PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can we IMPROVE cardiovascular outcomes through phosphate lowering in CKD? - Rationale and protocol for the IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease (IMPROVE-CKD) study
AUTHORS	Lioufas, Nicole; Toussaint, Nigel D.; Pedagogos, Eugenia; Elder, Grahame; Badve, Suni Vl; Pascoe, Elaine; Valks, Andrea; Hawley, Carmel on behalf of the IMPROVE-CKD Writing Committee

VERSION 1 – REVIEW

REVIEWER	Jordi Bover Fundació Puigvert Barcelona Spain I received honoraria for lectures and advisory boards from different phosphate-binder pharmaceutical companies
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	Congratulations for the excellent and absolutely needed initiative

REVIEWER	Antonio Bellasi Nephrology and Dialysis Unit, ASST Lariana, Como, Italy Speaking honoraria from Sanofi, Amgen, Research grant form Amgen
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	Dear editor, I have read the study protocol with great interest. It is my opinion that this study is of great importance in light of the great risk associated with phosphate balance abnormalities and the lack of RCT investigating the impact of phosphate metabolism manipulation on hard or surrogate outcome. Although nicely drafted a couple of aspects deserve mention: - why investigators have decided to include CKD subjects with normal levels of serum phosphate? Indeed, serum phosphate is only a weak marker of phosphate balance and normal levels of serum phosphate may be associated with normal, positive or negative phosphate balance - in light of the weak correlation between serum phosphate and markers of arterial stiffness, it probably would have been more advisable to stratify patients according to baseline PWV rather

	than age for example - is the randomization process blind to investigators? - drug dose adjustment: is this process centralized and blinded to investigators/study participants? - are PWV, vascular calcification, echocardiogram centrally read? - similarly, are biochemical analyses performed by a central lab? - concomitant medications: although lanthanum is not available for CKD patients, there are other calcium containing and calcium free phosphate binders available. Furthermore, if a patient starts dialysis, these drugs maybe prescribed to patients (drops in). Finally, what about other drug that may impact phosphate balance such as vitamin D? Is the use of these compounds free or per protocol?

REVIEWER	arif khwaja Sheffield Kidney institute, England
REVIEW RETURNED	07-Aug-2018

GENERAL COMMENTS	Well written methodology paper for an important study It would be good if the authors good include the following: I) what is the published daa (if any) with regard to the acceptability and concordance with long term lanthanum therapy ii) What is the rationale for a placebo-controlled rather than a calcium binder-controlled study. It will be difficult to ascertain if any positive impact is due to phosphate lowering per se or rather the specific use of a non-calcium binder iii) Given the negative outcome studies of Block (ref 21), Chue (ref 22) and seifert (ref 23) could the authors expand as to why think their study will be different/is justified

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Congratulations for the excellent and absolutely needed initiative.

Thank you for your comments.

Reviewer 2

Dear editor,
I have read the study protocol with great interest. It is my opinion that this study is of great importance in light of the great risk associated with phosphate balance abnormalities and the lack of RCT investigating the impact of phosphate metabolism manipulation on hard or surrogate outcome.
Although nicely drafted a couple of aspects deserve mention:

- why investigators have decided to include CKD subjects with normal levels of serum phosphate? Indeed, serum phosphate is only a weak marker of phosphate balance and normal levels of serum phosphate may be associated with normal, positive or negative phosphate balance.

We agree with the reviewer that serum phosphate is not truly reflective of overall phosphate balance. This study will measure several other markers that guide overall phosphate balance, including 24-

hour urinary phosphate excretion and serum FGF-23. In fact, rather than using biochemical parameters, such as serum phosphate, as the predominant endpoint, the measurement of surrogate markers of cardiovascular disease with primary and secondary end-points of arterial compliance and vascular calcification is crucial to why IMPROVE-CKD is an important study.

As serum phosphate is not a good marker of phosphate balance, this was one reason why we included participants with normal serum phosphate, similar to the Phosphate Normalization Study (PNT) study by Block et al (2012, Ref 21). Elevated serum phosphate is often a finding of advanced CKD, however elevations in FGF-23 (and concurrent klotho deficiency) generally occur much earlier with milder impairment in kidney function (despite normal serum phosphate). Even when phosphate levels are towards the upper normal range, numerous studies have reported associations with poor clinical outcomes including cardiovascular disease.

Therefore, the IMPROVE-CKD study is looking at 'phosphate lowering' in general, not necessarily reducing serum phosphate levels; and should this study not achieve a separation in serum phosphate values between the two arms of the trial, any differences in outcomes may reflect differences in FGF-23, as overall FGF-23 levels at 96 weeks may fall with lanthanum carbonate therapy (compared to placebo), even in participants with normophosphatemia.

- in light of the weak correlation between serum phosphate and markers of arterial stiffness, it probably would have been more advisable to stratify patients according to baseline PWV rather than age for example

We considered stratification of patients in this study by PWV, although the most significant factors associated with PWV in patients with CKD are age, diabetes and degree of kidney function. Randomization in the study, as outlined in the protocol, is therefore stratified according to these factors with pre-specified subgroup analyses to be performed according to CKD stage (3b vs 4), age groups (<60 years, ≥60 years) and presence of diabetes mellitus (page 16).

- is the randomization process blind to investigators?

Yes, randomization is blinded to investigators and is undertaken as outlined in the protocol via web-based access to a central electronic randomization system provided by The George Institute in Sydney, Australia (page 17).

- drug dose adjustment: is this process centralized and blinded to investigators/study participants?

The drug dose adjustment is not centralized and is left to individual investigators to titrate the dose of study medication according to local laboratory serum phosphate levels. We have added this clarification into the manuscript (page 16). However, the study is a placebo-controlled trial and investigators are therefore blinded to the study medication regardless of titration of dose.

