regression analysis was also used to assess the effect of baseline iPTH, serum calcium, phosphorus and Ca × P levels on iPTH reductions
Power calculation at design?	Not stated
Generalisability	High proportion of ethnic minorities in study: representative of dialysis population in UK? Many centres but relatively small numbers of subjects
Conflict of interest	Funding for study provided by Amgen

General comments

Maximum titrated dose was smaller than in some other trials; proportion of subjects achieving >30% PTH reduction was correspondingly lower

ANOVA, analysis of variance.

Lindberg and colleagues (2005)[66]

TABLE 94 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Lindberg *et al.*, 2005 *Country:* USA, Canada and Australia *Setting:* 60 centres *Recruitment dates:* May 2002 Study completed March 2003 *Study design:* Randomised, double-blind, placebo-controlled, parallel-group 26-week multicentre study of the efficacy and safety of cinacalcet in patients with SHPT and those who were on HD and PD and receiving traditional therapy	*Total number:* 395 Cinacalcet $n = 294$; placebo $n = 101$ *Inclusion criteria:* • ≥18 years of age • Mean of two central laboratory iPTH values ≥300 pg/ml obtained during screening phase • Mean of two central laboratory serum calcium values ≥8.4 mg/dl (2.1 mmol/l) obtained during screening phase • Prescribed HD or PD (CAPD or automated PD) for ≥1 month before day 1 *Exclusion criteria:* • Unstable medical condition • Parathyroidectomy • Received vitamin D sterol therapy for <30 days before day 1 or required a change in vitamin D sterol brand or dose within 30 days before day 1 • Experienced an MI within 3 months before day 1 *Subgroups:* Stratification into four groups: • HD and iPTH ≥300 pg/ml (31.8 pmol/l) to ≤500 pg/ml (53 pmol/l) • HD and iPTH >500 pg/ml ≤800 pg/ml (84.8 pmol/l)	**Placebo** / **Cinacalcet** *n*: 101 / 294 Age (years), mean (SD): 53.5 (13.9) / 51.8 (14.0) Gender Male: 64 (63%) / 181 (62%) Female: 37 (37%) / 113 (38%) Race Caucasian: 39 (39%) / 115 (39%) Black: 35 (35%) / 114 (39%) Other: 27 (27%) / 65 (22%) Duration of dialysis (months), mean (SD): 63.6 (65.0) / 56.4 (53.1) Baseline biochemistry values IPTH (pg/ml), mean (SE): 832.1 (48.4) / 847.9 (40.1) Serum calcium (mg/dl), mean (SE): 10.01 (0.09) / 9.79 (0.05) Serum phosphorus (mg/dl), mean (SE): 6.10 (0.14) / 6.10 (0.10) Ca × P (mg^2/dl^2), mean (SE): 60.9 (1.4) / 59.6 (1.0) Use of vitamin D sterol: 69% / 65%	After screening period, subjects were randomised in 3:1 ratio to cinacalcet or placebo *Intervention:* Cinacalcet *Intervention regimen*: 16-week dose-titration phase • Subjects initially received 30 mg cinacalcet orally, once daily • Doses were increased sequentially every 4 weeks during the dose-titration phase to 60, 90, 120 and 180 mg once daily – Increases in dose were permitted if: ◦ iPTH was >200 pg/ml and/or ◦ serum calcium was >7.8 mg/dl and ◦ symptoms of hypocalcaemia were not present and ◦ the highest study dose had not been reached and ◦ an adverse event that precluded an increase in dose had not occurred 10-week efficacy assessment phase *Comparator regimen:* • As above with placebo *Concurrent treatment:* • Concurrent phosphate binder permitted without restriction • Vitamin D sterols permitted – Dose increase permitted if:	*Primary outcome measure:* • Proportion of subjects with a mean plasma iPTH value ≤250 pg/ml during efficacy assessment phase *Secondary measures:* • Proportion of subjects with a reduction from baseline in mean iPTH of ≥30% • Percentage change from baseline in mean iPTH during efficacy assessment phase • Percentage changes from baseline in mean Ca × P, serum calcium and serum phosphorus during efficacy assessment phase • Proportion of patients with a mean iPTH level of ≤300 pg/ml or reductions in iPTH of ≥20, 40 or 50% from baseline • Proportion of patients with Ca × P <55 mg^2/dl^2 • Proportion of patients with a mean reduction in Ca × P of ≥5 or 10 mg^2/dl^2 *Method of assessing outcomes:* • Visits occurred biweekly during 16-week titration phase and 10-week efficacy-assessment phase

continued

TABLE 94 *Study details (cont'd)*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
	• HD and iPTH >800 pg/ml • PD and iPTH ≥300 pg/ml		◦ serum Ca^{2+} <8.4 mg/dl that did not respond to changes in calcium supplements and/or phosphate binders ◦ symptomatic hypocalcaemia – Dose reduction permitted if: ◦ serum Ca^{2+} ≥11 mg/dl or ◦ serum phosphorus ≥6.5 mg/dl or ◦ Ca × P ≥70 mg^2/dl^2	• Laboratory assessments of plasma iPTH, serum calcium and serum phosphorus were performed at a central laboratory • Plasma iPTH levels were determined using a double-antibody IRMA (Nichols) *Length of follow-up:* Study duration 26 weeks

TABLE 95 *Results*

Primary outcomes

	Placebo (*n* = 101)	Cinacalcet (*n* = 294)	*p*
Mean iPTH ≤250 pg/ml (overall)	7/100 (7%)	111/288 (39%)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml (*n* = 74)		54/70 (77%)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml (*n* = 84)		34/83 (41%)	
HD subgroup with baseline iPTH >800 pg/ml (*n* = 102)		10/101 (10%)	
PD subgroup with baseline iPTH >300 pg/ml (*n* = 34)		13/34 (38%)	

Secondary outcomes

	Placebo (*n* = 101)		Cinacalcet (*n* = 294)		*p*
% Change from baseline in mean iPTH (overall)	101	4.1 (3.4)	288	–40.30 (2.1)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml (*n* = 74)				–46.7 (3.9)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml (*n* = 84)				–44.0 (3.80)	
HD subgroup with baseline iPTH >800 pg/ml (*n* = 102)				–33.3 (3.6)	
PD subgroup with baseline iPTH >300 pg/ml (*n* = 34)				–38.8 (5.7)	
Mean iPTH ≤300 pg/ml (overall)	9/100 (9%)		132/288 (46%)		<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			57/70 (81%)		
HD subgroup with baseline iPTH >500 and ≤800 pg/ml			41/83 (49%)		
HD subgroup with baseline iPTH >800 pg/ml			17/101 (17%)		
PD subgroup with baseline iPTH >300 pg/ml			17/34 (50%)		

