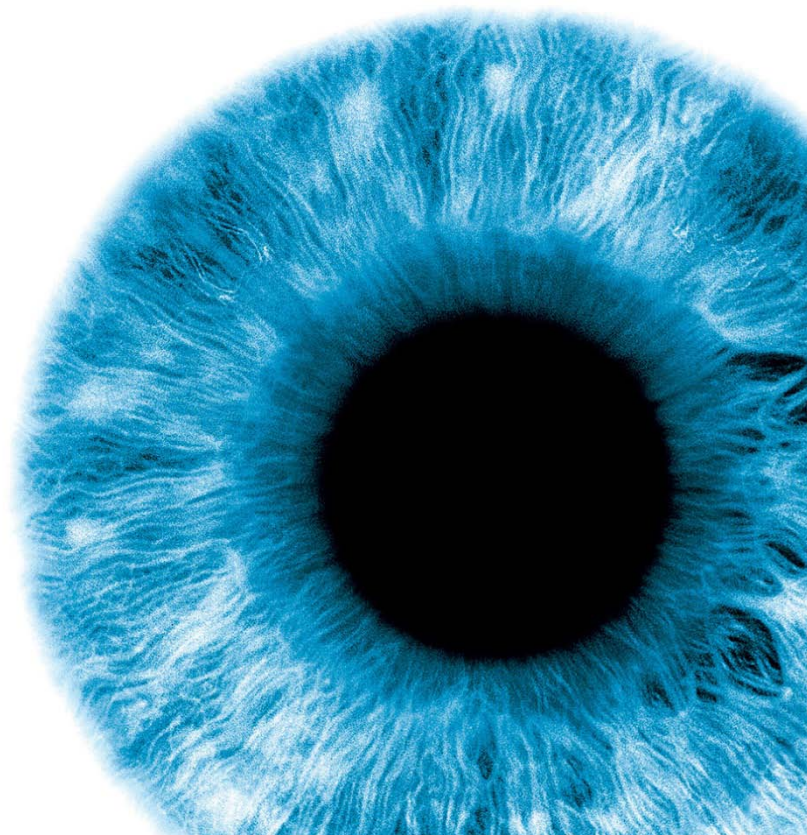


# Hyperphosphataemia in chronic kidney disease

Evidence Update December 2014

A summary of selected new evidence relevant to NICE clinical guideline 157 'Management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease' (2013)

**Evidence Update 72**



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# Introduction

**Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.**

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

<sup>1</sup>  [Hyperphosphataemia in chronic kidney disease](#). NICE clinical guideline 157 (2013)

A search was conducted for new evidence from 1 October 2011 to 14 July 2014. A total of 899 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 26 references underwent a rapid critical appraisal process and then were reviewed by an [Evidence Update Advisory Group](#), which advised on the final list of 8 items selected for the Evidence Update. See [Appendix A](#) for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 157 ([NICE CG157](#)). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guidelines [development methods manual](#) for further information about updating clinical guidelines.

## Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

 [Chronic kidney disease](#). NICE clinical guideline 182 (2014)

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<sup>1</sup> [NICE-accredited guidance](#)

## NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- [Hyperphosphataemia in chronic kidney disease](#). NICE Pathway

## Feedback

If you would like to comment on this Evidence Update, please email [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk)

## Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on [NICE CG157](#). Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from [NICE CG157](#).

**Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.**

Key point	Potential impact on guidance	
	Yes	No
<p><b>Phosphate binders and mortality</b></p> <ul style="list-style-type: none"> <li>A meta-analysis suggests that calcium-based phosphate binders may be associated with higher mortality than non-calcium-based phosphate binders in adults with chronic kidney disease (CKD). However, the meta-analysis has substantial limitations that reduce confidence in this result.</li> </ul>		✓
<p><b>Phosphate binders for adults not on dialysis</b></p> <ul style="list-style-type: none"> <li>Phosphate binders may reduce serum phosphate in people with CKD who are not on dialysis whose serum phosphate is within normal range, or near normal.</li> <li>Sevelamer<sup>2</sup> may be associated with greater phosphate control and lower mortality than calcium carbonate in people with CKD who are not on dialysis.</li> <li>An economic evaluation suggests that sevelamer may be cost effective for reducing serum phosphate in patients with CKD not on dialysis compared with calcium carbonate. However, the analysis has substantial limitations that reduce confidence in the results.</li> <li>Ferric citrate<sup>3</sup> may reduce serum phosphate compared with placebo in people with CKD who are not on dialysis.</li> </ul>	✓*	✓ ✓ ✓
<p><b>Phosphate binders for adults on dialysis</b></p> <ul style="list-style-type: none"> <li>Sevelamer hydrochloride may reduce serum phosphate and cardiovascular mortality compared with calcium carbonate in people with CKD who are on dialysis.</li> <li>Ferric citrate<sup>3</sup> may be as effective as sevelamer hydrochloride<sup>2</sup> for controlling serum phosphate in people with CKD who are on dialysis.</li> </ul>	✓*	✓
<ul style="list-style-type: none"> <li>Sevelamer<sup>2</sup> may be cost effective compared with calcium-based phosphate binders.</li> </ul>		✓

<sup>2</sup> At the time of publication of this Evidence Update, sevelamer hydrochloride did not have UK marketing authorisation for use in people with CKD who are not on dialysis.

<sup>3</sup> At the time of publication of this Evidence Update, ferric citrate did not have UK marketing authorisation and was not available in the UK.

\* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

# 1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from [NICE CG157](#).

## 1.1 Dietary management: children, young people and adults

No new key evidence for this section was selected for inclusion in this Evidence Update.