- are PWV, vascular calcification, echocardiogram centrally read?

Yes, all of these outcome measures, as surrogate markers of cardiovascular disease, will be centrally read. All readings and images will be submitted to central vascular/cardiology and radiology services for reporting of measurements by investigators who are blinded to patient details as well as the allocated study medication. A proportion of each of these measurements will also be reviewed by second investigators to assess inter-rater variability and reproducibility.

We have outlined in the protocol that these outcome measurements will be centrally read (page 21-22).

- similarly, are biochemical analyses performed by a central lab?

Routine serum biochemical parameters, for example serum phosphate, calcium and PTH, and the urinary phosphate measurements will not be performed by a central laboratory but will be performed locally at individual sites; however, samples for FGF-23 will be batched and tested at a central laboratory. We have added a statement in the protocol to address this issue (page 22).

- concomitant medications: although lanthanum is not available for CKD patients, there are other calcium containing and calcium free phosphate binders available. Furthermore, if a patient starts dialysis, these drugs maybe prescribed to patients (drops in).

Phosphate binders, in addition to the maximal titrated study medication, can be prescribed in this study for persistent hyperphosphatemia at the discretion of the local investigator (suggested for persistent serum phosphate levels >1.60mmol/L). Calcium, magnesium or aluminium-based binders will be used as these are currently the only available phosphate lowering agents for pre-dialysis CKD patients in Australia, New Zealand and Malaysia. This information has been added to our manuscript (page 17-18) Although unlikely to be a common occurrence in this trial, if patients require dialysis throughout the study period these binders will also be recommended to avoid drop-ins.

Finally, what about other drug that may impact phosphate balance such as vitamin D? Is the use of these compounds free or per protocol?

The use of other medications in this study is as per standard of care. Oral vitamin D administration, both 1,25 dihydroxy vitamin D (calcitriol) and nutritional vitamin D (cholecalciferol), is allowed and can be prescribed at the discretion of the treating physician. Calcitriol may be administered to study patients to treat secondary hyperparathyroidism or hypocalcemia, but with a maximal dose of 0.25mcg (one tablet) per day. We have added this information to our manuscript (page 17).

Reviewer 3

Well written methodology paper for an important study
It would be good if the authors good include the following:

I) what is the published data (if any) with regard to the acceptability and concordance with long term lanthanum therapy

There are numerous publications outlining the long-term safety of lanthanum carbonate in patients with CKD. For example:

1. Hutchison AJ, et al. Lanthanum carbonate: safety data after 10 years. *Nephrology (Carlton).* 2016;21(12):987-994.

2. Zhai CJ, et al. Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis. *Int Urol Nephrol.* 2015;47(3):527-35.

We have added information regarding the safety of lanthanum to our manuscript (page 16 and Refs 30 and 31).

ii) What is the rationale for a placebo-controlled rather than a calcium binder-controlled study. It will be difficult to ascertain if any positive impact is due to phosphate lowering per se or rather the specific use of a non-calcium binder

The problem with using a calcium-based phosphate binder as a comparator is that there is an increasing appreciation of harm with an exogenous calcium load in patients with CKD. The recent

calcium balance studies (Hill et al, Kidney Int 2013;83(5):959-66 and Spiegel et al, Kidney Int 2012;81(11):1116-22) have highlighted this issue extremely well. The previous RCT by Block et al (J Am Soc Nephrol 2012, Ref 21) also reported increased coronary artery calcification scores in non-dialysis CKD patients on a calcium-based binder (compared to placebo).

In fact, the concern in patients with CKD, including those on dialysis, where non-calcium-based binders are compared to calcium-based binders and reported to be more effective in reducing vascular calcification and improving outcomes (including mortality) is that perhaps patients do worse with the calcium-binders and perhaps experience no difference with the non-calcium binders (as discussed in the meta-analyses by Jamal SA, et al. Lancet. 2013;382(9900):1268-77 and Palmer SC, et al. Am J Kidney Dis 2016;68(5):691-702).

Therefore, there is a desperate need to undertake placebo-controlled studies looking at phosphate lowering to determine if this strategy is at all beneficial in reducing the cardiovascular burden in CKD. If the IMPROVE-CKD study shows a positive impact on phosphate lowering, the reviewer is correct in that it may be the specific non-calcium binder that leads to this effect, however either way this would be an important finding for future studies to target phosphate lowering through different means if this may be beneficial for CKD patients.

iii) Given the negative outcome studies of Block (ref 21), Chue (ref 22) and seifert (ref 23) could the authors expand as to why think their study will be different/is justified

The IMPROVE-CKD study was designed and it commenced recruitment prior to any of these studies being published. Nonetheless, our trial will be the largest and longest in follow up for any placebo-controlled phosphate lowering study in non-dialysis CKD patients. These advantages will hopefully determine whether the previous studies were in fact under powered with the smaller cohorts and shorter study periods, or whether phosphate lowering in this population does not improve cardiovascular risk.

VERSION 2 – REVIEW

REVIEWER	Antonio Bellasi ASST Papa Giovanni XXIII, Bergamo, Italy Speaking honoraria from Sanofi, Amgen, Research grant form Amgen
REVIEW RETURNED	25-Oct-2018

GENERAL COMMENTS	The study is of great interest for the Nephrology community and authors should be credited for this effort. Please author make sure that as few patients as possible start any phosphate binder or diet during follow-up in the control group. This may jeopardize the entire project. Antonio Bellasi

REVIEWER	arif khwaja Sheffield Kidney Institute England
REVIEW RETURNED	22-Oct-2018

GENERAL COMMENTS	very clear description of an important study looking at phosphate reduction in ckd