continued

TABLE 95 *Results (cont'd)*

Secondary outcomes			
	Placebo (*n* = 101)	**Cinacalcet (*n* = 294)**	***p***
Proportion of subjects with reduction from baseline in mean iPTH of ≥30% (overall)	13/100 (13%)	187/288 (65%)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml		55/70 (79%)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml		57/83 (69%)	
HD subgroup with baseline iPTH >800 pg/ml		53/101 (51%)	
PD subgroup with baseline iPTH >300 pg/ml		22/34 (65%)	
Proportion of subjects with reduction from baseline in mean iPTH of ≥20% (overall)	21/100 (21%)	213/288 (74%)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml		58/70 (83%)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml		64/83 (77%)	
HD subgroup with baseline iPTH >800 pg/ml		66/101 (65%)	
PD subgroup with baseline iPTH >300 pg/ml		25/34 (74%)	
Proportion of subjects with reduction from baseline in mean iPTH of ≥40% (overall)	10/100 (10%)	172/288 (60%)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml		49/70 (70%)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml		55/83 (66%)	
HD subgroup with baseline iPTH >800 pg/ml		48/101 (48%)	
PD subgroup with baseline iPTH >300 pg/ml		20/34 (59%)	
Proportion of subjects with reduction from baseline in mean iPTH of ≥50% (overall)	6/100 (6%)	139/288 (48%)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml		45/70 (64%)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml		42/83 (51%)	
HD subgroup with baseline iPTH >800 pg/ml		38/101 (38%)	
PD subgroup with baseline iPTH >300 pg/ml		14/34 (41%)	
Serum Ca^{2+} (mg/dl) (overall) (*n* = 288)	100 10.1 (0.1)	9.1 (0.1)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml (*n* = 70)		9.1 (0.1)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml (*n* = 83)		9.1 (0.1)	
HD subgroup with baseline iPTH >800 pg/ml (*n* = 101)		9.1 (0.1)	
PD subgroup with baseline iPTH >300 pg/ml (*n* = 34)		9.4 (0.1)	
% Change from baseline in mean Ca^{2+} (overall) (*n* = 288)	100 0.9 (0.5)	–6.5 (0.6)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml (*n* = 70)		–5.5 (1.0)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml (*n* = 83)		–5.8 (1.1)	
HD subgroup with baseline iPTH >800 pg/ml (*n* = 101)		–7.4 (1.0)	
PD subgroup with baseline iPTH >300 pg/ml (*n* = 34)		–7.4 (1.4)	
Serum phosphorus (mg/dl) (overall) (*n* = 289)	100 5.8 (0.1)	5.5 (0.1)	
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml (*n* = 71)		5.1 (0.2)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml (*n* = 83)		5.3 (0.2)	
HD subgroup with baseline iPTH >800 pg/ml (*n* = 101)		6.0 (0.2)	
PD subgroup with baseline iPTH >300 pg/ml (*n* = 34)		5.0 (0.2)	

continued

TABLE 95 *Results (cont'd)*

Secondary outcomes

	Placebo (n = 101)		Cinacalcet (n = 294)		p
% Change from baseline in mean phosphorus (overall)	100	−2.2 (2.5)	289	−7.2 (1.6)	0.039
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			71	−8.6 (2.7)	
HD subgroup with baseline iPTH >500 and ≤800 pg/ml			83	−2.9 (3.6)	
HD subgroup with baseline iPTH >800 pg/ml			101	−11.7 (2.3)	
PD subgroup with baseline iPTH >300 pg/ml			34	−1.5 (4.0)	
Ca × P (mg^2/dl^2)	100	58.1 (1.3)	288	50.0 (0.9)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			70	46.9 (1.8)	
HD subgroup with baseline iPTH ≥500 and ≤800 pg/ml			83	48.5 (1.7)	
HD subgroup with baseline iPTH >800 pg/ml			101	54.1 (1.5)	
PD subgroup with baseline iPTH >300 pg/ml			34	47.4 (2.2)	
% Change from baseline in mean Ca × P	100	−1.4 (2.4)	287	−12.8 (1.7)	<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			69	−12.0 (3.4)	
HD subgroup with baseline iPTH >500 and <800 pg/ml			83	−9.1 (3.5)	
HD subgroup with baseline iPTH >800 pg/ml			101	−18.0 (2.5)	
PD subgroup with baseline iPTH >300 pg/ml			34	−8.5 (4.1)	
No. (%) achieving Ca × P target <55 mg^2/dl^2	45/100 (45%)		186/288 (65%)		<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			51/70 (73%)		
HD subgroup with baseline iPTH >500 and ≤800 pg/ml			58/83 (70%)		
HD subgroup with baseline iPTH >800 pg/ml			51/101 (50%)		
PD subgroup with baseline iPTH >300 pg/ml			26/34 (76%)		
No. (%) achieving Ca × P target reduction ≤5 mg^2/dl^2	39/100 (39%)		175/287 (61%)		<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			41/69 (59%)		
HD subgroup with baseline iPTH >500 and ≤800 pg/ml			48/83 (58%)		
HD subgroup with baseline iPTH >800 pg/ml			67/101 (66%)		
PD subgroup with baseline iPTH >300 pg/ml			19/34 (56%)		
Number (%) achieving Ca × P target reduction ≤10 mg^2/dl^2	24/100 (24%)		135/287 (47%)		<0.001
HD subgroup with baseline iPTH ≥300 and ≤500 pg/ml			26/69 (38%)		
HD subgroup with baseline iPTH >500 and ≤800 pg/ml			32/83 (39%)		
HD subgroup with baseline iPTH >800 pg/ml			59/101 (58%)		
PD subgroup with baseline iPTH >300 pg/ml			15/34 (44%)		

Data are shown as n (%), or n and mean (SE).

continued

TABLE 95 *Results (cont'd)*

Safety	**Placebo (*n* = 101)**	**Cinacalcet (*n* = 291)**
Deaths on study (total):	2	3
Serious adverse events (total):	26	27
Withdrawal due to gastrointestinal events	3	9
All AEs (total)	93	91
Nausea	22	30
Vomiting	12	23
Headache	12	17
Upper respiratory infection	13	18
Abdominal pain	18	12
Diarrhoea	19	24
Asthenia	2	8
Hypotension	12	7
Hypocalcaemia <7.5 mg/dl	<1%	5

TABLE 96 *Comments*

Methodological comments

Selection/randomisation	Randomised 3:1 ratio to cinacalcet or placebo Stratification into four groups defined by baseline iPTH and dialysis modality Randomisation and dosing determined by a programmatic algorithm using an interactive voice-response system to maintain the blinded nature of the study design
Groups similar at baseline?	Yes At baseline, mean iPTH and serum calcium levels were similar between placebo and cinacalcet-treated patients overall, but were higher in cinacalcet-treated patients who received PD than in cinacalcet-treated patients who received HD
Eligibility criteria stated?	Yes
Blinding	Stated as double blind. Placebo and cinacalcet tablets were identical in appearance at the same dose strength
Outcome measures	Objective? Yes
ITT	No. Some patients are missing/added in to analysis in Table 2 compared with data from 20000188 For patients who withdrew before the efficacy assessment phase, the mean of the last two on-study, postbaseline values was carried forward Safety was analysed for all patients who received at least one dose of study medication
Protocol violations specified	No
Follow-up/attrition	All patients accounted for? No. A number of patients was removed/added to the analysis relative to the FDA document Withdrawal specified? 83% of placebo-treated and 81% of cinacalcet-treated patients completed 16-week dose-titration phase. 76% of placebo-treated and 74% of cinacalcet-treated patients completed 26-week study Withdrawal reasons given? Yes