## 1.2 Phosphate binders: children and young people

No new key evidence for this section was selected for inclusion in this Evidence Update.

## 1.3 Phosphate binders: adults

### **Phosphate binders and mortality**

[NICE CG157](#) recommends:

For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.

For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.

For adults with stage 4 or 5 chronic kidney disease (CKD) who are not on dialysis and who are taking a calcium-based binder:

- consider switching to a non-calcium-based binder if calcium-based phosphate binders are not tolerated
- consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops (having taken into account other causes of raised calcium), or if serum parathyroid hormone levels are low.

For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but:

- serum calcium goes above the upper limit of normal, **or**
- serum parathyroid hormone levels are low,

consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

[Jamal et al. \(2013\)](#) conducted a meta-analysis of 11 randomised controlled trials (RCTs) of calcium-based phosphate binders compared with non-calcium-based phosphate binders that reported mortality as an outcome (n=4622). In January 2014, this paper was covered by a [NICE Medicines Evidence Commentary](#), which highlighted the limitations of this study and reinforced that current recommendations on use of calcium acetate and calcium carbonate should continue to be followed.

This study was an update of a previous meta-analysis ([Jamal et al. 2009](#)) that showed no significant difference in mortality with non-calcium-based drugs versus calcium-based drugs in patients with CKD (risk ratio [RR]=0.68, 95% CI 0.41 to 1.11; 8 studies, n=2873). The present meta-analysis found that, overall, non-calcium-based phosphate binders were associated with lower mortality (436 of 2312, 18.9%) than calcium-based phosphate binders

(500 of 2310, 21.7%). This was an absolute risk reduction of 2.8% for non-calcium-based phosphate binders (RR=0.78, 95% CI 0.61 to 0.98; 11 studies, n=4622, p=0.04).

When studies were analysed by length of follow-up, a significant effect on all-cause mortality was seen only for studies reporting outcomes at 24 months (RR=0.86, 95% CI 0.76 to 0.96; 5 studies, n=3585). Mortality was not affected in studies reporting outcomes at 6, 12 or 18 months, or in longer-term studies reporting outcomes at 36–42 months. Similarly, significant results were seen in studies of patients on dialysis (RR=0.88, 95% CI 0.79 to 0.99; 12 studies, n=7168), but not in studies of people not on dialysis.

Non-calcium-based phosphate binders were associated with significant reductions in coronary artery calcification overall (mean difference in Agatston score=-95.26, 95% CI -146.68 to -43.84; 7 studies, n=704). However, when these results were analysed by length of follow-up, only outcomes at 12 months were significant (mean difference in Agatston score=-95.84, 95% CI -150.40 to -41.29; 6 studies, n=686), with results at 6, 18, and 24 months showing no significant difference.

Limitations of this study included that heterogeneity among the studies analysed was moderate ( $I^2=43%$ ) and only one-third of studies were assessed as having a low risk of bias. Some of the studies included in this meta-analysis were excluded from consideration when [NICE CG157](#) was developed because of their low quality. A funnel plot indicated that small studies showing no significant effect may be missing. This would result in an overestimate of the mortality risk with calcium-based phosphate binders.

Furthermore, calcium acetate and calcium carbonate were not considered separately in the meta-analysis. In [NICE CG157](#), calcium acetate is recommended as the first-line treatment for adults with hyperphosphataemia, with calcium carbonate an option if calcium acetate is unsuitable. In the [full version of NICE CG157](#), non-calcium-based phosphate binders were noted to have a slightly greater effect on quality-adjusted life years (QALYs) than calcium acetate, but this difference was not of sufficient size to justify the additional cost (almost £90,000 per QALY gained). However, the recommendations take into account that calcium-based phosphate binders may not be suitable for all patients. Non-calcium-based phosphate binders are an option after calcium-based drugs have been tried but not tolerated, or if hypercalcaemia develops or if serum parathyroid levels are low.

The meta-analysis by Jamal et al. (2013) suggests that calcium-based phosphate binders may be associated with higher mortality than non-calcium-based phosphate binders in adults with CKD. However, the meta-analysis has substantial limitations that reduce confidence in this result. Therefore, no impact on [NICE CG157](#) is expected.

Additional information about the study by Jamal et al. (2013) is also available from an independent [critical appraisal report](#) produced for the Centre for Reviews and Dissemination's Database of Abstracts of Reviews of Effects.

#### **Key reference**

Jamal SA, Vandermeer B, Raggi P et al. (2013) [Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis](#). *The Lancet* 382: 1268–77

#### **Supporting reference**

Jamal SA, Fitchett D, Lok CE et al. (2009) [The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis](#). *Nephrology Dialysis Transplantation* 24: 3168–74



## Phosphate binders for adults not on dialysis

[NICE CG157](#) recommends:

For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.

For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.

For adults with stage 4 or 5 chronic kidney disease (CKD) who are not on dialysis and who are taking a calcium-based binder:

- consider switching to a non-calcium-based binder if calcium-based phosphate binders are not tolerated
- consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops (having taken into account other causes of raised calcium), or if serum parathyroid hormone levels are low.

### ***Phosphate binders versus placebo***

[Block et al. \(2012\)](#) conducted a double-blind RCT (n=148) of phosphate binders versus placebo in people with moderate-to-severe CKD and normal or near-normal serum phosphate. Participants were randomly assigned to receive active treatment with calcium acetate<sup>4</sup> (n=30), lanthanum carbonate<sup>5</sup> (n=30) or sevelamer carbonate<sup>6</sup> (n=30), or were assigned to placebo (n=58). All participants also received colecalciferol 1000 IU daily. The primary outcome in this US study was serum phosphate at 3, 6 and 9 months of follow-up.

Inclusion criteria were glomerular filtration rate (GFR) of 20–45 ml/min/1.73 m<sup>2</sup>, serum phosphate of at least 3.5 mg/dl (1.13 mmol/l) and no more than 6.0 mg/dl (1.94 mmol/l), and willingness to not intentionally change diet. Exclusion criteria were use of phosphate binder drugs, vitamin D supplementation, or cinacalcet, as well as the presence of uncontrolled hyperlipidaemia or intact parathyroid hormone level of more than 500 pg/ml.

At baseline, participants in both the phosphate binder and placebo groups had mean serum phosphate of 4.2 mg/dl (1.36 mmol/l). Participants in the active treatment group had a GFR of 32 ml/min/1.73 m<sup>2</sup> and those in the placebo group had a GFR of 30 ml/min/1.73 m<sup>2</sup>, although the difference was not significant. Generally, baseline characteristics were similar between groups, apart from congestive heart failure, which was significantly more common in the phosphate binder group (27%) compared with the placebo group (11%, p=0.02). Missing data were accounted for in intention-to-treat analyses by using the last observation carried forward. However, 1 person in the placebo group and 2 people in the lanthanum carbonate group who were randomised but did not receive treatment were not included in analyses.

The mean daily doses administered in the phosphate binder group were 5.9 g for calcium acetate, 2.7 g for lanthanum carbonate and 6.3 g for sevelamer carbonate. Overall, a significant reduction in serum phosphate was seen in the phosphate binder group (0.3 mg/dl [0.097 mmol/l]) compared with no change in the placebo group (end value not reported, p=0.03). Daily mean urine phosphate excretion was reduced by 22% in the phosphate binder group but did not change over time in the placebo group (p=0.002). Parathyroid hormone

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<sup>4</sup> At the time of publication of this Evidence Update, calcium acetate did not have UK marketing authorisation for use in people with CKD who are not on dialysis.

<sup>5</sup> At the time of publication of this Evidence Update, lanthanum carbonate had UK marketing authorisation for use in people with CKD who are not on dialysis only if their serum phosphate is 1.78 mmol/l or higher.

<sup>6</sup> At the time of publication of this Evidence Update, sevelamer carbonate had UK marketing authorisation for use in people with CKD who are not on dialysis only if their serum phosphate is 1.78 mmol/l or higher.



levels were stable in the phosphate binder group, but increased by 21% in the placebo group (p=0.002).

Assessment of change in coronary artery calcification was done for 81 participants; those with no calcification were excluded from this analysis. In the phosphate binder group, 20 of 52 people (38%) showed progression of coronary artery calcification, compared with 5 of 29 people (17%) in the placebo group (p=0.03). People in the phosphate-binder group also showed significantly improved bone mineral density compared with placebo (p=0.03). Only 1 serious adverse event occurred, which was 1 case of hypothyroidism in the placebo group. Gastrointestinal adverse events seemed to be more common with lanthanum carbonate, but no statistical analysis was done.

Limitations of the study include its small sample size and that absolute data for many outcomes were not clearly reported. The study was conducted at a single-site in the USA, so differences in diet may limit generalisability of the findings to other countries. No attempts were made to standardise the participants' diet or the time of day that serum phosphate was measured. The routine use of colecalciferol in all patients is not consistent with clinical practice in the UK. 'Chronic kidney disease' ([NICE CG182](#)) recommends offering colecalciferol to treat people with CKD and vitamin D deficiency, but not for routine management or prevention of mineral and bone disorders associated with CKD.

This evidence suggests that phosphate binders may reduce serum phosphate in people with CKD who are not on dialysis and whose serum phosphate is within normal range, or near normal. This evidence is unlikely to affect [NICE CG157](#) because the need to treat people whose serum phosphate is within the normal range has not been established. Additionally, the population differed from that of [NICE CG157](#) which included only stage 4 and 5 kidney disease whereas this study also included people with stage 3 CKD.

#### **Key reference**

Block GA, Wheeler DC, Persky MS et al. (2012) [Effects of phosphate binders in moderate CKD](#). *Journal of the American Society of Nephrology* 23: 1407–15

#### ***Sevelamer versus calcium carbonate***

[Di Iorio et al. \(2012\)](#) reported an open-label RCT of sevelamer compared with calcium carbonate in adults (n=239) with stage 3 or 4 CKD who were not on dialysis. The report did not specify whether sevelamer hydrochloride or sevelamer carbonate was used in the study; however, the trial began in 2005, before sevelamer carbonate was licensed, therefore the trial drug was probably sevelamer hydrochloride<sup>7</sup>.

People in 12 nephrology clinics in south Italy were enrolled if they had at least 6 months history of CKD and did not have cardiovascular or hepatic conditions meeting exclusion criteria. People whose CKD was progressing rapidly were excluded. The primary outcome was mortality.

Baseline clinical characteristics and use of drugs for treating hypertension and dyslipidaemia were similar between groups. Initial doses were sevelamer 1.6 g daily and calcium carbonate 2 g daily, which were then titrated to maintain serum phosphate of 2.7–4.6 mg/dl (0.87–1.49 mmol/l) for people with stage 3 or 4 CKD and 3.5–5.5 mg/dl (1.13–1.78 mmol/l) for people with stage 5 CKD. The mean doses used were sevelamer 2.18 g daily and calcium carbonate 2.95 g daily.