	Placebo (%)	Cinacalcet (%)
Adverse events	8	13
Withdrawal of consent	1	4
Kidney transplantation	6	3
Parathyroidectomy	2	0
Death	2	1

Data analysis	Statistical tests used: Generalised Cochran–Mantel–Haenszel test was used for statistical comparisons
Power calculation at design?	Yes Sample size calculation was based on χ^2 test of equal proportions of subjects with a mean value of iPTH $\leq$250 pg/ml during the efficacy assessment phase, with a statistical significance level of 0.05 (two-sided) Placebo response was predicted on the basis of previous cinacalcet Phase II studies to be $\leq$13% With a cinacalcet response rate of 30% assumed for the purpose of sample size considerations, a sample size of 380 patients (285 cinacalcet, 95 placebo) yielded 91% power
Generalisability	Subgroup analysis allows for individual variation in iPTH and dialysis modality High proportion of non-Caucasians Compliance with study medication was 87% in each treatment group
Conflict of interest	Amgen study

Moe and colleagues (2005)[76]

TABLE 97 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Moe *et al.*, 2005 *Country:* Combined results from three trials Study A: North America (USA and Canada) Study B: Europe and Australia (Australia, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, UK) Study C: USA, Canada and Australia *Setting:* Multiple centres (182) *Recruitment dates:* Study A: December 2001 to December 2002 Study B: February 2002 to January 2003 Study C: May 2002 to March 2003	*Total number:* 1136 Study A: Cinacalcet $n = 205$, placebo $n = 205$ Study B: Cinacalcet $n = 165$, placebo $n = 166$ Study C: Cinacalcet $n = 294$, placebo $n = 101$ *Inclusion criteria:* Study A • iPTH ≥31.8 pmol/l • Serum Ca^{2+} ≥2.1 mmol/l • HD duration >3 months Study B • iPTH ≥31.8 pmol/l • Serum Ca^{2+} ≥2.1 mmol/l • HD duration >3 months Study C • iPTH ≥31.8 pmol/l • Serum Ca^{2+} ≥2.1 mmol/l • HD or PD duration >1 month *Exclusion criteria:* Studies A and B • History of an unstable medical condition • Change in dose or brand of vitamin D in the preceding 30 days • Change in dose or brand of phosphate binder, oral calcium supplement or dialysate calcium concentration in the preceding 30 days		Studies A and B 12-week dose-titration phase followed by 14-week maintenance phase Study C 16-week dose-titration phase followed by 10-week maintenance phase After screening period, subjects were randomised to cinacalcet or placebo *Intervention:* Cinacalcet *Intervention regimen:* • Subjects initially received 30 mg cinacalcet orally, once daily • Dose increased, through 60, 90, 120 and 180 mg daily every 3 weeks (trials A and B) or every 4 weeks (study C), if iPTH ≥21.2 pmol/l and Ca^{2+} ≥1.95 mmol/l • Dose reduced if iPTH <10.6 pmol/l *Comparator regimen:* Placebo *Concurrent treatment:* • Concurrent phosphate binders permitted without restriction • Vitamin D sterols permitted; – Dose increases permitted if: ◦ iPTH increased by >50% from baseline or ◦ serum Ca^{2+} <2.1 mmol/l or ◦ symptomatic hypocalcaemia – Dose reductions permitted if: ◦ serum Ca^{2+} ≥2.74 mmol/l or	*Primary outcome measure:* • Proportion of subjects during the maintenance phase achieving target values of the NKF KDOQI • For subjects on dialysis: – mean iPTH value <31.8 pmol/l – mean serum Ca^{2+} 2.10–2.37 mmol/l – mean serum phosphorus 1.13–1.78 mmol/l – mean Ca × P <4.44 $mmol^2/l^2$ – both a mean iPTH value <31.8 pmol/l and mean Ca × P <4.44 $mmol^2/l^2$ *Secondary measures:* • Frequency, severity and relationship of all reported adverse events • Changes in laboratory parameters and vital signs compared with placebo *Method of assessing outcomes:* Blood samples for the measurement of iPTH, serum calcium, serum phosphorus and Ca × P were obtained at least every 2 weeks during the dose-titration and maintenance phases Biochemical results obtained in the separate trials pooled and compared with the NKF KDOQI target values

	Placebo	Cinacalcet
n	471	665
Age <65 years	335 (71%)	510 (77%)
Gender		
Male	295 (63%)	407 (61%)
Female	176 (37%)	258 (39%)
Race		
White	265 (56%)	324 (49%)
Black	155 (33%)	245 (37%)
Other	51 (11%)	96 (14%)
Dialysis modality		
HD	459 (97%)	631 (95%)
PD	12 (3%)	34 (5%)
Use of vitamin D sterols	318 (68%)	437 (66%)
Use of phosphate binders	438 (93%)	617 (93%)
Baseline values, median (Q1, Q3)		
iPTH (pg/ml)	564 (411, 785)	596 (429, 863)
Ca^{2+} (mg/dl)	9.8 (9.4, 10.5)	9.9 (9.3, 10.4)
Phosphorus (mg/dl)	6.2 (5.1, 7.1)	6.0 (5.1, 7.1)
Ca × P (mg^2/dl^2)	61.3 (50.7, 70.8)	60.2 (49.0, 70.5)

continued

TABLE 97 *Study details (cont'd)*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Study design: Combined analysis of three Phase III randomised, double-blind, placebo-controlled trials	Study C • History of an unstable medical condition • Change in dose or brand of vitamin D in the preceding 30 days *Subgroups:* Trials A and B Stratification by baseline iPTH • >31.8 to 53.0 pmol/l • >53.0 to 84.8 pmol/l • >84.8 pmol/l and by baseline Ca × P • ≤5.65 $mmol^2/l^2$ • >5.65 $mmol^2/l^2$ Study C Stratification by dialysis modality and baseline iPTH level		◦ serum phosphorus ≥2.1 mmol/l or ◦ Ca × P ≥5.6 $mmol^2/l^2$ or ◦ iPTH <10.6 pmol/l on three consecutive study visits and the subject was on the lowest dose of cinacalcet *Notes:* Study C included PD and HD patients This paper presents a secondary analysis of the data from the trials to compare outcomes with target values of the US NKF KDOQI	*Length of follow-up:* Study duration 26 weeks

TABLE 98 *Results*

Primary outcomes

Number (%) of subjects achieving K/DOQI targets	**Placebo (*n* = 409)**	**Cinacalcet (*n* = 547)**	***p*[a]**
Mean iPTH ≤31.8 pmol/l			
Baseline	2 (<1%)	2 (<1%)	
Maintenance phase	42 (10%)	307 (56%)	<0.001
Mean serum Ca^{2+} 2.10–2.37 mmol/l			
Baseline	133 (33%)	176 (32%)	
Maintenance phase	100 (24%)	270 (49%)	<0.001
Mean serum phosphorus 1.13–1.78 mmol/l			
Baseline	126 (31%)	179 (33%)	
Maintenance phase	136 (33%)	250 (46%)	<0.001
Mean Ca × P <4.44 $mmol^2/l^2$			
Baseline	139 (34%)	203 (37%)	
Maintenance phase	148 (36%)	357 (65%)	<0.001
Mean iPTH ≤31.8 pmol/l and mean Ca × P <4.44 $mmol^2/l^2$			
Baseline	0 (0%)	0 (0%)	
Maintenance phase (from graph)	25 (6%)	224 (41%)	<0.001
Week 14	7.9%	38.6%	
Week 16	7.5%	39.9%	
Week18	8.8%	40.4%	
Week 20	8.8%	41.2%	
Week 22	9.7%	43.4%	
Week 24	8.8%	41.7%	
Week 26	7.9%	43.0%	