Overall, 27 people dropped out of the study and analyses were done only for the 212 people who completed the study (sevelamer n=107, calcium carbonate n=105). After 3 years of follow-up:

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<sup>7</sup> At the time of publication of this Evidence Update, sevelamer hydrochloride did not have UK marketing authorisation for use in people with CKD who are not on dialysis.

- Mortality was lower in the sevelamer group (12 of 107 [11%]) than in the calcium carbonate group (22 of 105 [21%]). The unadjusted hazard ratio (HR) for all-cause mortality with sevelamer was 0.45 (95% CI 0.23 to 0.91), and the HR was 0.35 (95% CI 0.15 to 0.83) after adjustment for baseline and time-dependent variables.
- Sevelamer was associated with a significant reduction in phosphate from baseline (mean baseline=4.82 mg/dl [1.56 mmol/l], final=4.16 mg/dl [1.34 mmol/l], change=-0.66 mg/dl [-0.21 mmol/l], p<0.01).
- Calcium carbonate was not associated with a significant reduction in phosphate from baseline (mean baseline=4.87 mg/dl [1.57 mmol/l], final=4.72 mg/dl [1.52 mmol/l], change=-0.15 mg/dl [-0.05 mmol/l]).
- The difference in phosphate control between groups was significant (p<0.01).

The authors noted that the proportion of patients meeting the serum phosphate target was similar between groups and that more people in the calcium carbonate group progressed to stage 5 CKD by the end of follow-up. However, it is impossible to establish whether people in the calcium carbonate arm had more severe disease because data on stage of CKD were not reported for either baseline or at end of follow-up.

Adverse events were not clearly reported, although hypercalcaemia was reported in 78% of people on calcium carbonate compared with 5% of those on sevelamer (p<0.01). Additionally, new onset coronary artery calcification was seen in 5 of 40 people (13%) in the sevelamer group and in 45 of 55 people (82%) in the calcium carbonate group who had no calcification at baseline.

Limitations of this study include the sample size, which was influenced by resource constraints and the lack of previous data on mortality associated with phosphate binders. Additionally, the open-label nature of this study could have led to bias in clinicians' treatment decisions such as when to start dialysis. The authors urged caution in interpreting the results because of the large number of covariates that could have affected outcomes.

This study suggests that sevelamer may be associated with greater phosphate control and lower mortality than calcium carbonate. These findings are consistent with data considered in the [full version of NICE CG157](#), which recognised that sevelamer had benefits in terms of QALYs over calcium acetate but the size of the benefits did not justify its substantial extra cost. Therefore no impact on guidance is expected.

#### Key reference

Di Iorio B, Bellasi A, Russo D (2012) [Mortality in kidney disease patients treated with phosphate binders: a randomized study](#). *Clinical Journal of the American Society of Nephrology* 7: 487–93

#### Cost effectiveness of sevelamer

[Thompson et al. \(2013\)](#) assessed the cost effectiveness of sevelamer compared with calcium carbonate in adults with stage 3–4 CKD who were not on dialysis. It used data from the Di Iorio et al. (2012) study reported above. Neither this cost effectiveness paper nor Di Iorio et al. (2012) specified whether sevelamer hydrochloride or sevelamer carbonate was used, although the dates of Di Iorio et al. (2012) indicate that sevelamer hydrochloride<sup>8</sup> was most likely. However, only sevelamer carbonate is licensed in the UK for people not on dialysis.

A Markov decision analytic model was developed to estimate the cost effectiveness of sevelamer compared with calcium carbonate from the perspective of the UK NHS. The base-case analysis assessed a lifetime horizon, and the model was based on a 1-month cycle in which outcomes were 'alive without dialysis', 'alive with dialysis', or 'dead'. Weibull regression

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<sup>8</sup> At the time of publication of this Evidence Update, sevelamer hydrochloride did not have UK marketing authorisation for use in people with CKD who are not on dialysis.

analysis was used to extrapolate longer-term mortality data from the 36-month data assessed in the RCT. In the mortality analysis for sevelamer 24% of people were alive at 10 years, and for calcium carbonate 4% were alive at 10 years. A further Weibull regression analysis was used to extrapolate longer-term data for starting dialysis from the 36-month data assessed in the RCT.

The health utility was calculated to be 0.72 for patients with CKD on dialysis and was 0.85 for patients with CKD not on dialysis. Costs were calculated for dialysis and drugs, and a 3.5% annual discount for costs and outcomes was applied. The model did not include costs of admissions to hospital, outpatient appointments, adverse events or additional drugs. Sevelamer was associated with an increase in QALYs of 1.56 compared with calcium carbonate, but cost more, with an incremental cost-effectiveness ratio (ICER) of £23,878. The authors noted that this suggested that sevelamer was cost effective against a threshold of £30,000.

In [NICE CG157](#), cost-effectiveness analysis was not done for use of sevelamer in people not on dialysis because the evidence base for phosphate binders in this population was considered to be insufficient to provide a worthwhile model.

This cost-effectiveness model also differed in substantial ways from cost-effectiveness analyses in people with CKD who are on dialysis including:

- The model did not account for admissions to hospital for adverse events, which were considered in both the cost-effectiveness analysis for [NICE CG157](#) (see appendix F of the [full version of NICE CG157](#)) and Bernard et al. (2013), reported in 'Phosphate binders for adults on dialysis' below.
- Sevelamer was assessed against calcium carbonate only, which is not consistent with either the cost effectiveness analysis for [NICE CG157](#) or Bernard et al. (2013).
- The 10-year survival estimates of 24% for people on sevelamer and 4% for those on calcium carbonate may overestimate the benefits of sevelamer.
- The dose of sevelamer used in this model was 2.2 g daily, which is around one-third less than the 6.4 g daily used for [NICE CG157](#) and the 6.9 g used in Bernard et al. (2013).
- The health utility for people on dialysis was 0.72, which was higher than both the 0.57 used for [NICE CG157](#) and the 0.61 used in Bernard et al. (2013).
- The health utility for people not on dialysis (0.85) was also higher than the 0.62 used for [NICE CG157](#).

The health utilities used in Thompson et al. (2013) were based on data for stage 4 and 5 CKD only, whereas the efficacy data for starting dialysis included people with stage 3 and 4 CKD, with some progression to stage 5 during the RCT.

The study by Thompson et al. (2013) was funded by the manufacturer of sevelamer. Furthermore, the cost-effectiveness analysis relied on the assumption that the improved phosphate control with sevelamer has a direct effect on the need to start dialysis – additional studies are needed to confirm this assumption.

This economic evaluation suggests that sevelamer may be cost effective for reducing serum phosphate in patients with CKD not on dialysis compared with calcium carbonate. However, the analysis has substantial limitations that reduce confidence in the results. Therefore, no impact on [NICE CG157](#) is expected.

#### **Key reference**

Thompson M, Bartko-Winters S, Bernard L et al. (2013) [Economic evaluation of sevelamer for the treatment of hyperphosphatemia in chronic kidney disease patients not on dialysis in the United Kingdom](#). *Journal of Medical Economics* 16: 744–55

### ***Ferric citrate versus placebo***

[Yokoyama et al \(2014a\)](#) reported a 12-week double-blind, placebo-controlled RCT of ferric citrate<sup>9</sup> in Japan in people (n=90) with stage 3–5 CKD who were not on dialysis. Participants were randomly allocated to ferric citrate (n=60) or to placebo (n=30). The primary outcome was change in serum phosphate from baseline.

All participants followed a protein restriction diet for at least 3 months before initial screening. Inclusion criteria were serum phosphate of at least 5.0 mg/dl (1.6 mmol/l) but less than 8.0 mg/dl (2.6 mmol/l), and any people already taking phosphate lowering drugs had been on a stable dose for at least 4 weeks. Exclusion criteria were scheduled start of dialysis or transplantation in the next 4 months, acute kidney injury in the previous 3 months, specified gastrointestinal conditions, or problems with serum iron and calcium levels.

The starting dose of ferric citrate was 1.5 g daily (6 tablets), which increased to 3 g daily at week 2. At weeks 4, 6 and 8, the daily dose was adjusted by adding or removing 2 tablets at a time to a total dose of between 1.5 and 6.0 g daily. The dose was increased if the serum phosphate was higher than 4.5 mg/dl (1.45 mmol/l) and was reduced if serum phosphate was below 2.5 mg/dl (0.81 mmol/l). Other drugs affecting serum phosphate were not allowed during the study, but vitamin D supplements and intravenous iron were allowed if needed. People stopped study treatment if they started dialysis or reached specified thresholds for serum iron, calcium or phosphate.

Efficacy analysis was done for only 57 people in the ferric citrate group and for 29 people in the placebo group. This analysis excluded people who did not have an efficacy assessment at week 2. Safety analyses included all participants.

Baseline characteristics were similar between groups, and the mean dose of ferric citrate was 3.5 g daily. By the end of treatment:

- Ferric citrate was associated with a significant reduction in mean serum phosphate from baseline (5.66 mg/dl [1.83 mmol/l]) to end of treatment (4.37 mg/dl [1.4 mmol/l]), mean change=-1.29 mg/dl [-0.42 mmol/l], p<0.001).
- Placebo was not associated with a significant reduction in mean serum phosphate from baseline (5.57 mg/dl [1.80 mmol/l]) to end of treatment (5.62 mg/dl [1.82 mmol/l]), mean change=0.06 mg/dl [0.02 mmol/l], p=0.66).
- The least squares mean difference between groups was -1.31 mg/dl [-0.42 mmol/l] 95% CI -1.80 to -0.82 mg/dl, p<0.001).

Overall, 70% of people in the ferric citrate group and 60% of people in the placebo group had an adverse event. Severe adverse events occurred in 8 people (13%) in the ferric citrate group and in 3 people (10%) in the placebo group. In the ferric citrate group, 1 person died from hyponatraemia, which was deemed to be unrelated to the study drug.

The authors did not discuss potential limitations of their study, although they recognised that longer-term studies of this drug are needed. However, the methods of randomisation and allocation concealment were not reported, so allocation and selection bias cannot be excluded.

This evidence suggests that ferric citrate may reduce serum phosphate compared with placebo in people with CKD who are not on dialysis. This evidence may have a potential impact on [NICE CG157](#), which did not consider this drug, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

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<sup>9</sup> At the time of publication of this Evidence Update, ferric citrate did not have UK marketing authorisation and was not available in the UK.

### Key reference

Yokoyama K, Hirakata H, Akiba T et al. (2014a) [Ferric citrate hydrate for the treatment of hyperphosphatemia in non-dialysis-dependent CKD](#). *Clinical Journal of the American Society of Nephrology* 9: 543–52

### Phosphate binders for adults on dialysis

[NICE CG157](#) recommends:

For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.

For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.