[a] *p*-Values are for comparison of cinacalcet and placebo during the maintenance phase

Proportion (%) of subjects achieving KDOQI targets in individual trials

	Study A		**Study B**		**Study C**	
	Placebo	**Cinacalcet**	**Placebo**	**Cinacalcet**	**Placebo**	**Cinacalcet**
PTH	10%	60%	11%	60%	10%	51%
Ca × P	34%	63%	35%	67%	43%	66%
Ca^{2+}	26%	54%	23%	55%	24%	43%
Phosphorus	32%	40%	30%	48%	42%	48%
PTH and Ca × P	5%	44%	7%	40%	6%	39%

continued

TABLE 98 *Results (cont'd)*

Proportion (%) of subjects achieving KDOQI targets by baseline PTH stratification

	Placebo (n = 409)					Cinacalcet (n = 547)				
	PTH	**Ca × P**	**Ca^{2+}**	**Phosphate**	**PTH and Ca × P**	**PTH**	**Ca × P**	**Ca^{2+}**	**Phosphate**	**PTH and Ca × P**
Mild (31–53 pmol/l)	21%	51%	28%	40%	14%	81%	70%	48%	48%	59%
Moderate (53.1–84.8 pmol/l)	4%	28%	24%	30%	<1%	60%	68%	54%	47%	42%
Severe (>84.8 pmol/l)	1%	21%	19%	26%	1%	22%	56%	45%	40%	18%

Proportion of subjects achieving KDOQI target levels by baseline Ca × P stratification

	Placebo (n = 409)					Cinacalcet (n = 547)				
	PTH	**Ca × P**	**Ca^{2+}**	**Phosphate**	**PTH and Ca × P**	**PTH**	**Ca × P**	**Ca^{2+}**	**Phosphate**	**PTH and Ca × P**
Ca × P <5.65 $mmol^2/l^2$	13%	46%	26%	42%	8%	60%	77%	51%	53%	50%
Ca × P ≥5.65 $mmol^2/l^2$	4%	10%	19%	10%	<1%	46%	37%	46%	27%	19%

Secondary outcomes

	Placebo (n = 470)	Cinacalcet (n = 656)
Adverse events		
Mortality	3%	2%
Withdrawal due to AEs	8%	15%
SAEs	31%	29%
AEs >5% more frequently in cinacalcet-treated subjects compared with placebo		
Nausea	19%	31%
Vomiting	15%	27%

TABLE 99 *Comments*

Methodological comments	
Selection/randomisation	Randomisation method not detailed Studies A and B: • Randomised in 1:1 ratio to receive cinacalcet or placebo • Randomisation stratified by mean baseline iPTH level (31.8–53, 53.1–84.8 or >84.8 pmol/l) and by baseline Ca × P level (<5.65 or >5.65 $mmol^2/l^2$) Study C: • Randomised in 3:1 ratio to receive cinacalcet or placebo • Randomisation stratified by dialysis modality, and randomisation of haemodialysis subjects was further stratified by baseline iPTH level
Groups similar at baseline?	Yes. More PD subjects in the cinacalcet group as the study from which these data were taken had 3:1 randomisation
Eligibility criteria stated?	Yes
Blinding	Double blind; no details provided
Outcome measures	Objective
ITT	No • Efficacy analyses included all subjects with at least one value recorded during the maintenance phase: 547/665 (82%) cinacalcet and 409/471 (87%) placebo • Safety analysis included all subjects who received at least one dose of study drug: 656/665 (99%) cinacalcet and 470/471 (99%) placebo subjects
Protocol violations specified	None specified
Follow-up/attrition	All subjects accounted for? No Withdrawal specified? Yes Withdrawal reasons given? Yes, but for adverse events only • 15% of cinacalcet-treated subjects withdrew from study because of adverse events • 8% of placebo-treated subjects withdrew from study because of adverse events • Withdrawals in the cinacalcet-treated group were primarily due to nausea or vomiting
Data analysis	Statistical tests used: • Logistic regression model was used to examine whether it was appropriate to combine data from the three trials (treatment effect did not differ between trials) • Cochran–Mantel–Haenszel test, stratified by study, was used to examine differences between treatment groups • Two-tailed *p*-values <0.05 were considered statistically significant
Power calculation at design?	Not stated
Generalisability	Nearly all subjects had iPTH values >31.8 pmol/l at baseline More than 20% of subjects overall had severe SHPT (iPTH >800 pg/ml) at baseline Approximately two-thirds of subjects had baseline values for serum calcium, phosphorus and Ca × P above the KDOQI targets Most subjects were undergoing HD (PD only accounts for 4% of subjects)
Conflict of interest	Study A (20000172), study B (20000183) and study C (20000188) were supported by Amgen
General comments	
Combined analysis of 20000172, 20000183 and 20000188	

Quarles and colleagues (2003)[74]