For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but:

- serum calcium goes above the upper limit of normal, **or**
- serum parathyroid hormone levels are low,

consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

#### ***Sevelamer hydrochloride versus calcium carbonate***

[Di Iorio et al. \(2013\)](#) conducted an open-label RCT of sevelamer hydrochloride compared with calcium carbonate in adults (n=466) with stage 5 CKD who had started dialysis in the past 120 days. The primary outcome was cardiovascular mortality, defined as death due to arrhythmia or sudden cardiac arrest.

Participants were enrolled at 18 dialysis centres in Italy. The trial did not include people older than 75 years, those taking drugs known to prolong the QT interval or those with hepatic dysfunction, hypothyroidism or cardiovascular disorders meeting exclusion criteria. Randomisation was stratified by age, sex, diabetes status, and recruitment site, but stratification by coronary artery calcification was not possible because most centres did not have access to computed tomography.

Target phosphate levels were 2.7–5.5 mg/dl (0.87–1.78 mmol/l), and participating physicians were instructed to control blood pressure, anaemia, acidosis, diabetes, dyslipidaemia, and parameters of bone mineral metabolism in line with US National Kidney Foundation guidelines. Drug doses were altered at the physician's discretion to achieve targets, and aluminium hydroxide could be used as a rescue therapy for uncontrolled phosphate.

Mean doses administered were sevelamer hydrochloride 4.3 g daily (n=232) and calcium carbonate 2.2 g daily (n=234). At 24-month follow-up:

- Sevelamer hydrochloride was associated with a mean reduction in phosphate from a baseline level of 5.6 mg/dl (1.81 mmol/l) to 4.2 mg/dl (1.4 mmol/l, p<0.001).
- Calcium carbonate maintained serum phosphate within the normal range, with a mean of 4.8 mg/dl (1.55 mmol/l) at both baseline and end of follow-up (p=0.4).
- Phosphate was higher in the sevelamer hydrochloride group than in the calcium carbonate group (mean difference=0.8 mg/dl [0.23 mmol/l]) at baseline but lower in the sevelamer hydrochloride group at follow-up (mean difference=-0.6 mg/dl [0.19 mmol/l]). This difference between groups was significant (p<0.001).

By the end of follow-up 128 deaths were recorded:

- Cardiovascular mortality due to cardiac arrhythmia occurred in 2 people taking sevelamer hydrochloride and 27 people taking calcium carbonate (adjusted HR=0.08, 95% CI 0.02 to 0.34, p<0.001).

- All-cause cardiovascular mortality occurred in 9 people taking sevelamer hydrochloride and 80 people taking calcium carbonate (adjusted HR=0.11, 95% CI 0.05 to 0.22, p<0.001).
- Non-cardiovascular mortality occurred in 19 people taking sevelamer hydrochloride and in 20 people taking calcium carbonate (unadjusted HR=0.75, 95% CI 0.39 to 1.40, p<0.4).
- Analyses were adjusted for baseline and time-dependent C-reactive protein, serum phosphate and coronary artery calcification. Coronary artery calcification score was lower in the sevelamer hydrochloride group (median=19) at baseline compared with the calcium carbonate group (median=30). However, coronary artery calcification was not measured again in follow-up.

Limitations of this study included that baseline coronary artery calcification scores in the 2 study groups differed at baseline, although adjusted analyses were similar to unadjusted data. The open-label design may have resulted in bias in clinicians' treatment decisions, although the known effects of sevelamer on low-density lipoprotein would have made treatment allocation obvious to investigators. The report stated that intention-to-treat analysis was done. However, only 59% of participants completed 36 months of follow-up and no method to account for missing data was reported.

This study suggests that sevelamer hydrochloride may reduce serum phosphate and cardiovascular mortality compared with calcium carbonate in people with CKD who are on dialysis. These results are unlikely to affect [NICE CG157](#) because the recommended first-line treatment is calcium acetate, and the drawbacks of calcium carbonate were considered in the development of the guideline.

#### Key reference

Di Iorio B, Molony D, Bell C et al. (2013) [Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomised clinical trial](#). *American Journal of Kidney Disease* 62: 771–8

#### ***Ferric citrate versus sevelamer hydrochloride***

[Yokoyama et al. \(2014b\)](#) reported an open-label RCT in Japan (n=230) of ferric citrate<sup>10</sup> (n=116) versus sevelamer hydrochloride (n=114) in people with CKD who were on dialysis. The primary outcome was the change in serum phosphate from baseline to the end of the 12-week treatment period. Participants had been on dialysis for at least 12 weeks and on a stable dose of phosphate binders for 4 weeks before enrolment or had ceased phosphate binder therapy and had serum phosphate of 1.97–3.23 mmol/l. Participants on vitamin D supplements, calcitonin or cinacalcet had to have stable doses for 4 weeks before enrolment.

Exclusion criteria included gastrointestinal disorders, severe heart disease, hepatic disorders, serum iron or calcium abnormalities, or parathyroidectomy or percutaneous ethanol injection therapy in the past 24 weeks. The trial started with a washout period for current phosphate binders then 12 weeks of treatment. Starting doses were administered 1 week after enrolment. The starting dose of ferric citrate was 1.5 g daily, with titration as needed to a maximum of 6.0 g daily. The starting dose of sevelamer hydrochloride was 3.0 g daily if the person's serum phosphate was lower than 2.58 mmol/l or 6.0 g daily if serum phosphate was 2.58 mmol/l or higher, with titration as needed to a maximum of 9 g daily.

Other drugs affecting serum phosphate were not allowed during the study, but vitamin D supplements and intravenous iron were allowed if needed. People stopped study treatment if they reached specified thresholds for serum iron, calcium or phosphate.