TABLE 100 *Study details*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
Quarles *et al.*, 2003 *Country:* USA *Setting:* Multiple centres (17) *Recruitment dates:* Not stated *Study design:* Randomised, double-blind, placebo-controlled study	*Total number:* 71 Cinacalcet $n = 36$; placebo $n = 35$ *Inclusion criteria:* • Treated for at least 3 months with HD • Subjects had uncontrolled SHPT (mean PTH ≥300 pg/ml) despite availability of standard care (phosphate binders and/or vitamin D sterols) • Age ≥18 years • Serum Ca^{2+} ≥8.8 mg/dl and <11.0 mg/dl • Serum phosphorus ≥2.5 mg/dl • Ca × P <70 mg^2/dl^2 *Exclusion criteria:* • Vitamin D sterol dose changes during 21 days before enrolment • Dialysis calcium concentration, the dose of any supplements and the dose of oral phosphate binders changed during the 7 days before enrolment • Evidence of active infectious or malignant process or diseases known to cause hypercalcaemia • Haemoglobin concentration <9 g/dl or a haematocrit <27% • Liver transaminases and bilirubin concentrations more than twice the upper limit of normal	**Placebo** / **Cinacalcet** *n*: 35 / 36 Age years (years), mean (SD): 47.9 (14.2) / 49.6 (8.5) Gender* Male: 17 (49%) / 27 (75%) Female: 18 (51%) / 9 (25%) Race African–American: 23 (66%) / 27 (75%) White: 11 (31%) / 9 (25%) Hispanic: 1 (3%) / 0 (0%) Duration of dialysis (months), mean (SD): 71.1 (66.2) / 71.3 (54.3) Use of vitamin D sterols: 24 (69%) / 22 (61%) Use of phosphate binders: 33 (94%) / 36 (100%) * Significant difference between control and cinacalcet in the number of women per group ($p = 0.022$).	After screening period, subjects were randomised in a 1:1 ratio to placebo or cinacalcet *Intervention:* Cinacalcet *Intervention regimen:* 12-week dose-titration phase • Initially cinacalcet 25 mg orally once daily • Dose increases through 50, 75 or 100 mg were permitted at week 3, 6 and 9 of the study, until subjects had achieved both a reduction in iPTH of ≥30% from baseline and an absolute PTH ≤250 pg/ml – Dose increase was permitted provided: ◦ serum Ca^{2+} was ≥7.8 mg/dl ◦ subject was not receiving the 100 mg per day dose ◦ subject was not experiencing an adverse event that would preclude a dose increase – Dose reduction occurred if the mean iPTH was <100 pg/ml 6-week maintenance phase • Subjects remained on dose of cinacalcet reached at end of the titration phase (25 mg $n = 7$, 50 mg $n = 4$, 75 mg $n = 6$, 100 mg $n = 17$) *Comparator regimen:* Placebo	*Primary outcome measure:* • Percentage of subjects achieving mean reduction of ≥30% iPTH during maintenance phase *Secondary measures:* • Percentage of subjects achieving mean reduction iPTH to ≤250 pg/ml • Mean percentage change from baseline in: – PTH – serum Ca^{2+} – serum phosphorus – Ca × P *Method of assessing outcomes:* • Biochemical measurements were made at weekly visits • All chemistry and PTH determination were performed at a central laboratory – Plasma PTH concentrations were determined using a double-antibody IRMA for the intact hormone – Calcium and phosphorus levels were performed using standard methodology • Safety information was collected from physical examinations, ECGs, safety chemistry and haematology laboratory assessments, and subject-reported symptoms and hospitalisations

continued

TABLE 100 *Study details (cont'd)*

Study	Subjects	Subject characteristics	Intervention	Outcome measures
	Subgroups: Randomisation was not stratified; however, sensitivity analysis was conducted on the following groups: Group 1: increase in vitamin D sterol from enrolment to maintenance phase Group 2: decrease in vitamin D sterol from enrolment to maintenance phase Group 3: no change in vitamin D sterol dose from enrolment to maintenance phase		*Concurrent treatment:* • Phosphate binders permitted without restrictions, dose changes permitted without restriction • Vitamin D sterols permitted – Increases in dose permitted if: ◦ iPTH ≥50% baseline and >600 pg/ml or ◦ serum Ca^{2+} <8.4 mg/dl – Decreases in dose permitted if: ◦ serum Ca^{2+} >11.0 mg/dl or ◦ serum phosphorus ≥6.5 mg/dl or ◦ Ca × P ≥70 mg^2/dl^2 or ◦ iPTH <100 pg/ml on lowest dose of cinacalcet • Dialysate Ca^{2+} concentration could be changed as needed	*Length of follow-up:* Study duration 18 weeks

TABLE 101 *Results*

Primary outcomes

	Placebo (n = 35)	Cinacalcet (n = 36)	p
% Subjects achieving mean PTH reduction ≥30% from baseline during maintenance phase	23%	53%	= 0.009

Secondary outcomes

	Placebo (n = 35)	Cinacalcet (n = 36)	p
% Subjects achieving mean reductions in PTH to ≤250 pg/ml during maintenance phase	20%	44%	= 0.029

Biochemistry measures

	Placebo			Cinacalcet			p (between groups)
	Baseline	Week 13–18	% Change	Baseline	Week 13–18	% Change	
Plasma PTH (pg/ml)	583 (72)	552 (87)	3.0 (8.5)	626 (53)	451 (74)	–32.5 (7.6)	<0.001
Serum Ca^{2+} (mg/dl)	9.7 (0.1)	9.9 (0.1)	2.6 (1.3)	9.6 (0.1)	9.2 (0.1)	–4.6 (1.4)	<0.001
Serum phosphorus (mg/dl)	5.5 (0.2)	5.7 (0.2)	7.0 (5.5)	6.0 (0.2)	5.8 (0.2)	–2.6 (3.4)	0.217
Ca × P (mg^2/dl^2)	53.4 (2.3)	56.6 (2.3)	11.0 (6.5)	57.6 (1.6)	53.1 (1.8)	–7.9 (2.9)	0.013

Data are shown as mean (SE).

Secondary outcomes (from graphical data)

	Week					
	13	14	15	16	17	18
Mean % change in PTH from baseline						
Placebo	1	6	2	6	6	6
Cinacalcet	–40	–30	–34	–31	–28	–25
Mean % change in Ca^{2+} from baseline						
Placebo	2.4	3.0	4.1	0.7	1.1	3.9
Cinacalcet	–5.7	–2.7	–2.5	–5.3	–7.2	–5.5
Mean % change in phosphorus from baseline						
Placebo	6.8	8.4	1.2	6.2	6.7	10.0
Cinacalcet	–1.6	–1.9	–3.2	–3.8	–5.4	–0.1
Mean % change from baseline in Ca × P at week						
Placebo	9.6	12.3	7.9	10.1	8.4	15.7
Cinacalcet	–8.2	–5.4	–6.0	–9.9	–12.7	–6.3

TABLE 102 *Comments*

Methodological comments	
Selection/randomisation	Subjects randomised by interactive voice response system in a 1:1 ratio No stratification factors
Groups similar at baseline?	Yes, with exception of gender: significant difference between number of women in treatment groups (51% in placebo group vs 25% in cinacalcet group, $p = 0.022$)
Eligibility criteria stated?	Yes
Blinding	Double-blind; not detailed
Outcome measures	Objective
ITT	Yes
Protocol violations specified	None stated
Follow-up/attrition	All subjects accounted for? No Withdrawal specified? Two subjects from cinacalcet group and four from the placebo group withdrew during the dose-titration phase. No subjects withdrew during the maintenance phase Withdrawal reasons given? No
Data analysis	Statistical tests used: • ANOVA model used to compare mean percentage change from baseline for iPTH, serum calcium, phosphorus and Ca × P between groups • Unclear what tests were used for primary end-point
Power calculation at design?	Sample size of 71 allowed an 84% power to show a 33% difference between treatment groups in the proportion of subjects who could achieve a mean reduction in iPTH of ≥30% during the maintenance phase of the study (primary end-point) Study not powered for secondary end-point
Generalisability	Yes, although proportion of African–American subjects fairly high Compliance was 96% Effects were independent of whether or not subjects received vitamin D sterols and whether the dose was changed
Conflict of interest	Funding provided by Amgen

General comments

Several of the authors were involved in Phase III trials (2000172, 2000183, 2000188)

Appendix 8

Estimating the annual death rate from death rates in 10-year age bands

The graph from which mortality rates are derived (Renal Registry, Figure 5.18[13]) shows death rates for age groups in 10-year bands. For each of these 10-year categories the probability of death at the start and end is very different. Therefore, annual probabilities were derived using the following method.