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<sup>10</sup> At the time of publication of this Evidence Update, ferric citrate did not have UK marketing authorisation and was not available in the UK.



Baseline characteristics did not differ between the ferric citrate group and the sevelamer hydrochloride group, and adherence to treatment was about 97% in both groups. By the end of treatment:

- Ferric citrate was associated with a reduction in mean serum phosphate from baseline (2.53 mmol/l) to end of treatment (1.72 mmol/l, mean change=-0.82 mmol/l,  $p<0.001$ ).
- Sevelamer hydrochloride was associated with a reduction in mean serum phosphate from baseline (2.52 mmol/l) to end of treatment (1.74 mmol/l, mean change=-0.78 mmol/l,  $p<0.001$ ).
- The least squares mean difference between groups was -0.03 mmol/l (95% CI -0.13 to 0.07 mmol/l,  $p=0.53$ ), suggesting that ferric citrate was non-inferior to sevelamer hydrochloride.

No deaths were recorded during the study, and 9 serious adverse events occurred that were considered to be not related to study drug treatments. The most common adverse events were gastrointestinal events, which occurred in 43 people in the ferric citrate group (37%) and 39 people in the sevelamer hydrochloride group (35%).

The authors did not address potential limitations of their study, such as its open-label nature or lack of a placebo-control group. The method of randomisation was not reported, so selection bias cannot be excluded.

This study suggests that ferric citrate may be as effective as sevelamer hydrochloride for controlling serum phosphate in people with CKD who are on dialysis. This evidence may have a potential impact on [NICE CG157](#), which did not consider this drug, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

#### **Key reference**

Yokoyama K, Akiba T, Fukagawa M et al. (2014b) [A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis](#). *Nephrology Dialysis Transplantation* 29: 1053–60

#### **Cost effectiveness of sevelamer**

[Bernard et al. \(2013\)](#) reported a cost-effectiveness analysis of sevelamer in adults with CKD who were on dialysis for at least 3 months. Treatments were sevelamer or calcium-based phosphate binders, of which 70% of people took calcium acetate and 30% of people took calcium carbonate. The paper did not clearly specify whether sevelamer hydrochloride or sevelamer carbonate was used. However, the RCT that formed the basis of the analysis ([Suki et al. 2007](#)) studied sevelamer hydrochloride only.

A Markov decision analytic model was developed to estimate the cost effectiveness of sevelamer compared with calcium-based phosphate binders from the perspective of the UK NHS. The base-case analysis assessed a lifetime horizon, and the model was based on a 1-month cycle in which outcomes were 'alive on phosphate binder' or 'dead'. Weibull regression analysis was used to extrapolate survival from the 44 months assessed in the RCT to 20 years. In the survival analysis for sevelamer, 57% of people were alive at 44 months, 22% were alive at 10 years, and 5% were alive at 20 years. In the survival analysis for calcium-based phosphate binders, 51% of people were alive at 44 months, 15% were alive at 10 years, and 2% were alive at 20 years.

Hospital admissions were estimated to be 0.22 days per month lower in people on sevelamer compared with people on calcium-based phosphate binders. The model accounted for the costs of drugs and the costs of days in hospital for chronic renal failure, acquired cardiac conditions, cardiac arrest and myocardial infarction. The base-case weighted average health utility was 0.61 for patients with CKD on dialysis. A 3.5% annual discount for costs and outcomes was applied. The base-case analysis showed that sevelamer was associated with a



gain of 0.44 QALYs per patient compared with calcium-based phosphate binders, with an ICER of £22,157, which the authors concluded was 'good value for money'.

In the cost-effectiveness analysis for [NICE CG157](#) (see appendix F of the [full version of NICE CG157](#)), the model used was more complex, also accounting the health outcomes of fractures and parathyroidectomy or start of cinacalcet treatment. Additionally, the cost-effectiveness modelling for [NICE CG157](#) used the results of a network meta-analysis of several studies, rather than data from 1 RCT. In survival analysis, the model for [NICE CG157](#) assumed that some patients would undergo renal transplantation, so a larger proportion of people were alive at 20 years than in the analysis by Bernard et al. (2013).

The study by Bernard et al. (2013) was funded by the manufacturer of sevelamer. Bernard et al. (2013) found a far greater benefit for sevelamer than in the [NICE CG157](#) analysis, and thus greater cost effectiveness. The model for [NICE CG157](#) found that sevelamer resulted in a QALY gain of 0.121 compared with calcium acetate, with an ICER of £87,916. All sensitivity analyses found sevelamer to have an ICER greater than £30,000.

This evidence suggests that sevelamer may be cost effective compared with calcium-based phosphate binders. However, because this analysis had some limitations and is more simplistic than the economic modelling used in [NICE CG157](#), no impact on the guidance is expected.

Additional information about the study by Bernard et al. (2013) is also available from an independent [critical appraisal report](#) produced for the Centre for Reviews and Dissemination's NHS Economic Evaluation Database.

#### **Key reference**

Bernard L, Mendelssohn D, Dunn E et al. (2013) [A modelled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom](#). *Journal of Medical Economics* 16: 1–9

#### **Supporting reference**

Suki WN, Zabaneh R, Cangiano JL et al. (2007) [Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients](#). *Kidney International* 72: 1130–7

## **1.4 Phosphate binders: children, young people and adults**

No new key evidence for this section was selected for inclusion in this Evidence Update.