A Weibull curve was fitted to the published data. The lambda and gamma parameters used to describe the curve were derived using the ordinary least squares method. The R^2 value derived for the fitted curve was 0.995, suggesting that the Weibull function was an acceptable fit to the data. *Figure 24* shows the curve fitted to the values shown in *Table 35* (p. 49).

The parameter values used in plotting the curve are:

lamda = 4.85×10^{-6}
gamma = 2.538

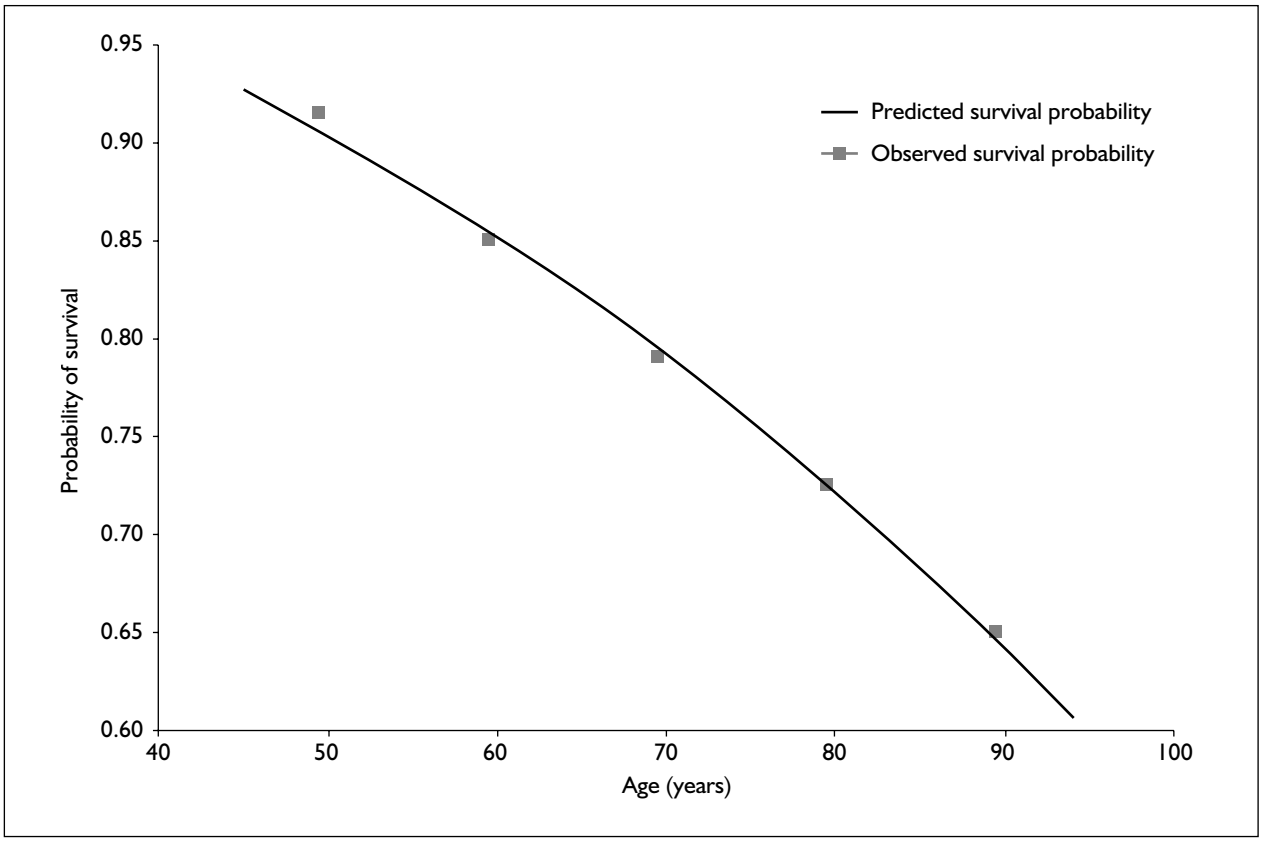

FIGURE 24 *Weibull curve fitted to Renal Registry mortality data*

Appendix 9

Calculating the relative risk of mortality based on PTH level

A plot of the midpoint of each of the PTH ranges reported by Block and colleagues[19] against the quoted relative risk is shown in *Figure 25*, with the reference case at 200 pg/ml (21.2 pmol/l) as the reference population has PTH of 100–300 mg/l. The fitted linear trend is shown as a dashed line and is an excellent approximation to the published data. The PenTAG model is based on PTH ranges reported in the RCTs of cinacalcet; these are <32, 32–85 and ≥85 pmol/l. Relative risk values for midpoints in these ranges can be calculated by interpolation.

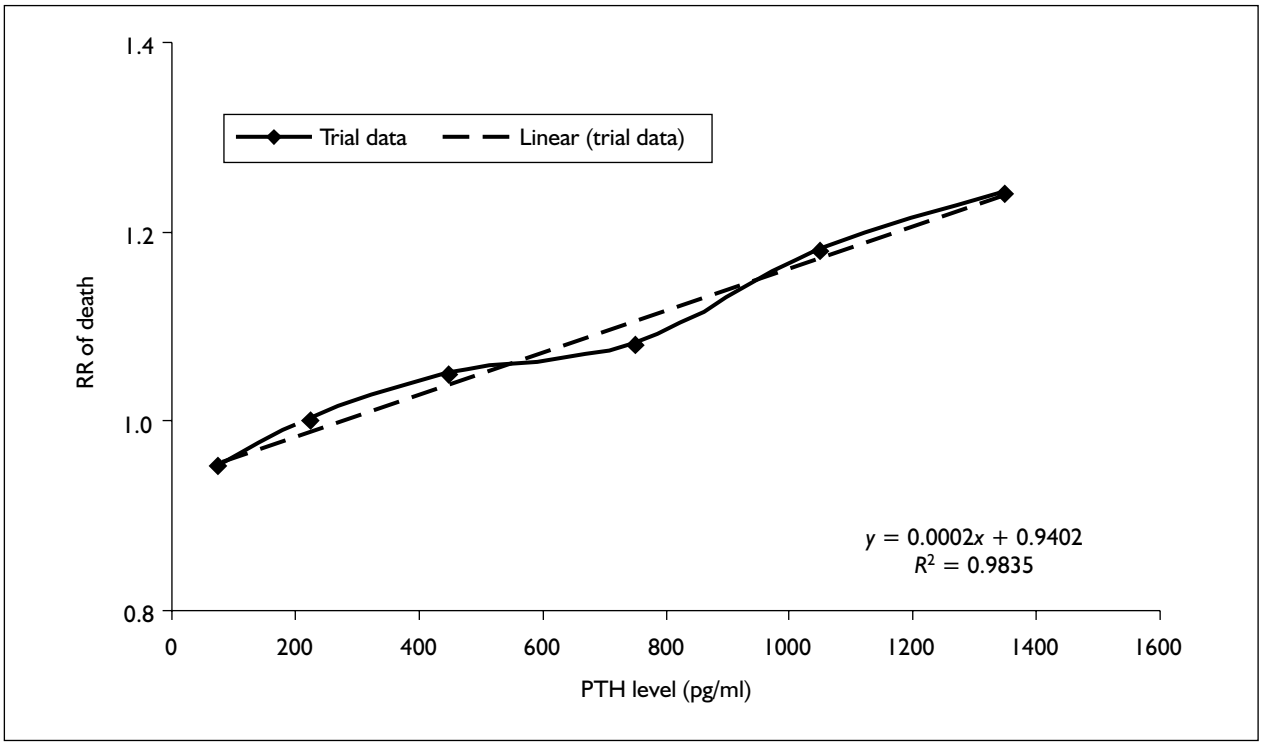

FIGURE 25 *Relative risk of death by PTH level reported by Block and colleagues[19]*