## **2 New evidence uncertainties**

No new evidence uncertainties were identified during the Evidence Update process, however current uncertainties for hyperphosphataemia in CKD can be found in the [UK Database of Uncertainties about the Effects of Treatments](#) (DUETs) and in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

# Appendix A: Methodology

## Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Hyperphosphataemia in chronic kidney disease](#). NICE clinical guideline 157 (2013)

## Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 October 2011 (the end of the search period of NICE clinical guideline 157) to 14 July 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

The Evidence Update search strategy replicates the strategy used by [NICE CG157](#) (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs, systematic reviews and observational studies](#).

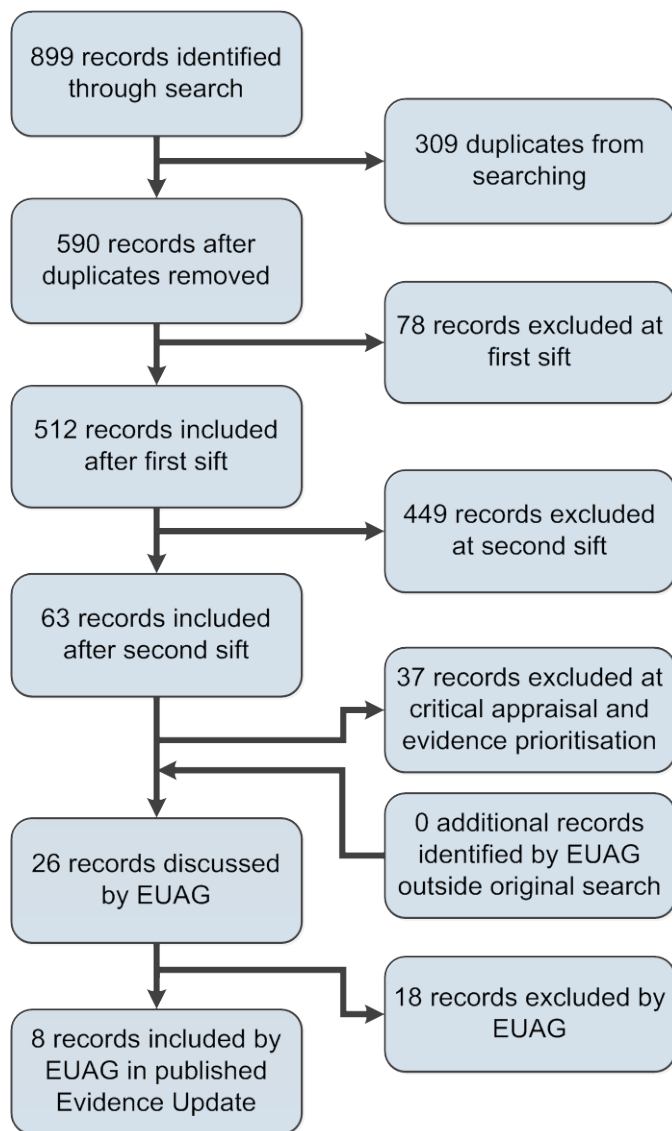
Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk)

See the [NICE Evidence Services](#) website for more information about [how NICE Evidence Updates are developed](#).

**Table 1 MEDLINE search strategy (adapted for individual databases)**

1	exp Renal Insufficiency, Chronic/	29	Aluminum Hydroxide/
2	ckd.tw.	30	aluminum hydroxide*.tw.
3	((chronic or progress*) adj1 kidney disease*).tw.	31	iron-magnesium hydroxycarbonate*.tw.
4	((chronic or progress*) adj1 renal disease*).tw.	32	ferric citrate*.tw.
5	((chronic or progress*) adj1 kidney failure).tw.	33	colestimide*.tw.
6	((chronic or progress*) adj1 renal failure).tw.	34	Sucralfate/
7	end-stage kidney.tw.	35	sucralfate*.tw.
8	end-stage renal.tw.	36	Chitosan/
9	((renal or kidney*) adj3 insufficien*).tw.	37	chitosan*.tw.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	38	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
11	exp Renal Dialysis/	39	15 and 38
12	((renal or peritoneal or kidney*) adj3 dialys*).tw.	40	Dietary Supplements/
13	(haemodialys* or hemodialys*).tw.	41	((diet* or food* or nutrition*) adj3 supplement*).tw.
14	11 or 12 or 13	42	Vitamins/
15	10 or 14	43	Minerals/
16	Diet Therapy/	44	Calcium, Dietary/
17	Phosphorus, Dietary/	45	Niacinamide/
18	Dietary Proteins/	46	exp Folic Acid/
19	Diet, Protein-Restricted/	47	((Nicotina* or niacin* or Vitamin* or folic or Mineral* or Fola* or (calcium adj3 diet*)) not vitamin d).tw.
20	((phosph* or protein*) adj3 (limit* or restrict* or reduc* or low* or intake or control*).tw.	48	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
21	(diet* adj3 regime*).tw.	49	15 and 48
22	16 or 17 or 18 or 19 or 20 or 21	50	23 or 39 or 49
23	15 and 22	51	Hyperphosphatemia/
24	(phosph* adj3 bind*).tw.	52	hyperphosphat*.tw.
25	(sevelamer or lanthanum).tw.	53	51 or 52
26	Calcium Carbonate/	54	15 and 53
27	(calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*).tw.	55	50 or 54
28	magnesium carbonate*.tw.		

**Figure 1 Flow chart of the evidence selection process**



EUAG – Evidence Update Advisory Group

# Appendix B: The Evidence Update Advisory Group and Evidence Update project team

## Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

**Dr Indranil Dasgupta – Chair**

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