Appendix 10

Cardiovascular death in the economic model

Cardiovascular deaths as a proportion of total deaths

To model the probability of cardiovascular death from each health state in the model a series of data points and a process of weighting were used (*Table 103*). First, the overall probability of death from cardiovascular causes was assigned from data provided by the Renal Registry.[13] This shows that for patients who spent 3–5 years on RRT, cardiac disease was responsible for 41.1% of deaths, and cerebrovascular disease, which is also likely to be influenced by calcification, was responsible for 7.8%. This gives a total of 48.9% of deaths due to cardiovascular causes. This value is similar to figures quoted for the USA.[83] Assuming that this reflects the proportion of deaths in patients with SHPT, the proportion of deaths due to other

TABLE 103 *Calculation of CV deaths in the economic model*

Baseline reference state	Index	Weight applied	State-specific scaling coefficient	Resultant transition probability (55-years-olds) per cycle	Effective yearly rate (%)
cEVF (average probability 0.0153)	cEVF	1	1*0.425 (3 d.p.)	0.0065	2.6%
	cCVE	1	13.21*0.425	0.0856	35.8%
	cFRE	1	1.91*0.425	0.0124	4.98%
	cCVH	1	2.9*0.425	0.0188	7.59%
	cFRH	1	1.87*0.425	0.0121	4.88%
	cCFE	1	1.91*0.425	0.0124	4.98%
	cCFH	1	1.91*0.425	0.0124	4.98%
uEVF (average probability 0.016)	uEVF	1.06131	1*0.425 (3 d.p.)	0.0069	2.76%
	uCVE	1.06131	13.21*0.425	0.909	38.11%
	uFRE	1.06131	1.91*0.425	0.0131	5.29%
	uCVH	1.06131	2.9*0.425	0.0199	8.06%
	uFRH	1.06131	1.87*0.425	0.0129	5.18%
	uCFE	1.06131	1.91*0.425	0.0131	5.29%
	uCFH	1.06131	1.91*0.425	0.0131	5.29%
vEVF (average probability 0.0229)	vEVF	1.1824	1 *0.425 (3 d.p.)	0.0077	3.19%
	vCVE	1.1824	13.21*0.425	0.1013	42.71%
	vFRE	1.1824	1.91*0.425	0.0146	5.9%
	vCVH	1.1824	2.9*0.425	0.0222	9%
	vFRH	1.1824	1.87*0.425	0.0143	5.78%
	vCFE	1.1824	1.91*0.425	0.0146	5.9%
	vCFH	1.1824	1.91*0.425	0.0146	5.9%
pEVF (average probability 0.0204)	pEVF	1.0287	1 *0.425 (3 d.p.)	0.0067	2.67%
	pCVE	1.0287	13.21*0.425	0.0881	36.89%
	pFRE	1.0287	1.91*0.425	0.0127	5.12%
	pCVH	1.0287	2.9*0.425	0.0193	7.81%
	pFRH	1.0287	1.87*0.425	0.0125	5%
	pCFE	1.0287	1.91*0.425	0.0127	5.12%
	pCFH	1.0287	1.91*0.425	0.0127	5.12%
aEVF (average probability 0.0204)	aEVF	1.0287	1 *0.425 (3 d.p.)	0.0067	2.67%
	aCVE	1.0287	13.21*0.425	0.0881	36.89%
	aFRE	1.0287	2.9*0.425	0.0127	5.12%
	aCVH	1.0287	1.22*0.425	0.0193	7.81%
	aFRH	1.0287	1.87*0.425	0.0125	5%
	aCFE	1.0287	1.91*0.425	0.0127	5.12%
	aCFH	1.0287	1.91*0.425	0.0127	5.12%

d.p., decimal places.

causes will be 51.1%. Since mortality rates increase with age, the value for overall cardiovascular death will be a time-dependent probability. This value is then modified using the methods described below to derive individual values for this transition probability for each state in the model.

- Base-level cardiovascular death probability (for those with 'controlled' levels of PTH) per cycle (55-year-olds) = 0.0312 × 0.489 = 0.0153
- Scale factors:
  controlled PTH = 1 (reference)
  uncontrolled PTH = 1.06131
  very unstable PTH = 1.1824
  postsurgical (no AE) = 1.0287
  postsurgical with AE = 1.0287

Calculation of age-dependent all-cause mortality probabilities

The general equation for the survival probability $S(t)$ for a variable that follows a Weibull distribution is:

$$S(t) = \exp\{-\lambda * t^{\gamma}\}$$

with the values of lambda and gamma being curve specific. Therefore, the probability of death in period t is 1-$S(t)$. In the model the period used in these calculations is a year. This death probability is then used to derive the age-dependent cycle rate using the formula:

$$\text{Cycle rate} = [-\ln(1 - \text{Yearly probability})]/\text{Number of cycles per year}$$

In the context of the model, these values represent the average rates of death per cycle for all people receiving RRT rather than for people with SHPT. Finally, the probabilities of death are derived from these rates using the formula

$$\text{Cycle probability} = 1 - \exp\{-\text{Cycle rate}\}$$

(see *Table 104*).

Calculation of transition probabilities

For each state within the model the transition probabilities for cardiovascular death have been calculated according to two basic constraints:

- the total number of cardiovascular deaths from each of the strata equals the expected number given the known proportion cardiovascular deaths overall
- the relative risk of cardiovascular deaths between states at each level of PTH control, as determined by the data sources described above, is maintained. The method for achieving this calculation is described textually and graphically below.

TABLE 104 *Age-dependent probabilities used in the PenTAG model*

Age (years)	Event probability	Age (years)	Event probability
45	0.01887	73	0.06299
46	0.01994	74	0.06513
47	0.02105	75	0.06731
48	0.02219	76	0.06953
49	0.02337	77	0.07179
50	0.02459	78	0.07409
51	0.02584	79	0.07643
52	0.02713	80	0.07881
53	0.02845	81	0.08123
54	0.02981	82	0.08369
55	0.03121	83	0.08618
56	0.03265	84	0.08872
57	0.03412	85	0.09130
58	0.03564	86	0.09392
59	0.03719	87	0.09658
60	0.03878	88	0.09927
61	0.04040	89	0.10201
62	0.04207	90	0.10479
63	0.04377	91	0.10760
64	0.04552	92	0.11045
65	0.04730	93	0.11335
66	0.04912	94	0.11628
67	0.05099	95	0.11925
68	0.05289	96	0.12225
69	0.05483	97	0.12530
70	0.05681	98	0.12838
71	0.05883	99	0.13150
72	0.06089	100	0.13466

To summarise, the average probability of dying due to cardiovascular-related causes is scaled in the following ways to compute a transition probability for each specific health state in the model:

- A scaled weighting factor is used to compute the average probability of cardiovascular-related death for each of the model strata.
- The relative risks of cardiovascular-related death from all other health states in the model (EVF, FRE, CVH, FRH, CVE, CFE, CFH) have been assessed from data provided by *Table 37* (p. 50). These relative risks are used together with the overall state occupancies to derive specific cardiovascular death transition probabilities for each health state. This is done

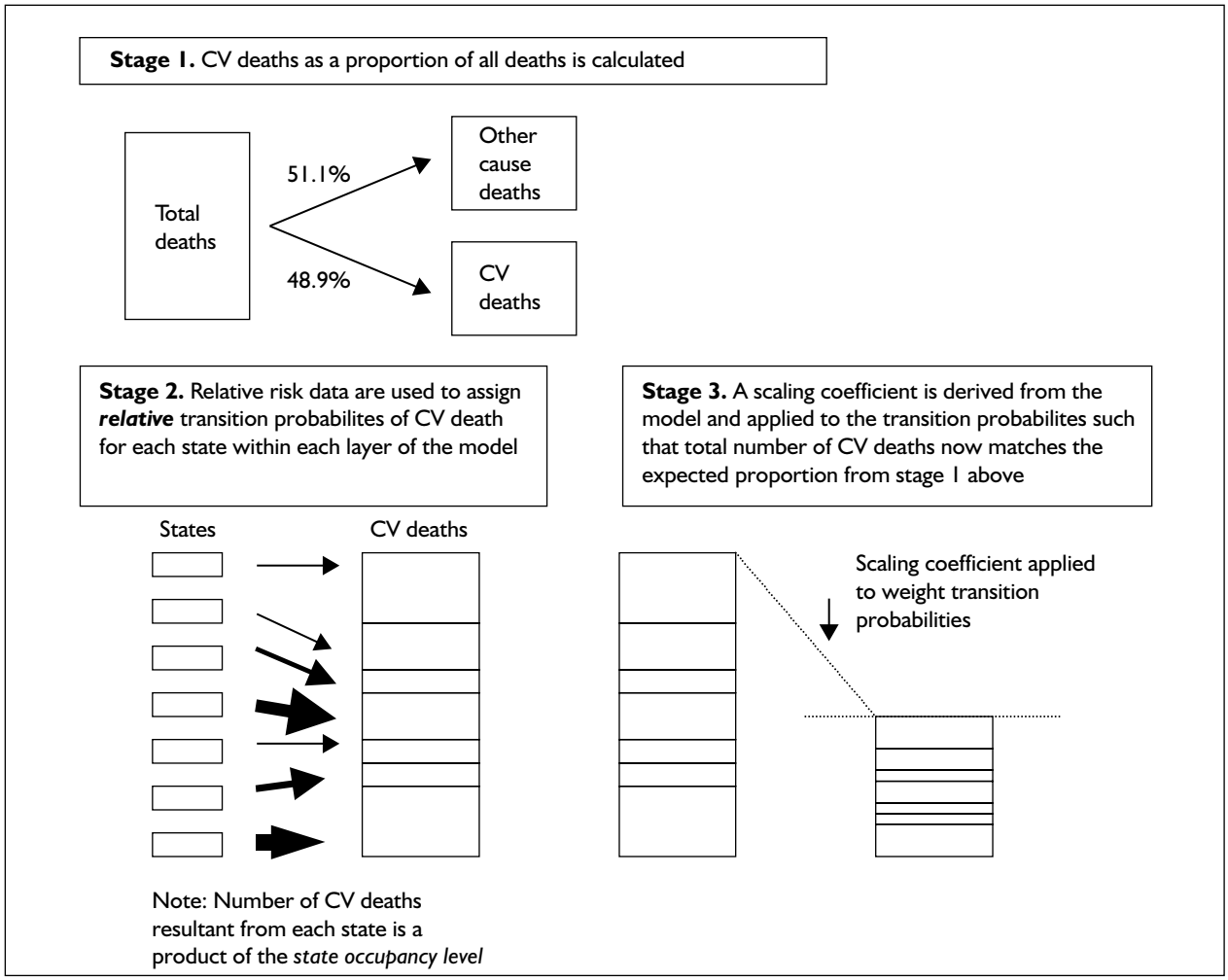

FIGURE 26 *Illustration of derivation of cardiovascular mortality*

by scaling the base level of cardiovascular death at each level of PTH control for each health state.

- The coefficients used for scaling transition probabilities described above are applied uniformly regardless of the degree of control of PTH levels. Microsoft Solver was used to derive the coefficients as a recursive process is involved in this calculation.

The scale factors used in the model and the calculation of the resultant transition probabilities for cardiovascular death from each health state are shown above.

The process of transition probabilities of cardiovascular death from each of the individual states within the model is described diagrammatically in *Figure 26*.

Appendix 11

Calculation of the cost of dialysis

There are few recent or good-quality data on the cost of either haemodialysis or peritoneal dialysis in the UK. In an earlier *Health Technology Assessment* report, Mowatt and colleagues estimated the cost of haemodialysis at hospital, at satellite renal units and at home.[100] This analysis used the hospital haemodialysis costs excluding training and access costs, and the cost of interdialytic complications (to avoid possible double-counting of fracture-related and cardiovascular event-related hospitalisations). The majority (64%) of haemodialysis patients receive haemodialysis in hospital, with most of the remainder receiving treatment in satellite dialysis units rather than at home.[16] The only available evidence suggests that the cost of receiving haemodialysis in hospital and satellite units is similar.[100]

UK Renal Registry data show that for 55–64-year-olds the proportion of dialysis patients on haemodialysis and peritoneal dialysis at the end of December 2003 was 71% and 29%, respectively (*Table 105*).[16] As patients become older and more unwell, a higher proportion switch from peritoneal dialysis to haemodialysis, so the proportion of ESRD patients with SHPT who would be on the more expensive mode of dialysis may have been underestimated.

The best estimates of the cost of peritoneal dialysis are based on international evidence suggests that it is considerably cheaper than haemodialysis. The only available UK evidence (a 1989 study from Wales, by Smith and colleagues, quoted by MacLeod and colleagues[108]) indicates that it was about half the cost of haemodialysis.[108] Therefore, it was crudely assumed that peritoneal dialysis is half the current cost of haemodialysis, but the whole weighted average cost of haemodialysis was varied widely in the sensitivity analysis.

TABLE 105 *Annual cost of dialysis*

	As per Mowatt, 2003[100] (£)[a]				Weighted average (£)		
	Mean	Low	High	%	Mean	Low	High
Annual cost of HD	18,296	9,148	27,445	71%[b]	12,990	6,495	19,486
Annual cost of PD	9,148	4,574	13,722	29%[b]	2,653	1,326	3,979
Weighted average cost of dialysis				100%	15,643	7,822	23,465

[a] Source: *Table 12*, p. 60 costs of hospital haemodialysis inflated to 2005 £ values (excluding access costs, training costs and the cost of interdialytic complications).[100]
[b] Source: *Table 5.10*, p. 13 of Chapter 5, of UK Renal Registry Seventh Annual Report.[16]

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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